TRANSCRANIAL DIRECT CURRENT STIMULATION AS AN ADJUNCT TO COGNITIVE TRAINING FOR OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

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Transcranial Direct Current Stimulation as an Adjunct to Cognitive Training for Older Adults with Mild Cognitive Impairment

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CERTIFICATE OF ORIGINALITY

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

Name: Pablo Cruz Gonzalez

Date: 10 August 2021

DEDICATION

Access to education is a privilege that should cease to be one; it is a universal necessity. I feel so fortunate to have embarked on this PhD journey. I have acquired knowledge and skills for a lifetime which will enable me to learn through different lenses, develop my thoughts, test my ideas, and implement them with a stronger critical sense. It is not just a degree or a profession that I am obtaining, but also the freedom that comes from having had access to education.

To my parents, Emiliano and Maria, this thesis would not exist without them. Being born and raised in the right place and time determines the course of a person's life. They belonged to a generation whose circumstances lacked resources and the access to education. While in contrast, I have had that access, that is due to their hard work, sacrifice, dedication, and love. To my grandmother, Leandra, I am very sorry to not have accompanied you in the last moments of your life. I remember you so deeply and I have reflected on the adversity you had to face in a life full of sacrifices. All this process, all this work, generation after generation, translates into the fact that I have studied a PhD at the Hong Kong Polytechnic University and now I can deliver this thesis.

This PhD is your legacy. It is your history.

DEDICACIÓN

El acceso a la educación es un privilegio que debería cesar de existir para convertirse en una necesidad universal. Me siento muy afortunado de haber embarcado en este doctorado en el cual he adquirido conocimientos y destrezas que me permitirán aprender con unas lentes diferentes, desarrollar pensamientos, poner a prueba mis ideas e implementarlas con un sentido crítico más sólido. No es solo una titulación o una profesión lo que obtengo sino también la libertad que conlleva el haber tenido acceso a la educación.

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Este doctorado es vuestra huella, es vuestra historia.

ABSTRACT

General background

Transcranial direct-current stimulation (tDCS), a kind of non-invasive brain stimulation (NIBS), delivers direct current to the brain and acts as a neuromodulator that can facilitate cognitive improvement. tDCS is increasingly used as a type of non-pharmacological therapy (NPT) in cases of mild cognitive impairment (MCI) and dementia. Cognitive training (CT), which falls under the umbrella of cognitive rehabilitation (CR), is a form of NPT and consists of repeated guided practice, in a structured manner, of tasks associated with specific cognitive domains. There is mixed evidence for the effectiveness of CT in enhancing cognitive function in persons with MCI (PwMCI).

CT is based on the principle that repetitive and structured practice of a task-specific domain with active therapist involvement will lead to changes in the neural processes that underlie the cognitive task, and in turn, transfer the skills to the respective cognitive domain. These benefits may also be generalized beyond the targeted cognitive domain, and as a result, CT could also improve daily living skills through the amelioration of cognitive functioning. As CT strengthens neural circuits during practice, these could be targeted by tDCS to increase the likelihood of transmission across neurons and thus alter behavior. Concurrent CT and tDCS may therefore produce synergistic effects that are superior to those of the administration of CT alone. This thesis accordingly aimed: 1) to evaluate the literature in order to determine the potential efficacy of tDCS in

improving cognitive outcomes in persons with dementia (PwD) and PwMCI; 2) to examine whether older adults with MCI would gain more cognitive benefit from receiving CT alone rather than receiving CT coupled with tDCS along three different dimensions (domain-specific cognitive outcomes, task-specific outcomes of CT, and everyday functioning outcomes); and 3) to provide physiological evidence using electroencephalography (EEG) to study brain responses to the interventions. This was a three-phase research project. Phase 1 consisted of a systematic review and meta-analysis, while Phase 2 was a pilot study. Phase 3 was a randomized controlled trial (RCT). The structure of the current abstract is accordingly composed of three mini-abstracts corresponding to the four studies carried out in the three phases in order to achieve the above aims.

1) Systematic review and meta-analyses (Phase 1)

Objective

To answer the following research question: Can tDCS serve as a clinical intervention to improve cognitive functions of PwMCI and PwD?

Methods

A systematic review was conducted of studies published up to November 2017 involving tDCS in cases of MCI and dementia. Studies were ranked according to the level of evidence (Oxford Center for Evidence-Based Medicine) and assessed for

methodological quality (Risk of Bias Tool in the Cochrane Handbook for Systematic Reviews of Interventions). Data was extracted on all protocol variables to establish a reference framework for clinical interventions. Different modalities, tDCS alone or combined with CT, compared with sham tDCS were examined for both short- and long-term effects. Four randomized control trials with memory outcomes were pooled using the fixed-effect model for the meta-analysis.

Results

Twelve studies with 195 PwD and four studies with 53 PwMCI met the inclusion criteria. Eleven articles were ranked as level 1b. The results of the meta-analysis on the pooled effects of memory indicated a statistically significant medium effect size of 0.39 (p = 0.04) for immediate effects. This improvement was not maintained in the long term 0.15 (p = 0.44).

Conclusion

Short term memory in PwD is improved by tDCS, which also seems to have a mild positive effect on memory and language in PwMCI. However, there is no conclusive advantage of coupling tDCS with CT. More rigorous evidence is needed to establish whether tDCS can serve as an evidence-based intervention for both populations.

2) Pilot study (Phase 2)

Objective

The aim of this pilot study was to investigate whether the application of anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) could boost the effects of a cognitive stimulation (CS) program using a tablet in five older adults with MCI.

Methods

A single-subject study of A-B-C-A design was used. After the baseline with the administration of CS (phase A), a sham treatment with CS was applied (phase B). Following the withdrawal of sham treatment, tDCS was introduced in combination with CS (phase C). Finally, phase A was replicated a second time.

Results

A significant effect of tDCS was observed for processing speed, selective attention, and planning ability in terms of task performance and completion time.

Conclusion

In PwMCI, tDCS appears to have a positive impact on some cognitive components of CS. Further study on the long-term effects of tDCS and generalization of power to daily activities is warranted.

3) Main study (Phase 3)

Objective

To investigate whether the receiving tDCS combined with CT would be superior to receiving CT alone on domain- and task-specific cognition and everyday functioning in older adults with MCI.

To explore the offline effects of multisession tDCS in combination with CT in older adults with MCI could influence the spectral analysis of absolute power relative to sham tDCS paired with CT and CT alone by means of resting EEG.

Methods

This double-blind, sham-controlled randomized trial included 67 older adults with MCI assigned to one of three groups: 1) tDCS combined with CT (tDCS+CT), 2) sham tDCS combined with CT (sham tDCS+CT) and 3) CT alone. Nine sessions of computerized CT based on executive function were administered to the three groups for three weeks. In addition, tDCS and sham tDCS was delivered to the left DLPFC in the tDCS+CT and sham tDCS+CT during CT, respectively. Standardized cognitive assessments were carried out at baseline, post-intervention, and at six-weeks follow-up (FU). Participants' performance in the CT tasks was rated in every session. The Rivermead Behavioural Memory Test-3 was administered to assess transfer effects in everyday memory. Neurophysiological responses were assessed in sixteen cases to study the offline effects of tDCS using EEG at baseline and at post-intervention.

Results

Improvements in global cognition and everyday memory ($p < 0.017$) were found within the three groups after the intervention and at FU with larger effect sizes noted in the tDCS+CT group ($d > 0.94$). However, there were no significant differences between groups. Regarding the CT outcomes, significant differences among groups were observed in favour of the tDCS+CT group with decreased completion and reaction times of working memory and attention activities ($p < 0.017$). A significant interaction effect (time x intervention) in channel 1LB (left prefrontal cortex) for absolute power of the theta band was evidenced ($p = 0.047$). *Post-hoc* comparisons revealed that this change was statistically significant in the tDCS+CT group ($p = 0.047$)

Conclusions

Computerized CT with or without tDCS may be useful to promote global cognitive functioning and everyday memory in older adults with MCI. The significance of this study fosters insights into a new approach of using CT coupled with tDCS could provide a superior non-pharmacological benefit as compared to CT in the absence of tDCS for older adults with MCI. The combination of tDCS and CT did not produce a superior effect on domain specific outcomes as compared to sham tDCS+CT or CT alone, but did provide comparatively larger effect sizes and improve the processing speed of task-specific outcomes. Computerized CT of executive function appears to produce robust transfer effects of enhanced everyday memory, yet concurrent tDCS provides no superior transfer effect.

Some sections of the mini abstracts have been previously published by the author of this thesis as a scientific manuscript which are cited accordingly in the general introduction of Chapter 4, 5, 6 and 7.

LIST OF RESEARCH OUTPUT DURING THIS CANDIDATURE

Journal publications during the study period (arising from this thesis):

Cruz Gonzalez, P., Fong, K. N. K., & Brown, T. (2021). Transcranial direct current stimulation as an adjunct to cognitive training for older adults with mild cognitive impairment: A randomized controlled trial. *Annals of Physical and Rehabilitation Medicine*, 64.

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Cruz Gonzalez, P., Fong, K. N. K., Chung, R. C. K., Ting, K. H., Law, L. L. F., & Brown, T. (2018). Can transcranial direct current stimulation be used as a clinical intervention to improve cognitive functioning in persons with mild cognitive impairment and dementia? A systematic review and meta-analysis. *Frontiers in Human Neuroscience*.

https://doi.org/10.3389/fnhum.2018.00416

Cruz Gonzalez, P., Fong, K. N. K., & Brown, T. (2018). The effects of Transcranial Direct Current Stimulation (tDCS) on the cognitive functions in older adults with mild cognitive impairment (MCI): A pilot study. *Behavioral Neurology*.

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Proceeding publications during the study period (arising from this thesis):

Cruz Gonzalez, P., Fong, K. N., & Brown, T. (2020). The impact of paired cognitive training with transcranial direct current stimulation on everyday functioning for older

adults with mild cognitive impairment: Beyond conventional testing. *Neurorehabilitation and Neural Repair*.

https://journals.sagepub.com/doi/pdf/10.1177/1545968320988381 (P0369)

Cruz Gonzalez, P., Fong, K., Brown, T. (2019). Is transcranial direct current stimulation (tDCS) an effective adjunct to cognitive training for older adults presenting with mild cognitive impairment (MCI)? *Brain Stimulation*, *12*, 448-449.

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Conference presentations during the study period (arising from this thesis):

Cruz Gonzalez, P., Fong, K., & Brown, T. (2020). *Transcranial direct current stimulation as an adjunct to cognitive training for older adults with mild cognitive impairment*. Oral presentation on 28th Nov 2020 at the 27th Annual Congress of Gerontology: Advances in Gerontology. Hong Kong Association of Gerontology, Hong Kong.

Cruz Gonzalez, P., Fong, K. N., & Brown, T. (2020). *The impact of paired cognitive training with transcranial direct current stimulation on everyday functioning for older adults with mild cognitive impairment: Beyond conventional testing.* Poster presentation at the 11th World Congress for Neurorehabilitation, October 2020, Lyon, France.

Cruz Gonzalez, P., Fong, K., & Brown, T. (2019). *Is Transcranial direct current stimulation (tDCS) an effective adjunct to cognitive training for older adults presenting with Mild Cognitive Impairment (MCI)?* Abstract presented at the 3rd International Brain Stimulation Conference, on 24th February to 27th February 2019, Vancouver, Canada.

Cruz Gonzalez, P., & Fong, K. N. (2016). *The effects of transcranial direct current stimulation on cognitive functions of an old adult with mild cognitive impairment: A case report.* Oral presentation at the 10th Pan-Pacific Conference on Rehabilitation, November 2016, Shanghai, China.

Cruz, P., & Fong, K. (2016). *The effects of Transcranial Direct Current Stimulation on cognitive functions in older adults with Mild Cognitive Impairment: A pilot study.* Oral presentation on November 19, 2016, at the 23rd Annual Congress of Gerontology: Growth and sustainability: Improving Quality Care Services for the Elderly. Hong Kong Association of Gerontology, Hong Kong.

Awards (arising from this thesis):

Merit award, outstanding paper presentation on 28th November 2020 at the 27th Annual Congress of Gerontology, Hong Kong Association of Gerontology, Hong Kong.

Journal publications during the study period (not arising from this thesis):

Li, C. T. L., Hung, G. K. N., Fong, K. N. K., Cruz Gonzalez, P., Wah, S. H., & Tsang, H. W. H. (2020). The Effects of a home-based occupational therapy telerehabilitation via smartphone for outpatients after hip fracture surgery: A feasibility randomized controlled study. *Journal of Telemedicine and Telecare*.

http://dx.doi.org/10.1177/1357633X20932434

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https://doi.org/10.1080/11038128.2016.1229811

Conference presentations during the study period (not arising from this thesis):

Cruz Gonzalez, P., Fong, K. N., Miller, T., & Brown, T. (2019). *Examining the mental health crisis in doctoral students using the model of human occupation (MOHO): Evaluating occupational adaptation and participation in doctoral graduate students*. Oral presentation at the 6th International Institute on Kielhofner's model of human occupation. MOHO: Client-centred practice in a global context, September 2019, Chicago, USA.

Fong, N. K. K., Kwok, K. C. D., Wong, G. P. Y., Cheung, Y. W. Q., Yau, K. Y., Yeung, H. W. Y., Cruz, G. P., Tong, C. Y., & Chan, Y. W. D. (2016). *Caregiver-recipient relationship closeness: Effects on people with dementia and their caregivers*. Oral presentation at the 23rd Annual Congress of Gerontology: Growth and sustainability: Improving Quality Care Services for the Elderly, November 2016, Hong Kong.

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Conducting clinical research with human subjects can become challenging and even tedious during some stages; furthermore, doing that as an international student involves more obstacles, such as culture issues or language. Professor Fong has always been there, offering me advice, options, and solutions to overcome all kind of contingencies, and has always made himself available every time I needed guidance and help. I have also had the opportunity to assist him in teaching for three years which has made the whole PhD experience even more completed. I have learned a lot from him about how to prepare and deliver tutorials to occupational therapy students. It deserves special mention also to express that I appreciate Professor Fong's patience, sympathy, and care when I struggled with facing difficulties in my personal life.

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Full term
AD	Alzheimer's disease
ADL	Activities of daily living
CDR	Clinical dementia rating
CONSORT	Consolidated standards for reporting trials
CR	Cognitive rehabilitation
CT	Cognitive training
CS	Cognitive stimulation
DLPFC	Dorsolateral prefrontal cortex
DST	Digit span test
DST-f	Digit span test forward part
DST-b	Digit span test reverse order part
EEG	Electroencephalography
FU	Follow-up

GDS	Geriatric depression scale
MCI	Mild cognitive impairment
mA	Milliamps
MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
NIBS	Non-invasive brain stimulation
NPT	Non-pharmacological therapy
PwMCI	Persons with MCI
PwD	Persons with dementia
RCT	Randomized Controlled trial
RCTs	Randomized Controlled trials
RBMT	Rivermead behavioral memory test
RBMT-3	Rivermead behavioral memory test, third edition
tDCS	Transcranial direct current stimulation
TMT	Trail making test

TMT-a	Trail making test part A
TMT-b	Trail making test part

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CHAPTER 1: GENERAL INTRODUCTION

Mild cognitive impairment (MCI) is an intermediate state which lies between the usual and natural cognitive decline associated with healthy ageing, and the pathological and devastating deterioration of dementia (Petersen, 2004). MCI is not always a permanent condition, so those who suffer from it may recover normal cognition; on the other hand, they might progress to dementia. MCI can therefore be considered a concept in constant motion. Accordingly, it has an important clinical meaning, given that it can be reversed, or at least progression to dementia can be slowed down (Aerts et al., 2017; Shimada, Doi, Lee, & Makizako, 2019).

At present, there are no pharmacological treatments which will cure MCI. In addition, drug trials have predominantly targeted PwD rather than PwMCI, and focus on treating the corresponding symptoms of the disease (Anderson, Murphy, & Troyer, 2012; Langa & Levine, 2014; Russ & Morling, 2012). Alternatively, however, NPT have the potential to improve both cognition and the ability to function in everyday situations (Livingston et al., 2017; Olazarán et al., 2010). The latter can become compromised in PwMCI (Albert et al., 2011; Langa & Levine, 2014). Cognitive rehabilitation (CR) is categorized as a form of NPT.

> CR is referred to “as a process whereby people disabled by injury or disease work together with health service professionals to remediate or alleviate cognitive deficits arising from a neurological insult” (Wilson, Evans, & Keohane, 2002, p.542)

with the ultimate goal of promoting everyday functioning by the amelioration of cognitive function (Sohlberg & Mateer, 1989). There are three main approaches in CR - a restorative approach (i.e. cognitive retraining), a compensatory approach (i.e. changes to the environment), and a holistic approach (cognitive, emotional, and motivational dimensions in an integrated manner) (Anderson, Winocur, & Palmer, 2010). One CR intervention that has been used to treat PwMCI is CT (Anderson, Winocur, & Palmer, 2010), which consists of repeated practice in a task-specific domain(s). CT can produce improvements in the trained, and perhaps also the nontrained, cognitive domains by changing the underlying neuronal processes (Glisky & Glisky, 2002). Over the past decade, increasing research into novel brain stimulation techniques, such as transcranial direct current stimulation (tDCS), has uncovered evidence of their potential as a new tool for the rehabilitation of cognitive disorders (Cappon, Jahanshahi, & Bisiacchi, 2016). tDCS can alter cognition by sending weak direct current to the brain and thus modulating neuronal activity (Kuo & Nitsche, 2012; Nitsche et al., 2008; Priori, Hallett, & Rothwell, 2009).

This thesis combines the use of CT and tDCS for the purpose of using them as a treatment modality for PwMCI. The aim was to use both interventions simultaneously, so that tDCS could boost the effects of CT, creating synergistic effects and providing greater therapeutic benefits.

This thesis consists of nine chapters, of which three are based on a randomized controlled trial (RCT). This chapter sets out the background to, and core concepts of, the thesis. Chapter 2 presents a literature review spanning the clinical spectrum from

healthy ageing to dementia, including topics such as structural and functional changes in the ageing brain, dementia, and an in-depth review of MCI. Chapter 3 sets out the conceptual framework of the interventions used (CT and tDCS) and the mechanisms, operations, evidence, and effectiveness of each, before presenting a rationale for the use of tDCS as an adjunct to CT. Chapter 4 presents a systematic review and meta-analysis of the use of tDCS, either alone or combined with CT, as a clinical intervention to improve cognitive abilities in PwMCI and PwD. Chapter 4 provides a detailed review of the numerous tDCS protocols (with or without CT) to justify the selection of the design and methods of the experimental studies reported in this thesis. Chapter 5 reports on a pilot study, using a single-subject, four-phase design, which aimed to investigate whether tDCS could boost the effects of a CS practice on older adults with MCI. This pilot study, along with the review presented in Chapter 4, lay the foundations of the following chapters, which are the experimental core of the thesis. Chapter 6, 7, and 8 report on the three parts of the double-blind, sham-controlled RCT. The first part of the RCT (Chapter 6) focuses on investigating whether the administration of tDCS paired with CT was superior to sham tDCS combined with CT, or CT alone, in terms of domain-specific (standardized cognitive outcome measures taken at baseline, immediately post-intervention, and six weeks post-intervention) and task-specific (performance in activities measured in each of nine intervention sessions) outcomes of CT for older adults with MCI. The second part (Chapter 7) reports on the effects of the intervention in everyday functioning, particularly in the domain of everyday memory. The last part (Chapter 8) reports on a neurophysiological study of resting EEG conducted at

baseline and post-intervention, following the same timeline of the multisession intervention. The final chapter (Chapter 9) summarizes the conclusions of the study.

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CHAPTER 2: LITERATURE REVIEW

This chapter covers the background knowledge, which lays the foundations of the thesis. Some of the information in this chapter was included in the submission for confirmation of registration as a full-time PhD candidate in the Department of Rehabilitation Sciences entitled “The Effects of Transcranial Direct Current Stimulation on Attention in Clients with Mild Dementia and its Impact on activities of daily living and Quality of Life” in February 2017.

The chapter will begin by describing a general representation of the continuum of changes associated with ageing, from natural changes that can be attributed to the passage of time to pathological conditions correlated with ageing. A brief description of the cognitive structural changes in the ageing brain will then be introduced, followed by a contextualization of dementias. Finally, the core features and development of the concept and of MCI, and its criteria, diagnosis process, and types, will be explained in detail.

The aim of this chapter is also to provide information on the population targeted in the experimental studies.

2.1 Introduction

Age-related changes occur across the entire lifespan. Normative age-graded changes manifest in every individual and are associated with specific ages:

> "Some universal changes happen because humans are biological organisms subject to a genetically programmed maturing process" (Boyd & Bee, 2015, p. 29-30).

These changes can be classified into three domains. The physical domain encompasses transformations in the size, shape, and characteristics of the body. The social domain involves shifts in how the individual interacts with the world and maintains relationships. The last domain, which is the focus of this thesis, is the cognitive domain. This includes changes in thinking, memory, attention, orientation, problem solving, and other mental skills (Boyd & Bee, 2015). The variations within these domains across time help us to identify periods of development in the human lifespan, starting in the prenatal period followed by infancy, early and middle childhood, adolescence, early and middle adulthood, and finally late adulthood. While all these periods are influenced by demographic variables, gerontologists have categorized older adults into three groups; young-old (aged 60-75), old-old (aged 75-85), and the oldest-old (over the age of 85) (Boyd & Bee, 2015).

2.2 Cognitive changes in the ageing brain

According to The American Psychological Association (APA), cognition is defined as:

> "All forms of knowing and awareness, such as perceiving, conceiving, remembering, reasoning, judging, imagining, and problem solving" (APA, 2021) (Source: https://dictionary.apa.org/cognition)

All these high-level mental processes have critical implications in how humans understand and interact with life, enabling them not just to acquire knowledge, but to synthesize and use information by way of thought, senses, and experience (Oxford, 2021) (Source: https://www.lexico.com/definition/cognition). Therefore, cognition is a dynamic entity that is malleable across time. The cognitive changes associated with ageing are heterogeneous among older adults. However, there are common patterns of decline in cognitive abilities linked to normal ageing.

The ageing brain presents a duality of intellectual ability that affects the course of cognition in the elderly. This duality refers to fluid and crystallized intellectual ability (Spreng & Turner, 2019). Fluid intelligence relates to cognitive-control processes which are essential for goal-directed behaviors in daily life. These processes encompass elements of core executive functions such as directing attentional resources towards environmental stimuli, inhibiting distractions, and the cognitive ability to switch between tasks (Spreng & Turner, 2019). In other words, fluid intelligence refers to the ability to process and learn new information as well as skills related to novel problem solving. On the other hand, crystallized intelligence is grounded on a repertoire of prior knowledge

that consists of habits, routines, thoughts, and behaviors that have been repeated over the life course of a person. It is the accumulation of information based on experience (Harada, Love, & Triebel, 2013; Spreng & Turner, 2019). These two components of cognition, fluid and crystallized intelligence, age differently. Crystallized abilities, also referred to as semantics, usually preserve well or even improve for the young-old and the old-old (aged 60-75 and 75-80, respectively), whereas cognitive-control abilities tend to worsen with age, especially in the old-old and oldest-old that show significant declines in a variety of intellectual measures such as processing speed and working memory (Boyd & Bee, 2015; Salthouse, 2012; Spreng & Turner, 2019). Regardless of the duality, cognition has a natural deteriorating tendency associated with ageing which manifests in distinctive cognitive domains that are affected by the passage of time. In conclusion, there is a measurable decline that occurs earlier in fluid abilities with ageing (e.g. memory, calculation, etc.). However, it is important to note that exercise of either physical or cognitive abilities (e.g. cognitive training) can improve performance at any age, although the upper limit declines with increasing age (Berlucchi, 2011; Fernández-Ballesteros, Zamarrón, Tárraga, Moya, & Iñiguez, 2003; Lee, 2013, p. 46-47; Kurz, 2019). Harada and colleagues describe in their narrative review the functional alterations that accompany ageing and lead to cognitive changes, which can be as follows (Harada, Love, & Triebel, 2013):

a) *Processing speed,* which refers to the speed of mental processing of information and the completion of cognitive tasks (Beall, Holdnack, Saklofske, & Weiss, 2016). The decline of certain cognitive domains in healthy older adults is due to a reduction in

processing speed, which starts in the third decade of life (Harada et al., 2013). Slow processing can have a negative impact on performing certain activities, such as not finishing tasks within an expected or reasonable time, difficulties in keeping up with a conversation, or doing mathematical calculations (Harada et al., 2013).

b) *Attention*, which William James defined as:

> "Taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence" (James, 2007, p.403).

Attention can be classified into various domains such vigilance, selective attention, switching attention and divided attention (Cohen, 2011). A substantial decline in attention subdomains has been identified in relation to age. For instance, healthy older adults have difficulties with selective attention, or inhibiting irrelevant information to focus on specifics (de Fockert, Ramchurn, Van Velzen, Bergström, & Bunce, 2009; Healey, Campbell, & Hasher, 2008; Quigley, Andersen, Schulze, Grunwald, & Müller, 2010; Salthouse, Fristoe, Lineweaver, & Coon, 1995). This deficit can be translated into problems choosing the stimuli to focus on, which may be important in specific contexts such as looking out for cars when using a pedestrian crossing (Peelen & Kastner, 2014). Additionally, there are also signs of the effect of ageing in divided attention, which involves the ability to attend to two or more stimuli simultaneously, such as driving a car while having a conversation (Harada et al., 2013).

c) *Working memory* plays an important role in everyday life, as it stores information while it is manipulated (Baddeley, 1992). This is an essential process that enables people to be functional in all kind of environments. For instance, in a social context, this may involve listening to a conversation while at the same time remembering parts of the same conversation and interacting with others' responses. Similar processes take place in a work meeting or academic class. Elderly persons may experience difficulty in doing arithmetical operations such as calculating a tip on a bill, double-checking the cost of a dinner bill, or organizing a string of letters and numbers in sequential order (Harada et al., 2013; Salthouse, Mitchell, Skovronek, & Babcock, 1989). Interestingly, the age differences reported in measures of working memory may be caused by reduced processing speed (Salthouse, 1994). Following this line of reasoning, working memory is closely related to attention because it lasts for a few seconds and acts like a filter when storing information in long-term memory. Working memory is divided into two processes: attentional online maintenance which is associated with central executive agency, and the volitional manipulation of information which is attributed to the executive aspects of working memory that stimulate the activation of the DLPFC (Mesulam, 2000).

d) *Memory* decline associated with ageing may be related to decreased attention and slowed processing speed. Regardless of the reasons why memory is generally affected in the elderly, it is the most usual cognitive complaint in this population (Harada et al., 2013). Both semantic and episodic memory worsen with ageing (Reisberg, 2013). The former denotes general knowledge acquired across the lifespan, for example, knowing

how to ride a bike for or recalling the capital cities of different countries. The latter, which usually declines significantly in the oldest-old group, is memory associated with biographical events in time and place such as recalling the first day at school or reminiscing about one's wedding (Bigler, 2012; Harada et al., 2013; Salthouse et al., 1989). It is also important to note that the memorization process changes across the lifespan, as shown by an increasing difficulty with encoding new information into memory and then retrieving it (Delis, Kramer, Kaplan, & Ober, 2000; Economou, 2009; Haaland, Price, & Larue, 2003; Harada et al., 2013; Price, Said, & Haaland, 2004).

e) The *language* domain tends to be stable and does not deteriorate significantly in healthy older adults, although a decline in verbal fluency and naming objects has been observed after the age of 70 (Harada et al., 2013; Hayden & Welsh-Bohmer, 2011; Park & Reuter-Lorenz, 2009; Salthouse, 2009; Singh-Manoux et al., 2012; Zec, Markwell, Burkett, & Larsen, 2005).

f) *Visuospatial construction,* which denotes the ability to observe an object as a set of parts and being able to put these parts together in the original form (Mervis, Robinson, & Pani, 1999). This includes tasks such as assembling furniture, buttoning shirts, or drawing. Skills in this domain also deteriorate over the passage of time (Harada et al., 2013; Howieson, Holm, Kaye, Oken, & Howieson, 1993).

g) *Executive function* is a mental process that involves cognitive effort and includes achieving goals or completing tasks through planning, organizing, reasoning, problem solving, and self-monitoring (Harada et al., 2013). It has three core elements: inhibition

and interference control (behavioral, cognitive inhibition, and selective attention); working memory; and cognitive flexibility (mental set-shifting) (Diamond, 2013). Essentially, executive functions are for planning our behaviour, and are critically associated with activity of the frontal lobe, especially the prefrontal cortex. Except for the capacity to reason with familiar material, executive function is severely affected by ageing. When executive functions are impaired, there are difficulties in integrating new behaviors and predicting the consequences of our actions (Diamond, 2013; Harada et al., 2013; Oosterman et al., 2010; Wecker, Kramer, Hallam, & Delis, 2005).

2.3 Structural changes in the ageing brain

Harada et al. (2013) also describe how the cognitive changes associated with healthy ageing are related to structural and functional changes in the brain. One of the common factors for the elderly is neuronal loss, which contributes to a decrease in the volume of gray matter. However, what causes more functional damage to the brain is the reduction of the size and connections between neurons, arising from the fact that both the length of dendrites and the amount of neuritic spines decrease (Harada et al., 2013; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Terry & Katzman, 2001). This reduced synaptic speed and decline in the number of dendrites may translate into slower processing speed and increased reaction time, that ultimately affects the performance on ADL (Bee & Boyd, 2014). The loss of volume in gray matter is more noticeable in the prefrontal areas, followed by the temporal cortex where there is a

shrinkage of the hippocampus; these changes could explain why executive function is negatively affected, and memory complaints are usual in older adults, respectively (Harada et al., 2013).

Furthermore, brain imaging studies have shown volume reduction in white matter in the ageing brain (Harada et al., 2013). This could also lead to slow processing speed or decreased executive function, as white matter is responsible for protecting the axons which transmit signals, allowing the neurons to communicate (Filley, 2012). Different studies have found that the anterior white matter, corpus callosum, precentral gyrus, and gyrus rectus are the areas where the volume loss is more prominent (Harada et al., 2013; Meier-Ruge, Ulrich, Brühlmann, & Meier, 1992; O'Sullivan et al., 2001).

2.4 Model of cognitive change in ageing

Structural changes in the ageing brain lead to the promotion of new compensatory functional connections (Spreng & Turner.,2019; Park & Reuter-Lorenz., 2009; Reuter-Lorenz & Cappell, 2008) that subsequently produce a shift in the so-called architecture of the brain across the adult lifespan. As such, the elderly begin relying more on crystallized abilities rather than fluid intelligence (Spreng & Turner, 2019). As aforementioned in the previous section (2.2 Cognitive changes in the ageing brain), both components of cognition - fluid and crystallized intelligence - age differently. The former is characterized by a continuous decline with the passage of time in fluid abilities such as processing speed, working memory, and long-term memory, etc. The latter

accumulates more crystallized abilities across time which is referred to as world knowledge. This shift is defined as the semanticization of cognition in older adulthood (Spreng & Turner, 2019) and can be explained by the default-executive coupling hypothesis of aging (DECHA). The DECHA model dictates that reduced modulation of prefrontal brain activity in the event of increased demand for executive control occurs simultaneously with reduced suppression of the default network (Turner & Spreng, 2015).

It is known that age-related neurodegeneration is more exacerbated in the prefrontal cortex than any other brain area. The prefrontal cortex chairs high cognitive functions and volume loss of this region results in executive control deficits (Cabeza & Dennis, 2012; Salat, Kaye, & Janowsky, 2001). The default network system is highly activated during self-mental explorations including autobiographical memory retrieval, thinking about hypothetical social interactions, and envisioning the future. It is suggested that this brain function helps to prepare for upcoming self-relevant events. The default network has shown reduced activity when the brain is engaged in a particular task that requires paying attention, whereas activity of the medial temporal subsystem is maintained to provide information from prior experience (memories) and associations (Buckner, Andrews-Hanna, & Schacter, 2008). As such, the medial prefrontal subsystem enables the flexible use of this information during the elaboration of self-relevant mental simulations. The DECHA model also claims that:

> “As goal-directed cognition becomes less dependent on declining control resources and increasingly influenced by prior knowledge (i.e., the

> semanticization of cognition), the default network is engaged and becomes increasingly—and inflexibly—coupled with lateral prefrontal brain regions" (Spreng & Turner, 2019, p.525).

Although there is a gradual decline with respect to cognitive functioning and brain structure, all the characteristics summarized above are normal over the course of ageing. The most notorious mental health problem in late adulthood is the dementias (Bee & Boyd, 2014). However, it is important to clarify that this is a neurodegenerative disease and not an inevitable consequence of ageing; nor is there a cause and effect relationship between ageing and dementia.

2.5 Dementias

Older adults are more likely to develop dementia than younger people because physical health problems are more common in this stage of life. Some medical conditions, namely diabetes or hypertension, increase the risk of dementia (Livingston et al., 2017). Likewise, cognitive and physical deficits are more frequent after the age of 65; these can have a negative impact on physical fitness and social life, which subsequently could speed up the degenerative process of dementia (Livingston et al., 2017). According to the World Health Organization (WHO):

> "Dementia is a syndrome, usually of a chronic or progressive nature, in which there is deterioration in cognitive function (i.e. the ability to process thought)

> beyond what might be expected from normal ageing. It affects memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. The impairment in cognitive function is commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behavior, or motivation" (WHO, 2020) (Source: https://www.who.int/news-room/fact-sheets/detail/dementia).

Generally, dementia is diagnosed when the presence of acquired cognitive impairment has become severe enough to negatively affect autonomy in everyday activities (Hugo & Ganguli, 2014). However, this is actually a probable diagnosis of dementia since a reliable diagnosis can only be done postmortem (Leiros et al., 2018). Although each person suffers from dementia in a different way, the signs and symptoms can be classified in three stages (see Table 2.1).

Stage	Description	Symptoms
Early	Dementia can be unnoticed as the onset is gradual	Forgetfulness Losing track of the time Loss of orientation in familiar places
Middle	The signs and symptoms exacerbate. Dementia becomes more obvious and restricts functional independence	Forgetting recent events and people's names Loss of orientation at home Trouble communicating Repeated questioning Needing help with personal care
Late	The person with dementia progressively becomes dependent and inactive	Loss of temporal-spatial orientation Trouble recognizing relatives and friends Progressive assisted self-care Motor difficulties walking Changes in mood and behavior

Table 2.1. Stages and symptoms of dementia.
(Adapted from: https://www.who.int/news-room/fact-sheets/detail/dementia)

2.5.1 Types of Dementia

The etiopathology of dementia varies depending on the type. The most common forms of dementia are described as follows.

In Alzheimer's disease (AD), amyloid plaques and neurofibrillary tangles are abnormally deposited in the brain, and there is also a deficit of the neurotransmitter acetylcholine.

This seems to cause a loss of synapses and neurons (Dening & Sandilyan, 2015). The cognitive deterioration usually starts by affecting memory and executive function, with visuoconstructional/perceptual-motor functions, language, and social cognition declining progressively with the development of the disease (Dening & Sandilyan, 2015). AD has the highest prevalence of all dementias, with about 60% of cases in western countries being attributable to it (Rizzi, Rosset, & Roriz-Cruz, 2014).

Vascular dementia is linked to either a history of stroke or transient ischemic attack which subsequently leads to the death of brain cells (Hugo & Ganguli, 2014). Cognitive decline is influenced by the nature and location of the tissue insult; apart from memory and language, it mainly affects executive function and attention (Dening & Sandilyan, 2015). Vascular dementia has the second-highest incidence of dementia, accounting for about 20% of cases (Rizzi et al., 2014).

Fronto-temporal dementia presents with atrophy of the frontal and temporal lobes and accumulations of neuropathological proteins (Dening & Sandilyan, 2015). There are two clinical subtypes, depending on the brain area which is more damaged: the behavioral variant, which includes changes in personality and behavior such as loss of interest in personal matters or socially disinhibited behavior, and the language variants, which manifest with different types of aphasia (Dening & Sandilyan, 2015; Hugo & Ganguli, 2014).

Dementia with Lewy Bodies (DLB) and Parkinson's Disease share similar characteristics:

> “While both conditions are marked by alpha-synuclein misfolding and aggregation within the pathognomonic Lewy bodies, the main difference is that in Dementia with Lewy Bodies, cognitive impairment precedes the onset of parkinsonism, while in the latter, the cognitive impairment occurs in the context of established Parkinson’s disease” (Hugo & Ganguli, 2014, p.10).

The main clinical characteristics of DLB are loss of memory and spatial orientation and difficulties with alertness. Motor problems include trembling in limbs, recurrent falls, and shuffling in gait which also occur in Parkinson’s disease (Dening & Sandilyan, 2015; Hugo & Ganguli, 2014).

It may be the case that a person presents with more than one type of dementia. In these cases, the clinical characteristics of these dementias surface as a mix of symptoms and brain changes. The most common one is mixed Alzheimer’s and vascular dementia (Dening & Sandilyan, 2015; Hugo & Ganguli, 2014; Rizzi et al., 2014).

The foregoing has described the effect of ageing in the brain and presented an overview of dementias which are a common pathological issue in the brain for older adults. At one end of the spectrum, there are the normal cognitive changes that older adults experience which do not interfere with ADL. At the other end, there are the dementias, which involve severe cognitive deterioration and affect participation in all sorts of ADL. The manifestation of dementia is not subtle, and both sides of the spectrum are extremely far away from each other. This suggests multiple questions: How does the ageing brain move from one end of the spectrum to the other? Are there other

pathological conditions in between? Are these processes reversible? How long does it take to develop dementia? There is a term that can help us to answer these questions – MCI.

2.6 Mild Cognitive Impairment

MCI itself is a syndrome; it can be regarded as the landmark in the middle of the cognitive deterioration spectrum (Anderson, Murphy, & Troyer, 2012a; Petersen, 1995). There is a difference between normal ageing and MCI. In the latter, the cognitive deficits are serious enough to be detected by the individual experiencing them or their loved ones, but they are not severe enough to interfere with independent daily functioning although certain ADL may be performed in a less efficient manner (Albert et al., 2011; Langa & Levine, 2014). There is also a significant difference between MCI and a formal diagnosis of dementia. The latter describes a far more brutal cognitive decline to an extent that results in an enormous negative impact on functional independence (Albert et al., 2011).

2.6.1 Prevalence and prognosis of mild cognitive impairment

Epidemiological studies with large sample sizes have estimated a range of prevalence for MCI of 12-18% in adults aged 65 years and older (Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006; Ganguli et al., 2010; Manly et al., 2008; Mitchell & Shiri-Feshki, 2009; Petersen, 2016) and a rate of progression from an unimpaired

condition to MCI of approximately 5-6% per year in individuals aged over 70 (Manly et al., 2008). It has been suggested that the overall prevalence rate of MCI in Hong Kong is 8.5% for those aged 70 or above (Lam et al., 2008). These figures show that a minority of older adults have MCI and most of the elderly population are experiencing only subtle cognitive changes which would be expected at their age (Anderson et al., 2012a; Petersen et al., 1999). It is possible that there can be a progression from MCI to dementia; the likelihood that adults with MCI will convert to dementia is approximately 10-15% within the first year (Petersen et al., 1999), and 50% will develop dementia in the following five years (Anderson et al., 2012a). It is also estimated that 40–65% will eventually progress to AD at some stage (Petersen et al., 1999). However, it is important to clarify that having MCI is only a risk factor for having dementia in the future and does not make it a certainty. Individuals with MCI can also revert to normal cognition or maintain a stable condition (Anderson et al., 2012a; Anderson, Murphy, & Troyer, 2012b). As shown in Figure 2.1, MCI departs from normal ageing, and dementia departs from MCI. Normal ageing does not necessarily lead to MCI, and MCI does not necessarily lead to dementia, but dementia is preceded by MCI and normal ageing.

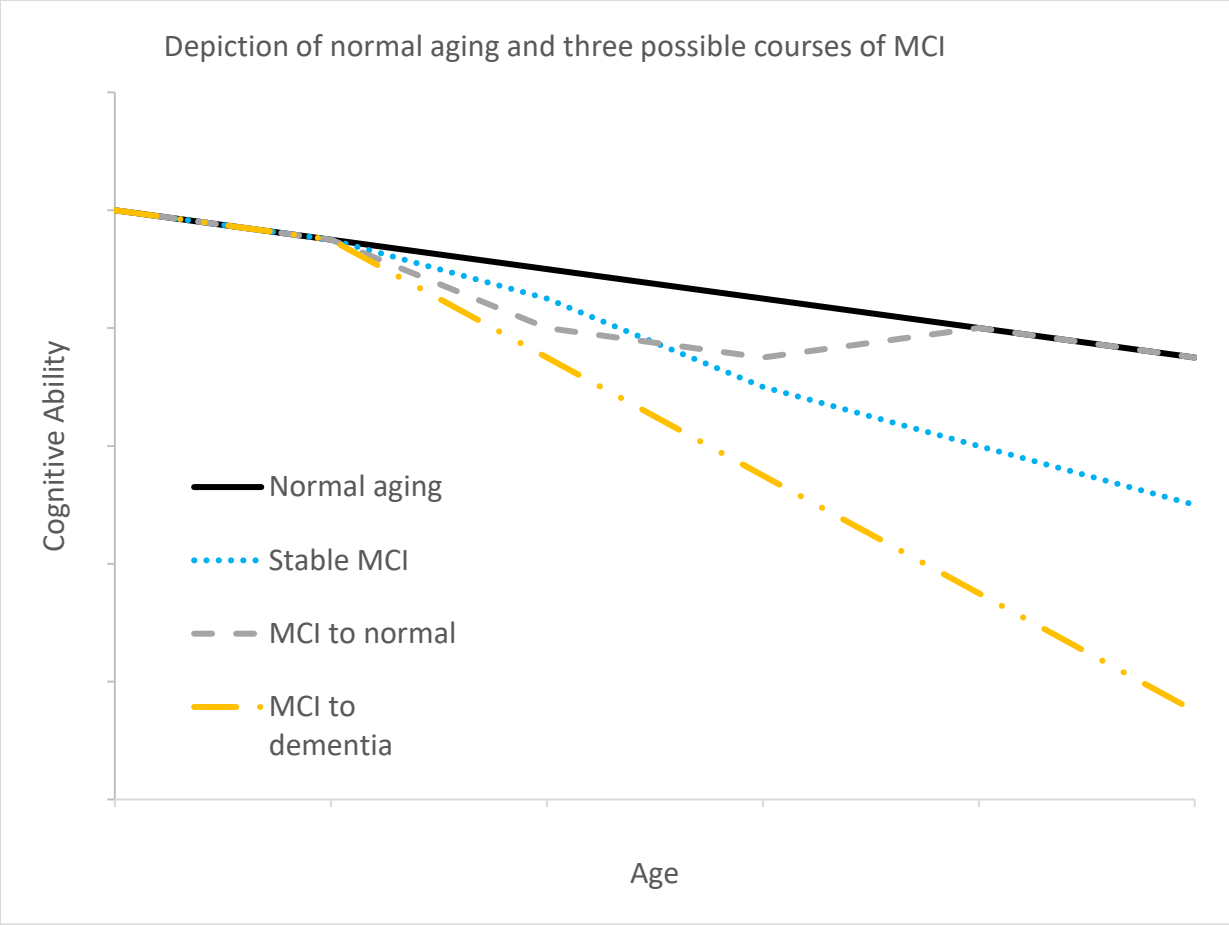
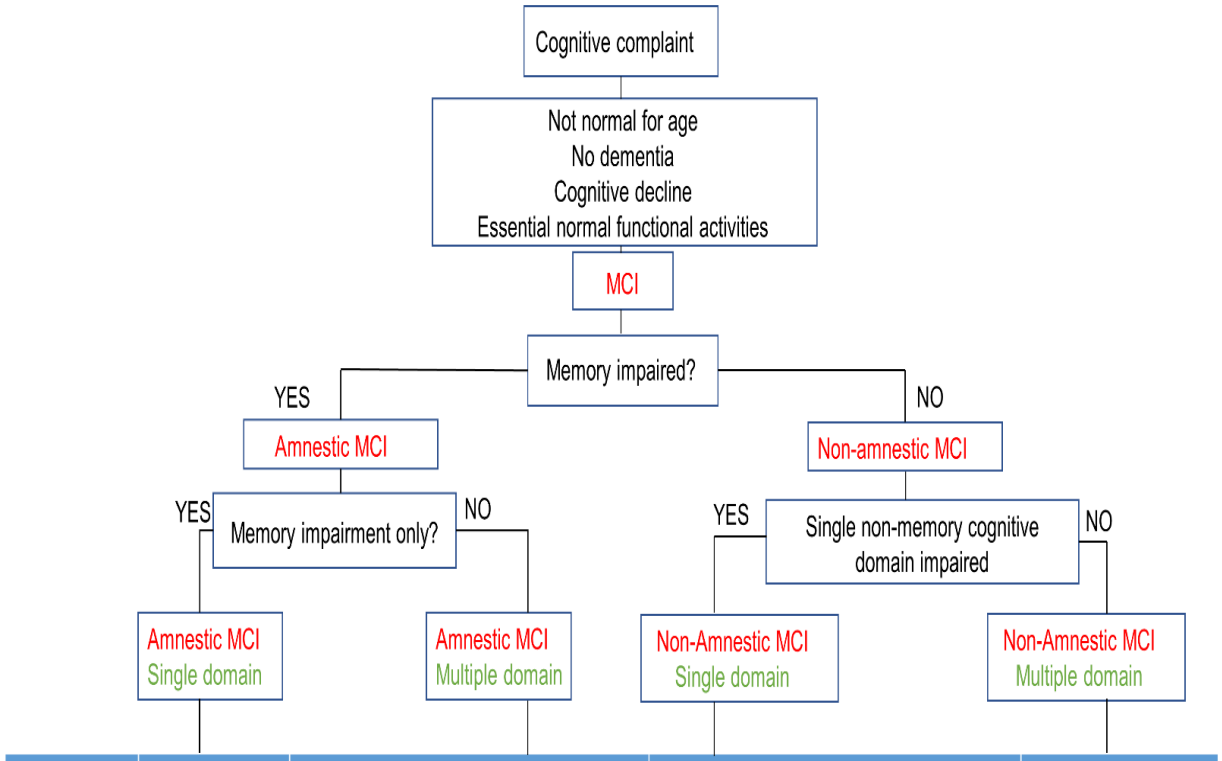


Figure 2.1. Depiction of normal ageing and three possible courses of MCI.
(Adapted from Anderson et al. (2012a, b))

2.6.2 Criteria for mild cognitive impairment

The model of cognitive impairment, no dementia encompasses all individuals falling in between healthy and demented states and includes cognitive impairment that may or may not evolve to dementia (Graham et al., 1997). The international symposium working group on MCI (2004) have proposed specific recommendations for the general criteria of MCI, including: (1) the individual is neither normal nor demented; (2) there is evidence of cognitive deterioration, shown either by objectively measured decline over

time or subjective report of decline by the individual or another informant accompanied by objective cognitive deficits; and (3) ADL are preserved and complex instrumental functions are either intact or minimally impaired (Winblad et al., 2004). During this symposium, the syndromic phenotypes of MCI were defined in two forms, the amnestic and non-amnestic types, as shown in Figure 2.2 (Petersen, 2016).



Etiology				
Degenerative	AD	AD	FTD AD	DLB AD
Vascular		VCI		VCI
Psychiatric	Depression	Depression		
Medical				

Figure 2.2. MCI criteria showing the syndromic phenotypes associated with potential etiologies. Abbreviatures: VCI = Vascular cognitive impairment.
(Adapted from Petersen (2016))

It is worth repeating that not all MCI corresponds to the early stages of dementia. To date, most of the characteristics identified in the key symposium criteria remain valid. Moreover, in 2011 the National Institute on Aging (NIA) and the Alzheimer's Association added more detailed specifications to the diagnosis of MCI due to AD, such as the use of biomarkers (Petersen, 2016).

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) (APA, 2013) was published in 2013 and incorporates a section entitled neurocognitive disorders. This new term replaces the category of delirium, dementia, and amnesiac and other cognitive disorders presented in the DSM-IV (APA, 2000). Neurocognitive disorders can be categorized as mild or major. Major neurocognitive disorder corresponds to the term dementia, whereas mild neurocognitive disorder is described as an evident decline in cognitive functioning that does not correspond with the usual cognitive changes in ageing and may or may not progress to dementia (Sachs-Ericsson & Blazer, 2015).

It can be seen that an extensive terminology and research foundation has been set out in the past two decades to identify cognitive impairment and characterize the clinical spectrum from healthy ageing to dementia. Taking into account all these sets of criteria, it is apparent that there is some overlap in definitions, etiology, and clinical features and so this framework could be considered as being in constant evolution.

Petersen (2016) sets out a comparison of the common criteria to characterize MCI that goes beyond the key symposium criteria (2004); see Figure 2.3. The biomarkers for

amyloid-β (Aβ) or tau could be derived from either fluorodeoxyglucose positron emission tomography (FDG-PET) or magnetic resonance (MRI) imaging or analysis of cerebrospinal fluid (CSF) to accompany the clinical syndromes described in the diagram.

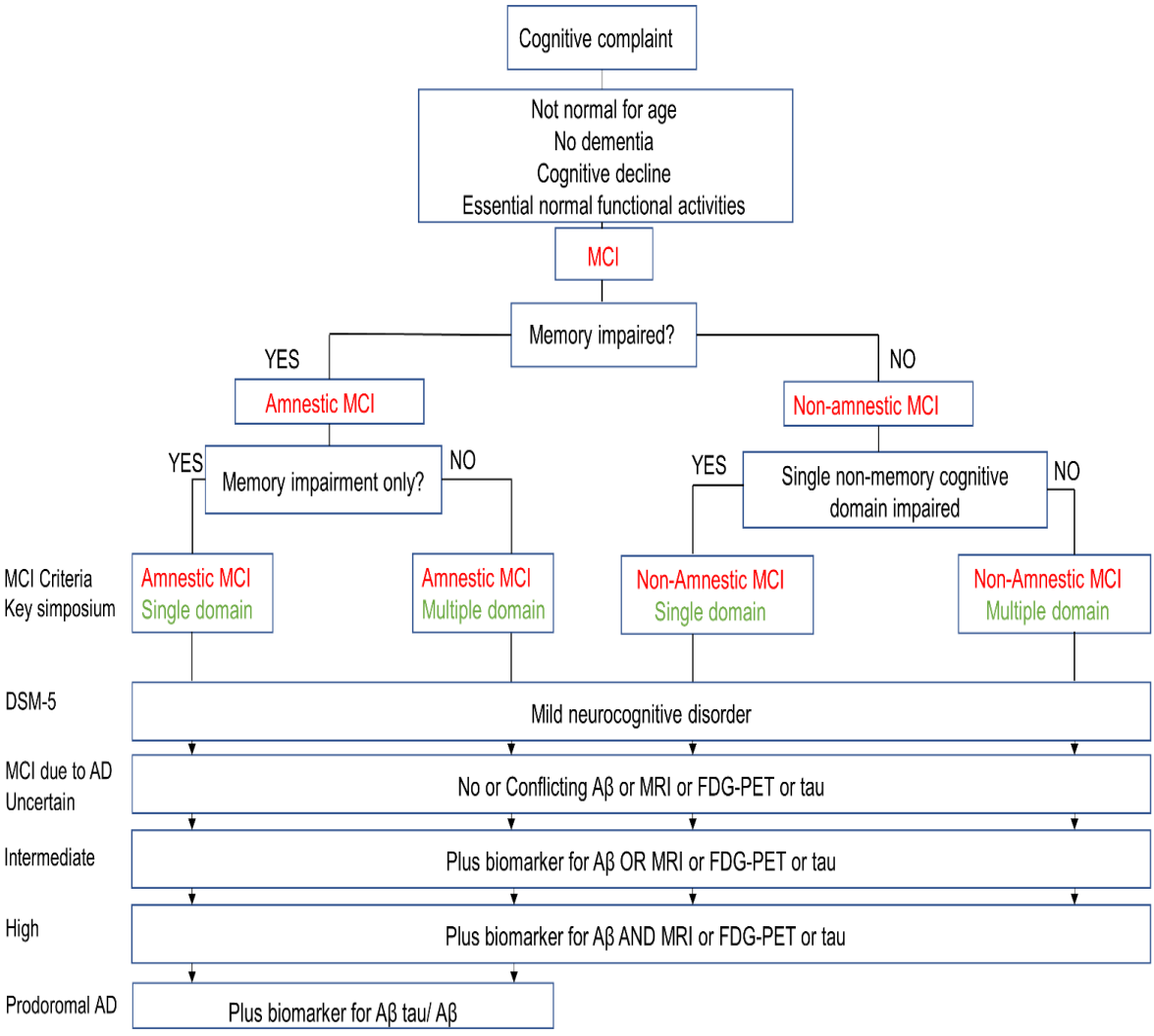


Figure 2.3. MCI criteria showing the syndromic phenotypes and various terms including biomarker testing. (Adapted from Petersen (2016))

Having explained the criteria and possible progressions for MCI, this chapter will now focus on describing the diagnostic process involving the person with MCI and his/her history and environment. Figures 2.2 and 2.3 will help the reader to follow the diagnostic sequence set out in the following sections.

2.6.3 Diagnostic process of mild cognitive impairment

The most important criterion for diagnosis of MCI is a memory complaint from the patient. The clinician can then rule out that the patient is not suffering from dementia at that stage and that the memory problem is not aged-related memory decline (Lam, Lui, Tam, & Chiu, 2005).

The patient with suspected MCI will report subjective cognitive complaints over time. Ideally, these will be verified by a knowledgeable informant. The clinician will then evaluate these cognitive changes by elaborating a clinical history so as to explore the onset, time course, and nature of the cognitive symptoms (Langa & Levine, 2014; Petersen, 2016).

If the main complaint is related to the memory domain, the evaluation should focus on recent episodes (over the last year) of forgetfulness, such as appointments, events, or conversations. The patient may repeat answers or give explanations that suggest the existence of memory deficits. If so, the question that needs to be addressed is whether there are other cognitive domains are affected or the changes are memory specific (Petersen, 2016). Patients and informants have a tendency to express cognitive changes in relation to memory, but they may in fact be attention- or language-oriented

impairments (Petersen, 2016). The physician will then conduct a mental status assessment using tests such as the Montreal Cognitive Assessment (MoCA) which is a 30-item test covering several cognitive domains (visuospatial/executive, naming, memory, attention, language, abstraction, delayed recall, and orientation) used as a screening tool for MCI and dementia. In a validation study of the Mini Mental State Examination (MMSE) and MoCA where a cutoff score 26 was used (lower scores mean worse cognitive function) the MMSE had a sensitivity of 18% in detecting MCI, whereas the MoCA detected 90% of MCI subjects with a specificity of 87% (Nasreddine et al., 2005). MoCA is therefore a more reliable option than MMSE when differentiating PwMCI from healthy individuals (Roalf et al., 2013). Clinicians may consider other options, for instance, the Mini-Cog test that uses the Clock Drawing Test with a three-word recall test (Langa & Levine, 2014; Lin et al., 2013) or the Short Test of Mental Status (Kökmen, Smith, Peterson, Tongolas, & Đvnik, 1991). All these screening tests can yield valuable information about specific cognitive domains but they are not sufficient to diagnose MCI (Petersen, 2016).

Clinicians can also gather more information by administering the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm, 1994). At the same time, assessments to confirm that the patients do not meet the criteria for dementia should also be considered, such as the administration of the Clinical Dementia Rating (CDR) (Morris, 1993), and a subjective evaluation of functional performance of ADL such as paying bills, doing grocery shopping, cooking, or driving that could be compromised by dementia. The Functional Activities Questionnaires would be a good

candidate for assessing the level of independence in daily tasks (Pfeffer, Kurosaki, Harrah Jr, Chance, & Filos, 1982). Although preservation of functional activities is normal in MCI, they may be performed more slowly and less efficiently (Langa & Levine, 2014; Pfeffer et al., 1982).

The evaluation of the patient will be complemented by reviewing his/her medication history, since drugs like benzodiazepines and antihistamines can suppress brain activity, diminishing cognitive capacity, and intensive treatments for diabetes or high blood pressure have also been shown to have a negative impact on cognitive functioning (Langa & Levine, 2014). The clinician will continue the examination by performing an extensive assessment of the neurological condition of the patient (see Figure 2.4). Changes in behavior and personality may suggest depression or fronto-temporal dementia, respectively. Symptoms such as visual hallucinations could be indicative of DLB and alterations in speech could suggest stroke (Langa & Levine, 2014; McCarten, 2013).

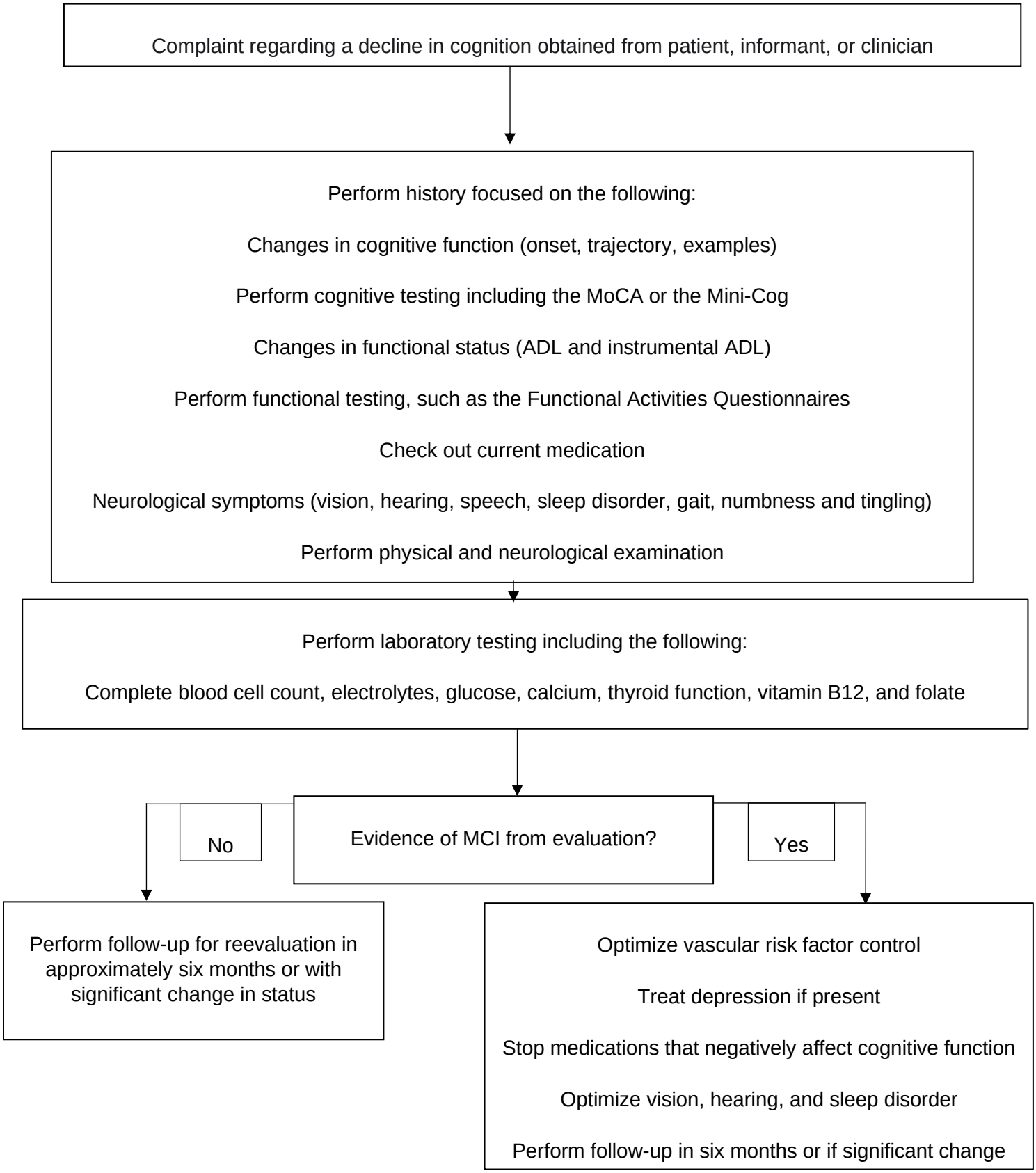


Figure 2.4. Modified approach to diagnosing and managing MCI.
(Adapted from Langa & Levine (2014))

Cognitive impairment can arise in depression, so it is also important to continue the evaluation with a psychiatric examination using assessment tools such as the Geriatric Depression Scale (GDS) that helps to identify depressive symptoms and depression in older adults (Yesavage, 1988).

Neuroimaging can also provide useful information to determine the etiology and type of MCI. For instance, measuring excessive volume loss of brain regions such as the hippocampus using structural MRI could be an indicator of MCI progressing to dementia. The presence of amyloid plaques and deposits of other neurodegenerative proteins such as tau can be detected by PET which can be suggestive of suspected MCI or AD (Langa & Levine, 2014 Petersen, 2016). Laboratory testing can pinpoint reversible forms of MCI such as infection (Langa & Levine, 2014).

After such an extensive evaluation, the physician must conclude whether there is a clinical syndrome, starting with the confirmation of an objective change in cognitive functioning (determined by scores in specific cognitive tests which are 1.5 standard deviations away from the population mean); whether this change impacts the patient's performance in ADL, reducing somewhat the level of independence; and whether or not the patient meets the criteria for dementia (Langa & Levine, 2014; Petersen, 2016).

The physician will also establish the etiology by examining the onset of the disorder. This is a critical phase of the diagnosis of MCI since an abrupt cognitive decline may indicate the presence of an underlying nondegenerative disorder. However, if the course has been slow and only slightly progressive, a degenerative disorder would be

the most likely explanation. If the patient has suffered any vascular pathology, such as stroke, or presents with a psychiatric disorder such as depression, the chances are that the etiology of the cognitive impairment could be due to an underlying vascular dementia or one of the symptoms associated with depression, respectively (Langa & Levine, 2014; Petersen, 2016).

The cause of the syndrome is an essential component of the diagnosis that allows the clinician to characterize the cognitive impairment by defining its phenotype and outlining the prognosis and intervention. The etiology of the syndrome and the phenotype have a bidirectional relationship when it comes to diagnosis of MCI; in other words, both elements must be determined, but not in any specific order (Anderson et al., 2012a; Petersen, 2016).

2.6.4 Types of mild cognitive impairment

The most common form of MCI is the amnestic type (single domain) which is characterized by subjective memory complaint and objective memory loss. Nonmemory cognitive abilities and functional activities are relatively intact, and the diagnosis of dementia is not justified. If functional activities are not preserved, or in other words the patient is not functionally independent in performing activities such as paying bills, using public transportation, cooking, taking medication, and keeping appointments, it is likely the patient presents as MCI amnestic type due to underlying AD, also acknowledged as prodromal AD (Anderson et al., 2012a; Petersen, 2016).

There are also other clinical presentations of MCI amnestic type in which PwMCI present with slight memory impairment in conjunction with other mild impairments such as language, visuospatial skills or executive function problems. This is known as amnestic type, multiple domain. This type of MCI could be caused by depression, history of cerebrovascular accident, or AD (Anderson et al., 2012a; Petersen, 2016).

A third clinical variety of MCI is referred to as the non-amnestic type and is characterized by relatively isolated impairments in a single, nonmemory-related domain. Persons with non-amnestic MCI may be at increased risk for other dementias apart from AD, such as fronto-temporal dementia (Petersen, 2003). Non-amnestic MCI may present in conjunction with other mild nonmemory impairments such as language, visuospatial skills, or executive function problems. This may indicate the development of DLB or AD, although it may also be due to cerebrovascular disorder (Anderson et al., 2012a; Petersen, 2003, 2016).

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CHAPTER 3: CONTEXTUAL AND CONCEPTUAL FRAMEWORK FOR COGNITIVE REHABILITATION INTERVENTIONS

This chapter sets out background knowledge about NPT and CR as a basis for the research reported in this thesis. Some of the information in this chapter was included in the submission for confirmation of registration as a full-time PhD candidate in the Department of Rehabilitation Sciences entitled “The Effects of Transcranial Direct Current Stimulation on Attention in Clients with Mild Dementia and its Impact on Activities of Daily Living and Quality of Life” in February 2017.

An exhaustive review of CR will be presented. Aspects of CT, such as mechanism, theories, means of delivery and potential therapeutic benefits in terms of cognitive functioning will be presented in detail. Similarly, this chapter provides an extensive description of the NIBS technique tDCS, including but not limited to the fundamentals, mechanism, operation, and protocols. Finally, the concept of “adjunct” therapies will be set out, in which both CR and tDCS are given at the same time with the purpose of creating synergistic effects.

In summary, this chapter intends to provide the reader with information about the interventions used in the experimental study.

3.1 Introduction

Nowadays, the pace of population ageing around the world is increasing dramatically, as people in every corner of the word are living longer (WHO, 2018). Most people can now expect to live beyond their sixties. As mentioned in the previous chapter, the range of prevalence for MCI is 12-18% in adults aged 65 and older (Busse, Hensel, Gühne, Angermeyer, & Riedel-Heller, 2006; Ganguli et al., 2010; Manly et al., 2008; Mitchell & Shiri-Feshki, 2009; Petersen, 2016). The prevalence of dementia increases exponentially with age, doubling every five years after the age of 65 (Hugo & Ganguli, 2014). Taking all these figures into account, and considering the increase in life expectancy across the globe, every industrialized country is predicted to face a demographic crisis in the near future (Bee & Boyd, 2014). For this reason, it is essential to find treatments that can prevent the development of dementia or slow down cognitive deterioration, thus reducing the burden of healthcare costs and minimizing the financial and other impact on families whose relatives are suffering from MCI or dementia.

3.2 Pharmacological therapies

What can be done to tackle MCI? To date, there are no approved pharmacological treatments. Moreover, drug trials are mainly targeted at persons with AD or other dementias rather than those with MCI. Such trials are focused on alleviating symptoms. Drugs in use include cholinesterase inhibitors (such as donepezil, galantamine, or rivastigmine) that help prevent the breakdown of acetylcholine, a neurotransmitter

associated with attention and memory processes. Another class of medications used are the glutamate inhibitors (such as memantine) which are administered to avoid an excessive concentration of this neurotransmitter, which arises when neurons die and become toxic. However, there is no evidence any of these drugs stop the progression from MCI to dementia, and some may also produce adverse effects. For these reasons, these pharmacological therapies are not currently approved by entities such as the US Food and Drug Administration (FDA) for use with PwMCI (Anderson, Murphy, & Troyer, 2012; Langa & Levine, 2014; Lin et al., 2013; Russ & Morling, 2012).

3.3 Non-pharmacological therapies

Although some intervention studies tend to be more focused on the use of medication, NPT have been increasingly studied in recent years. NPT include psychological, psychosocial, interpersonal, behavioral, emotional, exercise-oriented, and environmental approaches (Livingston et al., 2014). According to the International Non-pharmacological Therapies Project (2013):

> "NPT should target at particular goals or outcomes and enable effective care practices that build on and add to the effects of good quality day-to-day care" (Woods, 2013, p.1) (Source: http://www.nptherapies.org/pdf/NPT%20Fact%20Sheet.pdf).

The goals of NPT are to improve the person's cognition, improve ability to function in everyday situations, reduce distress and mood disturbances, and to enhance quality of life (Olazarán et al., 2010).

3.3.1 Cognitive rehabilitation

CR falls under the umbrella of NPT and is defined:

> "As a process whereby people disabled by injury or disease work together with health service professionals to remediate or alleviate cognitive deficits arising from a neurological insult" (Wilson, Evans, & Keohane, 2002, p. 542).

Sohlberg and Mateer (1989) add an important element to this definition, namely that CR aims to increase functioning in everyday life by the amelioration of cognitive function (Sohlberg & Mateer, 1989). There are three approaches to be taken in administering CR with patients (Anderson, Winocur, & Palmer, 2010).

First, the restorative approach (cognitive retraining), which is based on the premise that repeated practice of a task-specific domain will lead to improvements of task-specific procedures (near transfer effects) and in the corresponding cognitive domain (intermediate transfer effects) by producing changes in the underlying neural processes (Glisky & Glisky, 2002). These benefits may also be generalized beyond the targeted cognitive domain (far transfer effects). For example, a memory training intervention designed to improve different aspects of memory could also achieve benefits in the attention domain (far transfer) or even in everyday functioning (very far transfer effect)

(Peters & Winocur, 2020). However, this is still a challenging enterprise since retraining has been shown to mainly affect the targeted cognitive abilities (Anderson et al., 2010; Ball et al., 2002; Peters & Winocur, 2020). Metacognition is defined as:

> "The knowledge about knowledge: the knowing how we think and the awareness of our limitations" (Birnboim, 1995, p. 61)

Metacognitive training encompasses three variables: personal variables related to oneself, cognitive abilities and limitations and task variables which imply the features and nature of the task and strategy variables.

Metacognitive training incorporates these variables along with three components: acquisition of new information, application of knowledge, and transfer abilities (Birnboim, 1995). Another approach that deserves attention, given its importance in the occupational therapy literature and in severe traumatic brain injury, is the neurofunctional approach. The neurofunctional approach is occupation oriented, based on learning by doing, and takes place in the patient's natural environment. This approach is grounded in the following 8 principles: client-centered, current functioning in the natural environment, observation of performance in everyday situations, formulation of the patient's goals, retraining programmes, generalization and maintenance of skills in everyday life, and the provision of feedback (Clark-Wilson, Giles, & Baxter, 2014).

The second type of CR, compensatory approaches, involves the use of preserved abilities that are normally employed for other purposes (Glisky & Glisky, 2002; Peters & Winocur, 2020). For instance, this may involve the use of compensatory techniques or

behavioral modifications, such as associating words with images to improve recall (Kurtz, 2011) or changes to the environment such as the use of signage in the home for someone with memory or orientation deficits (Peters & Winocur, 2020).

Thirdly, holistic approaches involve participants with brain injury taking part in a variety of activities including retraining tasks, learning compensatory techniques, and simple drills. Holistic approaches are multidisciplinary and focus on the cognitive, emotional, and motivational dimensions in an integrated manner. Their main characteristic is that they aim to enable patients to be aware of their strengths and weaknesses so that they can form a more objective understanding about the potential improvement for restructuring their lives (Peters & Winocur, 2020). Based on the patient's impairment and needs, the clinician will set the goals of the treatment following a patient-centered practice. On this basis, he or she will be responsible for choosing one of the aforementioned approaches to carry out the CR program (Anderson et al., 2010). One of the interventions in this category, implemented in this research, is CT.

3.4 Cognitive training

CT consists of the repeated guided practice of a task associated with specific cognitive domains. It is normally performed without giving the patient instructions about strategies to complete the task (such as mnemonics) (Kurz, 2019). CT can be delivered to groups or to individuals. It can be administered by a therapist in a conventional way using pencil and paper or through oral instruction and practice. Alternatively, it can make use

of technology, an approach which appears to be more appealing and engaging due to the flexibility and feedback it offers for both therapists and patients (Peretz et al., 2011). In addition, CT can be adaptive, with the difficulty of the tasks adjusted for each individual based on his or her cognitive deficits, or nonadaptive in which the same task level is always maintained (Brehmer, Westerberg, & Bäckman, 2012). Another modality is tailored CT, which is individualized and customized to the needs of the patient. In contrast, standard CT is not individualized (Lawrence, Gasson, Bucks, Troeung, & Loftus, 2017). The duration and frequency of any CT program varies among patients and depends on their goals and rate of progress, among other factors (Peretz et al., 2011). CT is different from cognitive stimulation (CS) in that the former is structured and planned according to the patients' problems, while the latter purely provides environmental stimulation to patients, although both techniques have been shown useful for improving cognitive performance (Tsantali, Economidis, & Rigopoulou, 2017).

3.4.1 Mechanism of cognitive training

The justification for using CT is that repeated exercise will enhance the targeted cognitive domain which is being trained, and this improvement may generalize to other, nontrained cognitive domains as well (Kurz, 2019). There is very little theory covering the mechanism of CT in relation to global cognition. The following paragraphs discuss the three dominant principles.

The first theory is based on the idea that CT resembles physical training, such as weight training or jogging. A person who runs frequently can improve their cardiovascular

system and develop stronger leg muscles. This improvement will potentially translate to better performance in other physical activities that involve cardiovascular effort, such as biking or swimming. In the same way, someone who regularly performs leg strength training will grow certain specific muscles (calves, hamstrings, and quadriceps) and consequently will be able to run faster or jump further, as well as performing better (as a result of being faster and more powerful) in sports that involve the constant use of the legs such as football or rugby. Therefore, according to this theory, it is not necessary to practice a variety of physical activities to improve general fitness due to the transfer benefits from the trained activity to the untrained (Jaeggi, Buschkuehl, Jonides, & Shah, 2011). This analogy with physical training explains how CT works and it indicates that a physiological system needs to improve (that is, to become better and stronger, or at least less weak). If, for instance, attention is regarded as a cognitive system with a certain capacity, this capacity could be expanded by performing attention-oriented activities. The same would be applicable to other cognitive systems that can be seen as making up the muscles of the mind (Taatgen, 2016).

In contrast, the second proposal suggests that what is learned in CT is highly specific and cannot produce a transfer effect. This is called the production rule (Singley & Anderson, 1989; Taatgen, 2016). To illustrate this theory, one can think about the process of completing a multicolumn addition. Production rules suggest that individuals will take different steps to perform this task, starting from directing the attention into a specific column, retrieving arithmetic operations from memory, writing down the solution under the column, and remembering the carry-over number for the next column. All

these sequential processes are broken down into small steps that need to be carried out one by one to complete the whole task. This theory suggests that the production rules for multicolumn addition are different for those for multicolumn subtraction, and this is why the transfer effect is restricted (Singley & Anderson, 1989; Taatgen, 2016).

Both theories are somewhat vague and not yet completely developed due to the inconsistent findings of empirical research on CT (Taatgen, 2016). For this reason, a new theory has emerged in recent years; the primitive information processing element principle, known as PRIMs theory. This attempts to find some common ground between the muscle analogy and production rule approach (Taatgen, 2013). The PRIMs theory is based on the idea that:

> "When people learn specific cognitive skills, the by-product of the learning process consist of general cognitive skills. The general skills can be reused for different tasks without the need of explicit transfer between tasks. Moreover, the two tasks that share general skills can be quite different: they just share the same patterns of routing information through the cognitive system" (Taatgen, 2016, p. 21).

For instance, when comparing multicolumn addition to multicolumn multiplication, PRIMs theory makes the assumption that part of the exchange of information is identical, in that information from the visual system has to be conveyed to the memory retrieval system along with the information that is necessary to retrieve the sum or multiplicand, even though the goal and the arithmetical process are different. This

principle could explain the effects of CT and classical transfer effects (Taatgen, 2016). The majority of previous research concerns the use of CT in relation to specific domains such as working memory in which the theoretical foundation seems to be better understood. For instance, it has been shown that working memory training induces positive gains in the performance of non-trained tasks that rely on working memory and control of attention components. Furthermore, the effect of this transfer of skills may be caused by training induced plasticity in a parietal-prefrontal neuronal pathway that is associated with working memory and control of attention (Klingberg, 2010; Spencer-Smith & Klingberg, 2015).

3.4.2 Neuroplasticity and cognitive training

Despite the difficulty of rationalizing the mechanisms underpinning CT theories, the factor that governs all theories and processes is neuroplasticity; how the brain changes in response to experience or environmental stimulation (Rosario Rueda, Combita, & Pozuelos, 2016). The brain learns by taking advantage of new experiences, a process that can occur at any time in the lifespan. The brain is able to form new neural circuits even when mental health is compromised (Berlucchi, 2011; Fernández-Ballesteros, Zamarrón, Tárraga, Moya, & Iñiguez, 2003):

> "Neural reorganization takes place where undamaged axons can sprout out nerve endings and connect with other undamaged neurons to form new neural pathway and network" (Lee, 2013, p. 46-47).

Neuroplasticity is evidenced when there are changes in the brain, such as the growth of the neural regions associated with navigation and memory shown by taxi drivers, whose hippocampal region was shown to be larger than control subjects in one study (Maguire et al., 2000; Park & Bischof, 2013). Neuroplasticity can also be manifested through the activation of new circuits and decreases or increases in neural activity in brain areas associated with the cognitive task activated before the training. However, these functional changes are also poorly understood, since one plausible explanation is that CT improves cognitive functioning and by repetition it will consequently increase neural efficiency, leading to the expectation of decreased neural activity due to decreasing demand in terms of cognitive effort (Brehmer et al., 2011; Park & Bischof, 2013). On the contrary, several studies have reported an increase in activation in specific brain regions in older adults who demonstrated behavioral gains after receiving CT (Carlson et al., 2009; Nyberg et al., 2003; Park & Bischof, 2013).

3.4.3 Effectiveness of cognitive training

A systematic review and meta-analysis of the impact of CT on cognitive functioning across 31 RCTs involving healthy older adults concluded that CT significantly improved measures of executive function such as working memory or processing speed, memory domains, and measures of cognitive function. This study also evaluated the effect these interventions had on everyday functioning. Unfortunately, only a couple of the studies had included objective measures to determine this relationship. This is an area that requires more research in the future. If it is shown that the way to produce benefits in everyday functioning depends critically on executive function, a solution would be to

tailor cognitive interventions that target the latter (Kelly et al., 2014). One specific study, which deserves special mention because of the huge sample size (n = 2832), encouraged the use of CT as an effective therapy to improve the cognitive domains targeted in the training for healthy older adults. However, these gains do not seem to have generalized to other, nontrained domains (Ball et al., 2002).

Evidence for the use of CT as a potential treatment for PwMCI is mixed, largely as a result of the heterogeneity of the studies in terms of the content of the intervention, number of sessions, frequency, dose, outcome measures employed, FU evaluations, and criteria for including participants. One systematic review and meta-analysis examining the effects of computerized CT determined that it is a valid intervention for improving general cognitive functioning as measured by the MMSE and the AD Assessment Scale, cognitive subscale, based on the results of 17 RCTs with a moderate effect size (g = 0.35) (Hill et al., 2017). However, 14 of those studies had a high risk of bias. For this reason, another systematic review was carried out around the same time, including only RCTs with low or medium risk of bias. Five trials were eligible and the results were less encouraging (Butler et al., 2018). What seems to be clear from these studies with MCI populations is that the effect of CT interventions in everyday activities has not been sufficiently investigated and this needs to be addressed in future trials (Chandler, Parks, Marsiske, Rotblatt, & Smith, 2016; Ge, Zhu, Wu, & McConnell, 2018; Reijnders, van Heugten, & van Boxtel, 2013).

The effectiveness and impact of CT for persons with AD and vascular dementia has been evaluated in a Cochrane review (Bahar-Fuchs, Clare, & Woods, 2013). The main

finding was that there was no benefit obtained from CT and the quality of evidence of the RCTs also needed to improve. For instance, the trials reported gains as consequence of the use of CT but these may not have be adequately evaluated using standardized outcome measures, although these findings are consistent with meta-analyses reported by another research group (Hill et al., 2017).

Based on this evidence, it appears that CT has the potential to induce gains in cognitive functioning; however, the “how,” or the method to optimize it, is not yet well established and neither is the population that can benefit from this treatment. Therefore, it would be reasonable to consider boosting the potential effect of CT by introducing a supplementary intervention. The following section describes NIBS techniques that may have the potential to enhance the effects of CT.

3.5 Transcranial direct current stimulation

NIBS, compared with invasive procedures, have the advantage of placing the stimulation devices or their extensions externally without breaking the skin or entering the body cavity, so no surgery is required (Dmochowski, Datta, Bikson, Su, & Parra, 2011; Gebodh et al., 2019). tDCS is a NIBS technique that employs sustained direct current that targets brain regions and subsequently modulates neural activity (Nitsche et al., 2008; Priori, Hallett, & Rothwell, 2009). The conventional administration of tDCS requires a battery-powered device that passes a constant current using damp sponges in NaCL solution as the electrodes. These can be placed anywhere on the scalp or on

any other part of the body (extracephalic) using elastic bands to attach them (Higgins & George, 2019). An example of a tDCS device is illustrated in Figure 3.1.

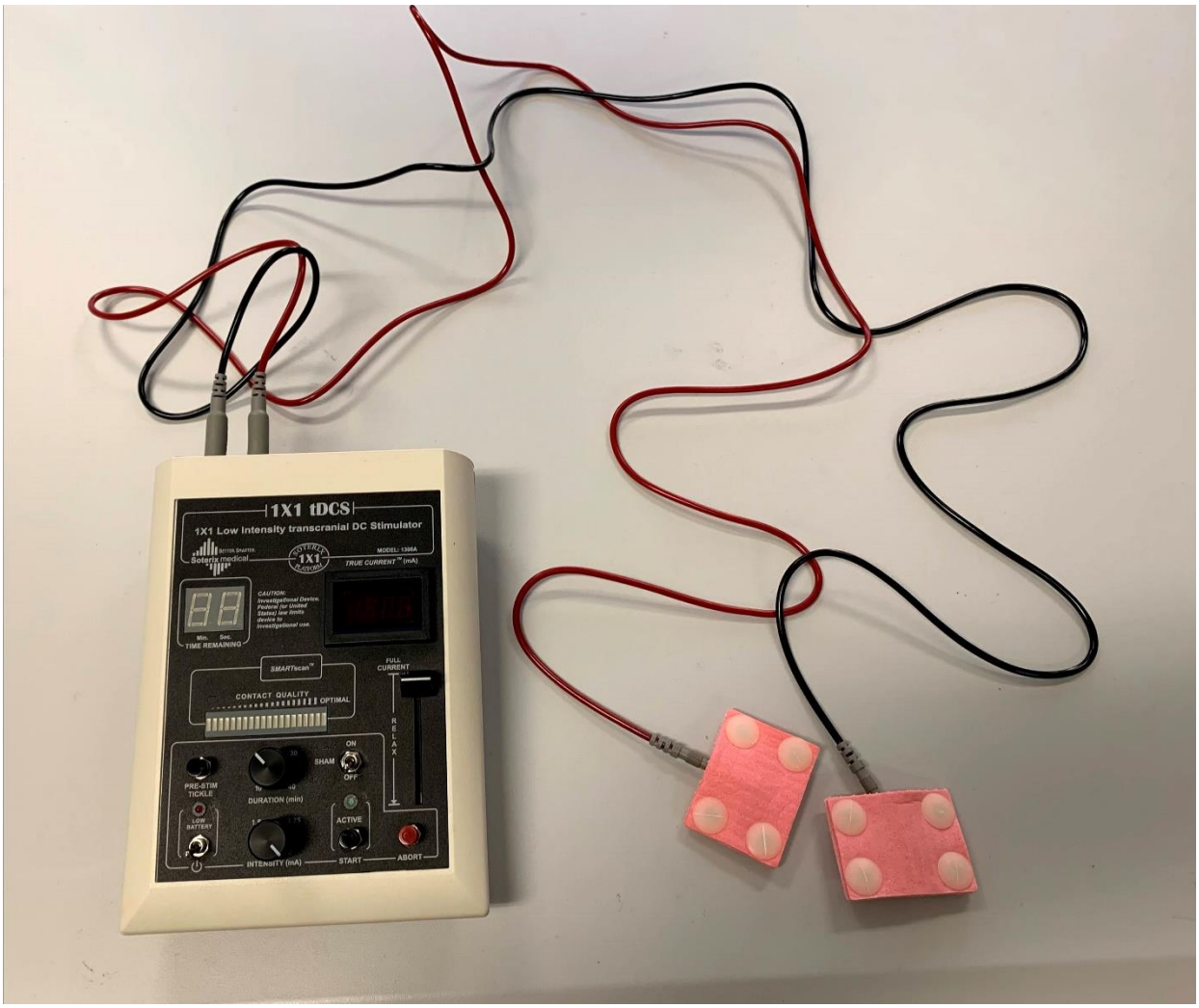

Figure 3.1. Illustration of a typical tDCS device.

tDCS is categorized as a non-invasive procedure as the electrodes are placed on areas like the scalp or forehead. Several forms of transcranial electrical current stimulation apply similar principles to that of tDCS, whereby electrical current delivered to the scalp via electrodes modulates underlying brain activity. Such techniques include high

definition-tDCS (HD-tDCS), transcranial alternating current stimulation (tACS), transcranial random noise stimulation (tRNS), transcranial pulsed current stimulation (tPCS), oscillating tDCS (o-tDCS), and sinusoidal oscillating tDCS (so-tDCS). The main difference between tDCS and other types of transcranial electrical stimulation is that tDCS is the only neuromodulation technique that uses sustained direct current (Gebodh et al., 2019).

Over the past two decades, tDCS and transcranial magnetic stimulation (TMS) have dominated clinical research in comparison to other NIBS techniques. The main distinction between the two techniques is that TMS, via alternating focal magnetic fields, causes neurons to depolarize. On the other hand, tDCS alters the depolarization threshold of neurons via direct electric current passed through the brain (Gebodh et al., 2019; George & Aston-Jones, 2010).

A turning point in the history of tDCS was the revelation that TMS evoked responses could be modulated by the prior application of tDCS (1 mA, 10 min). This event set the foundations of the neurophysiological potential of tDCS administration. Over the next twenty years, hundreds of studies involving tDCS have shown its effects in physiology and behavior (Gebodh et al., 2019). Regarding the mechanism of tDCS, it is a concept that keeps expanding as new research studies emerge. In the following sections, we will explain in detail its operation, administration, mechanism and conduction and how it relates to neuroplasticity.

3.5.1 Administration and fundamentals of transcranial direct current stimulation

When administering tDCS, it is important to follow a rigorous protocol governing the session, the montage selection, the dose (current intensity and stimulation duration), and the electrode assembly. All these parameters will induce changes in the membrane polarity of neurons accordingly. For example, the positioning of the electrodes on the scalp can result in significant differences in the amount of current sent to specific parts of the brain (Woods et al., 2016). Duration of stimulation is a relevant issue in research, since the duration of tDCS after-effects is affected by maintaining a constant current density and increasing the duration of the stimulation (Nitsche & Paulus, 2000).

tDCS programs can be administered in the form of a single session or multiple sessions. Single tDCS sessions are defined as the time from commencement of current flow (start of ramp-up) to the end of current flow, although the core of the session refers to the time during which tDCS is sustained at the target current. Multisession tDCS refers to the frequency with which it is delivered for a period of time in an intervention (Gebodh et al., 2019).

Montage, in NIBS techniques, refers to the pictorial representation of where the electrodes are placed. Normally, one or more surface positive (anode) and negative (cathode) electrodes are attached. One is placed over the target area and the other is positioned over another part of the head (intracephalic) or elsewhere on the body (extracephalic). These electrodes are labeled as active and reference respectively, but

that does not mean that the reference electrode is physiologically inert, since the positioning of it does have a critical impact on the orientation of the electrical field.

For this reason, this reference electrode is better labeled as the return electrode and the active one as the target electrode (Nasseri, Nitsche, & Ekhtiari, 2015). The anode electrode, which has depolarizing properties, acts to excite neural activity, whereas the cathode electrode has hyperpolarizing effects and inhibits it (Nasseri et al., 2015; Nitsche et al., 2008). The current starts travelling through the brain from the area underneath the anode electrode and exits through the cathode electrode. When the current is administered, it follows the anode-cathode circuit, which is likely to cause neurons to fire in the stimulating and neighboring areas as well (Nitsche et al., 2008):

> "As tDCS dose is defined as the waveform of a sustained direct current, only the intensity (in milliamps [mA]), duration (in seconds or minutes), and ramp up/down details, are needed to specify the waveform to each electrode" (Gebodh et al., 2019, p. 15).

The electrode assembly encompasses all the elements that conduct current between the device lead wire and the scalp, such as the electrode which is made of conductive materials (metal or rubber), the electrolyte (normally saline solution, which is in contact with the electrodes and the scalp), the electrode size, and the type and shape of sponges.

tDCS has been an emerging research field since the turn of the century. However, 20 years later, the same dose paradigms are common practice in research. These

parameters involve the use of a 1-2 mA current for 10-30 minutes to increase or decrease function based on the selected montage, with a relatively large sponge electrode positioned on the scalp over the target area associated with a specific functional role and the other electrode placed on another region assumed to be functionally irrelevant (Gebodh et al., 2019).

Given such an explanation of how tDCS is administered and its components, parameters, and operation, the question which comes to mind is what is going on in the brain during the delivery of weak direct currents.

3.5.2 Mechanism and effects of transcranial direct current stimulation

When there is a current flowing across the brain from the anode to the cathode electrode, part of it penetrates the membrane of the neurons, producing a polarization of the cell membranes exposed to the current. This effect is sustained during the administration of tDCS (Bikson et al., 2004; Bikson, Paulus, Esmaeilpour, Kronberg, & Nitsche, 2019). Which compartments of the neuron are polarized and:

> "In which direction depends on the neuronal morphology relative to the direct current electric field. Simplistically, for a typical cortical pyramidal cell, with a large apical dendrite pointed toward the cortical surface, a surface anode (positive electrode, generating a cortical inward current flow) will result in somatic (and basal dendrite) depolarization and apical dendrite hyperpolarization. For this same neuron, a surface cathode (negative electrode, generating cortical outward current flow) will result in opposite polarization effects." (Bikson et al., 2019, p.85)

This principle is known as somatic doctrine in a traditional tDCS montage design (Bikson et al., 2019; Gebodh et al., 2019; Jackson et al., 2016; Radman, Ramos, Brumberg, & Bikson, 2009).

tDCS anode electrodes do not always elicit action potentials. The electric fields produced by tDCS are subthreshold, so they are too weak to guarantee action potentials. However, tDCS is likely to change the probability that an incoming action potential will result in post-synaptic firing (Prehn & Flöel, 2015). As a matter of fact, a few seconds after being exposed to tDCS, immediate alterations in cortical excitability can be seen based on polarity specificity (Bikson et al., 2019; M. A. Nitsche et al., 2007; Nitsche et al., 2004).

The instantaneous physiological effects of tDCS appear to be well understood. The long-term effects have been shown to last for more than 24 hours after the end of stimulation (Nitsche et al., 2003; Nitsche & Paulus, 2001). However, the mechanism underlying these long-lasting effects is not yet clear. What is less questionable is the long-term outcome of tDCS. It appears to induce synaptic plasticity (Bikson et al., 2019) which term:

> “Refers to the activity-dependent modification of the strength or efficacy of synaptic transmission at preexisting synapses” (Citri & Malenka, 2008, p.18)

and is mediated by long-term potentiation (LTP) and depression (LTD). LTP leads to a persistent enhancement of synaptic transmission, whereas LTD reduces the efficacy of synaptic transmission. Both processes are associated with learning and memory.

Thereby, manipulating both LTP and LTD could translate to therapeutic benefits in terms of neurological disorders related to lost or excessive synaptic transmission (Bliss & Cooke, 2011). tDCS has shown how current delivered to the human brain can change the event-related potential (ERP) amplitude. It has also produced changes in the firing rate of cortical neurons in animal models as well (Bindman, Lippold, & Redfearn, 1962; Bliss & Cooke, 2011; Paulus, 2004). These are indicators of the potential of tDCS to modulate synaptic plasticity.

3.5.3 Application of transcranial direct current stimulation as a neuromodulator to alter behavior

Learning processes require functional changes that involve the modulation of excitability in the brain. The induction of neuroplastic changes by tDCS is considered a potential intervention to modulate this process (Marcolin & Padberg, 2007). Indeed, it has been shown that placing the anode, but not the cathode, of tDCS on the left DLPFC for a period of 10 minutes using a 1mA current increased the performance of a sequential-letter working memory task in healthy young adults (Fregni, Boggio, Nitsche, et al., 2005). A similar pattern was found while targeting the left DLPFC with the anode while administering a complex verbal associative thought task, in comparison with either cathode or sham stimulation on the same region. Interestingly, the same experiment was replicated targeting the right DLPFC and no significant effects on task performance were found (Cerruti & Schlaug, 2009). Hence, an externally induced increase in the excitability of this brain region might be beneficial to cognitive function and learning process, whereas decreasing cortical excitability seems not to yield benefits. However,

in another study, placing both the anode and cathode of tDCS over the left DLPFC for a period of 15 minutes using a current of 1 mA enhanced planning ability skills in the performance of a cognitive task. Furthermore, these gains in function were maintained after six- and 12-month FU in healthy young participants (Dockery, Hueckel-Weng, Birbaumer, & Plewnia, 2009).

tDCS has also been shown to induce positive effects on attention (Weiss & Lavidor, 2012). One 30-minute 2mA session of tDCS (anode) on the left posterior parietal cortex but not on the right PPC, with the cathode located on the contralateral deltoid, had a positive impact on a visual field exploration training task performed by neurologically unimpaired participants. In addition, results have showed that tDCS alone without adjunct training can lead to the enhancement of visual search (Bolognini, Fregni, Casati, Olgiati, & Vallar, 2010).

Recent research has also indicated that healthy older adults could benefit from tDCS (stimulation provided over the right temporo-parietal cortex for 20 minutes using a current of 1mA) through the enhancing of retention skills in object-location learning after one week of task completion, compared to participants who participated in the sham condition (Flöel et al., 2012).

Apart from altering cognition in healthy populations, there is evidence that tDCS at least temporarily improves motor performance in people with chronic stroke (Hummel et al., 2005). Interestingly, motor improvement was observed in two different experiments; one targeting the unaffected hemisphere with the anode electrode and the other

administering tDCS when placing the cathode on the affected hemisphere (Fregni, Boggio, Mansur, et al., 2005). tDCS enhances naming accuracy skills in stroke patients presenting with aphasia (Baker, Rorden, & Fridriksson, 2010) and has also been shown to decrease the frequency and intensity of depressive symptoms (Bueno, Brunoni, Boggio, Bensenor, & Fregni, 2011). Recent research has indicated that tDCS-based interventions could potentially be used during rehabilitative activities to improve cognitive functioning, such as the attention domain of patients after stroke. It has been shown that the application of one session of tDCS to the left DLPFC improved Go/No-Go test accuracy after intervention compared with sham tDCS stimulation (Kang, Baek, Kim, & Paik, 2009).

An animal study conducted with rats with dementia confirmed an improvement in cognition after application of a tDCS treatment which was maintained 28 days after the tDCS administration ceased (Yu, Park, & Sim, 2014). The application of tDCS has also been investigated for persons with known MCI and fronto-temporal dementia, mild vascular dementia, and Parkinson's disease. Encouraging results were found in the performance of visual recognition memory tasks by persons with AD when anodal tDCS was applied to the left temporal cortex (Paulo Boggio et al., 2009) and in working memory tasks in persons with Parkinson's disease (Paulo Boggio et al., 2006). After five consecutive sessions over a five-day period (two anode electrodes placed over both hemispheres of the temporal cortex and the cathode positioned away from the scalp, for 30 minutes using 2mA) without an adjunct task, the results showed that performance in a visual recognition memory test significantly improved; more importantly, this

improvement persisted after four weeks. However, there was no significant improvement in the other cognitive assessments conducted (Boggio et al., 2012). In another study which involved participants with mild vascular dementia, four consecutive tDCS sessions were given at home (20 minutes using 2mA) with the anode located on the left DLPFC. Positive additional effects were found for visual short-term memory, verbal working memory, and executive control (André et al., 2016). The following chapters will explore in more detail the research on the application of tDCS that has been done in the area of dementia and MCI.

3.5.4 Transcranial direct current stimulation protocols

There are differences in the protocols employed in the studies discussed above involving both healthy adults and people with neurologically impairment. As mentioned earlier, the effects of tDCS are polarity dependent, so it is expected that placing the anode electrode over the targeted brain region will result in increased cortical excitability in that area. However, when the cathode electrode is applied to a brain area, this will produce decreased cortical excitability (Bikson et al., 2004; Jaberzadeh, Martin, Knotkova, & Woods, 2019; Nitsche et al., 2007; Radman et al., 2009). This explanation is a way of simplifying the mechanism of action of tDCS. Although the concept is true, there may be more factors affecting the polarity dependence, which are discussed in the following sections.

3.5.4.1 Transcranial direct current stimulation current

For instance, delivering cathode tDCS for 20 mins with an intensity of 1mA has been shown to reduce cortical excitability. Interestingly, when using the same protocol but altering the intensity to 2 mA, cortical excitability increased. Consequently, it is reasonable to think that the effects of tDCS are not only polarity specific but protocol dependent (Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Jaberzadeh et al., 2019). Thus, it is important to explain all the components of the protocol. For example, lower intensities have been shown to produce larger changes in brain excitability. In terms of current applied, it has been shown that at least 0.6 mA for five minutes is needed to modulate cortical activity (Jaberzadeh et al., 2019; Nitsche & Paulus, 2000). In neuromodulation it may be said that greater intensity does not create larger changes in brain excitability; the relationship seems to be nonlinear. In spite of this, many research trials use currents of 1-2 mA in their protocols (Jaberzadeh et al., 2019).

3.5.4.2 Transcranial direct current stimulation electrodes

The size of the electrodes and the sponges in which they are inserted play an important role in the spatial distribution of the current. tDCS might also stimulate cortical areas adjacent to the targeted one (Rush & Driscoll, 1968). It has been suggested that the larger the sponges, the more diffusely the stimulation will be spread across the brain; while on the other hand, the smaller the sponges, the more focal the stimulation. However, there are other aspects that will affect the breadth of the stimulation. Even the

> “Smallest brain regions can be functionally connected to other distal brain regions” (Jaberzadeh et al., 2019, p. 213)

making it possible to extend the stimulation to distal areas or adjacent regions that are anatomically connected. Therefore, controlling the focality of tDCS may be considered unrealistic (Jaberzadeh et al., 2019; Nitsche et al., 2007; Polanía, Paulus, & Nitsche, 2012). As brain areas are functionally connected, the same concept is applicable to the stimulation area; tDCS will not isolate its effects on the targeted regions, although the location should be reasonably selected based on the desired changes produced by tDCS. For instance, placing the anode electrode on the motor cortex area of the affected hemisphere in stroke survivors likely increases excitability and may enhance the motor performance of the affected upper limb (Allman et al., 2016; Jaberzadeh et al., 2019).

3.5.4.3 Transcranial direct current stimulation montages

In order to avoid the confounding effects of two electrodes with opposite polarities being placed together on the brain, an extracephalic return electrode is recommended as an alternative (Nitsche et al., 2008). The selection of an extracephalic electrode raises concerns regarding the flow of current through the brain, although it has been shown than by placing the return electrode on the shoulder, larger total current densities in deeper brain regions are created compared to cephalic montages. In addition, extracephalic montages may also reduce the applied current through the frontal cortex when the cathode electrode is positioned at the supraorbital region, making this a

method for avoiding hyperpolarizing effects in the cortex which inhibit brain activity (Noetscher, Yanamadala, Makarov, & Pascual-Leone, 2014).

Most of the studies investigating the cognitive changes induced by tDCS have shown that the facilitative effect for the task performance is usually reported on the anode electrode (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Cerruti & Schlaug, 2009; Cotelli et al., 2014; Hill, Fitzgerald, & Hoy, 2016). However, there is also evidence for an improvement in cognitive performance if the cathode electrode is placed on the relevant brain region (Antal et al., 2004; Dockery et al., 2009). One possible explanation is that the cathode electrode decreases global neural activity and eliminates competing activation below the threshold (Weiss & Lavidor, 2012). The cathode electrode appears to act as a kind of noise filter, helping the recipient of tDCS to focus on the right stimuli in order to perform cognitive tasks more efficiently (Weiss & Lavidor, 2012).

In conclusion, cortical inhibition induced by the return (cathode) electrode of tDCS does not inevitably mean a degradation of performance, and cortical excitation induced by the target electrode of tDCS (anode) does not necessarily mean that cognitive enhancement occurs. The physiological mechanism of tDCS seems to be broadly understood, but its effects on behavior when applied to specific stimulation sites needs more research, as some of the findings of the trials are difficult to interpret.

3.5.4.4 Transcranial direct current stimulation frequency

Another factor adding to the complexity of the picture is the frequency of tDCS application required in order to create larger and more lasting effects. The results for the

most efficient number of sessions are still ambiguous (Jaberzadeh et al., 2019), although it is thought that the effects of tDCS on neural excitability are cumulative in multisession interventions (Alonzo, Brassil, Taylor, Martin, & Loo, 2012; Gálvez, Alonzo, Martin, & Loo, 2013; Jaberzadeh et al., 2019).

3.5.4.5 Transcranial direct current stimulation safety

There are fewer doubts about the appropriate duration of each session. In general terms, tDCS can be applied continuously and safely for a maximum of 30 minutes (Nitsche et al., 2008). Some people who have received tDCS have experienced some side effects in the form of mild headaches, tingling sensations, and redness under the electrode area. In a study of the safety aspects of tDCS, 567 participants received it without requesting that the stimulation be stopped. Seventy percent reported a mild tingling sensation and 33% an itching sensation (Grossman, Woods, Knotkova, & Bikson, 2019; Nitsche et al., 2007; Poreisz, Boros, Antal, & Paulus, 2007). However, there are some contraindications for tDCS such as epilepsy or acute eczema, in which it should not be used. In addition, participants with metal implants in the head and pregnant women should not be exposed to stimulation (Nitsche et al., 2008). The latest research involving animal models suggests that brain injury produced by direct current stimulation occurs in the range of 6.3-13 A/m^2. Below certain parameters (≤40 minutes duration, current of ≤4 mA, charge of ≤7.2 Coulombs), tDCS has not caused serious adverse effects (Bikson et al., 2016). Most recipients will experience a slight itching sensation which fades after a few minutes (Nitsche et al., 2008).

3.5.4.6 Sham transcranial direct current stimulation

Sham tDCS is another type of stimulation to consider in research protocols. Also known as placebo stimulation, this acts as a control in experiments to mimic the sensations that real tDCS creates. A current is provided at the beginning and at the end of the process for a short period of time, but in between it is turned off. A study looking at safety issues in tDCS suggests that most of the subjects who participated in the experiment were not able to differentiate sham from real stimulation (Poreisz et al., 2007).

3.6 Transcranial direct current stimulation as an adjunct to other therapies

It is not just the safety, frequency, or target areas that are the significant issues when administering tDCS. It can be used as a standalone intervention or as an adjunctive technique. It has been shown that when tDCS is delivered alone across multiple sessions, it can alleviate pain and reduce symptoms in major depression (Brunoni et al., 2016; Jaberzadeh et al., 2019). However, in CR combining tDCS with other forms of brain stimulation such as CT, lasting neuroplastic changes can be induced. The rationale is that tDCS seems to cause small changes in postsynaptic membrane potential during the ongoing endogenous synaptic activity that occurs when performing a cognitive task. Interestingly, tDCS ameliorates LTP exclusively in neural circuitry that is undergoing plasticity (Kronberg, Rahman, Parra, & Bikson, 2019).

In clinical settings, tDCS should not be regarded as an inducer of synaptic plasticity; it should be used as a modulator whose effects are dependent on the location of the active synapses and the temporal characteristics of the endogenous synaptic activity (Kronberg, Bridi, Abel, Bikson, & Parra, 2017). Consequently, the interaction of tDCS with an endogenous plasticity mechanism, produced by CT tasks, would make the effects of tDCS task-specific; the performance gains would be specific to the learned tasks (Kronberg et al., 2019) and probably also to the underlying domain. In other words, if a patient with MCI is performing arithmetic operations, namely multiplications, and the clinician decides to administer tDCS with the aim of improving performance while the patient is calculating, the gains would be specific to the multiplication operation and could also be beneficial to the underlying cognitive domains involved in mathematical calculations, such as working memory or attention.

The following chapters set out the existing literature so as to evaluate the effectiveness of combining tDCS with CT in improving cognitive functioning in persons with MCI. They go on to review a series of cases in order to explore the behavioral responses of an MCI population to a CS practice. The next stage is to report on the findings of a RCT conducted for two reason: firstly to examine whether older adults with MCI will get more cognitive benefit from receiving CT alone rather than receiving CT coupled with tDCS, in terms of domain-specific cognitive outcomes and task-specific outcomes, and secondly to determine if the stimulation generated by the use of tDCS results in a real-world transfer effect to cognitive domains, particularly everyday memory. As well as studying the behavioral effects of the interventions, the project also investigated the physiological

responses to tDCS and CT in the cortex of persons with MCI. For this reason, the final set of analyses looks at the spatial responses relative to brain activity using EEG studies.

The significance of the thesis is to add new evidence to the fields of neuromodulation, cognitively impaired populations, and CR about the potential application of tDCS as an effective adjunct to CT. This enables a contribution of knowledge to the use of NPT in persons with MCI.

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CHAPTER 4: CAN TRANSCRANIAL DIRECT-CURRENT STIMULATION, WITH OR WITHOUT COGNITIVE TRAINING, BE USED AS A CLINICAL INTERVENTION TO IMPROVE COGNITIVE FUNCTIONING IN PERSONS WITH MILD COGNITIVE IMPAIRMENT AND DEMENTIA? A SYSTEMATIC REVIEW AND META-ANALYSIS

This chapter covers the experimental knowledge concerning the administration of tDCS, both used alone or combined with CT, in cognitively impaired populations, specifically, persons with MCI and dementia. All the information and data were obtained following a systematic process, targeting exclusively clinical trials that were published in the literature. This section of the thesis has expanded our understanding of how tDCS can influence cognition and has also infused us with new ideas and approaches to implement in our research studies. The chapter begins introducing and contextualizing tDCS, MCI and CR. Following with the explanation of the purpose for carrying out the systematic-review and meta-analyses and finally formulating the research questions. To answer the questions, the methods we have used, will be presented and then the results will be explained and given in the form of tables and figures. The chapter will end with a discussion of our findings and the conclusions we have elaborated along with recommendations for future research studies to follow.

In this chapter, we aim to provide the reader with evidence regarding protocols that could potentially be used in future research and clinical settings.

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Cruz Gonzalez, P., Fong, K. N., Chung, R. C., Ting, K.-H., Law, L. L., & Brown, T. (2018). Can transcranial direct-current stimulation alone or combined with cognitive training be used as a clinical intervention to improve cognitive functioning in persons with mild cognitive impairment and dementia? A systematic review and meta-analysis. Frontiers in Human Neuroscience, 12, 416. https://doi.org/10.3389/fnhum.2018.00416

4.1 Introduction

tDCS is a type of NIBS. tDCS delivers weak direct currents to the brain that can alter spontaneous firing rates on neural activity, which subsequently translates into behavioral changes (Nitsche et al., 2008). It is a process that has been described as “portable, painless, inexpensive and safe” (Kadosh, Levy, O'Shea, Shea, & Savulescu, 2012, p. 108). During the administration of tDCS, depolarization or hyperpolarization of the neuronal membrane of target neurons may be induced, even though the small electric fields of tDCS are considered to be below the intensity required to evoke action potentials (Miniussi, Harris, & Ruzzoli, 2013; Nitsche et al., 2003; Tatti, Rossi, Innocenti, Rossi, & Santarnecchi, 2016).

In other words, tDCS causes a shift in the membrane potential threshold which is likely to change the probability that an incoming action potential will result in post-synaptic firing during and after its administration (Prehn & Flöel, 2015). Such changes in neuronal excitability modulates the cognitive processes and tDCS can induce physiological processes. Due to the proposed resemblance of the effects of tDCS and cognitive processes on cerebral physiology, researchers have been using NIBS to alter cognition (Kuo & Nitsche, 2012; Prehn & Flöel, 2015).

MCI is defined as the stage between normal and dementia-type pathological aging. MCI is a syndrome of cognitive decline in nondemented persons that does not affect the capacity to be independent in ADL (Portet et al., 2006). In contrast, people who suffer from dementia present a more severe cognitive decline and do not preserve

independence in functional abilities and ADL (Langa & Levine, 2014). Epidemiological investigations suggest a range of prevalence for MCI of 7–24% among adults aged over 65, and the manifestation of MCI is consistently shown to have a high risk of progression to dementia (Langa & Levine, 2014; Petersen et al., 2014).

To date, there is no pharmaceutical treatment shown to be effective in improving cognitive functioning in MCI and dementia (Langa & Levine, 2014), although CT interventions show promise for improving targeted cognitive functions in elderly persons without cognitive impairments (Ball et al., 2002). CR is defined as:

> "The therapeutic process of increasing or improving an individual's capacity to process and use incoming information so as to allow increased functioning in everyday life. This includes methods to train and restore cognitive function and compensatory techniques" (Sohlberg & Mateer, 1989, p. 871)

CR is therefore essential and research has indicated that NIBS can positively affect the cognitive performance of populations affected by cognitive disorders (Miniussi et al., 2008). Differences in tDCS experimental protocols regarding the parameters employed such as the montage, the current, the intensity or the size of the electrodes can affect the electric field strength. All of these variables contribute to increase the heterogeneity of the electric field's properties among studies thus producing different outcomes (Woods et al., 2016). Furthermore, targeting a neural network with tDCS while it is engaged by a CS activity, during or after the administration of tDCS, may yield better therapeutic effects than stimulating the same cortical region lacking cognitive stimuli

(Cruz Gonzalez, Fong, & Brown, 2018). tDCS may increase the strength of transmission across synaptic circuits in pathways that are stimulated by cognitive practice. Thus, coupling both techniques could create a synergistic positive effect on behavior (Birba et al., 2017; Cruz Gonzalez et al., 2018; Miniussi et al., 2013). The effectiveness of tDCS in CR targeting people with MCI or dementia must therefore be established. It is fundamentally important to learn about all the different configurations and protocols in which tDCS has been employed to assess its utility.

We systematically reviewed the literature regarding effects of tDCS on persons with MCI and dementia to address the following questions: (1) Does tDCS alone improve cognitive functioning in persons with MCI and dementia? (2) Does tDCS coupled with CT, or as a priming to other cognitive interventions yield greater benefits in cognitive functioning than the administration of tDCS alone? (3) Are the effects of tDCS on the cognitive functions able to maintain across time?

In this study, we reviewed and evaluated the effects of tDCS on cognitive functions in people with MCI or dementia from all the available clinical trials. A systematic review of the available information up to the present will enable researchers to better understand the potential of tDCS to offer solutions for cognitive deterioration, with the aim of outlining more robust interventions in the future for people with MCI and dementia. Other reviews involving the use of different NIBS on healthy aging (Prehn & Flöel, 2015), dementia (Freitas, Mondragón-Llorca, & Pascual-Leone, 2011; Hsu, Ku, Zanto, & Gazzaley, 2015), MCI (Birba et al., 2017) have been carried out since 2011, but we

provide an update and meta-analysis of recent trials to focus exclusively on the use of tDCS in MCI and dementia populations.

4.2 Methods

4.2.1 Eligibility criteria

We performed a systematic review and meta-analysis following the PRISMA guidelines (Liberati et al., 2009) Studies were selected based on the following criteria:

-Participants: Participants included in the study were older adults with MCI and persons with a diagnosis of dementia. The criteria for MCI includes (a) subjective memory complaint; (b) objective cognitive decline; (c) preserved ADL, and (d) not demented (Petersen et al., 1999). The diagnosis of dementia followed the criteria of the NINCDS-ADRDA (McKhann et al., 1984) and the DSM-IV (American Psychiatric & American Psychiatric Association. Task Force on, 2000). Participants with any other neurological disease that was not dementia, such as only the Parkinson's disease, were excluded.

-Interventions: tDCS alone (anodal, cathodal, or sham), or a combination of tDCS (online or offline) with an additional cognitive task (CT).

-Comparisons: The comparison group could be a placebo with sham tDCS, sham tDCS in combination with a CT, or a control group performing a cognitive intervention. In order to establish evidence on tDCS protocols for people with MCI or dementia, studies without sham tDCS were included.

-Outcome measurements: The outcomes were measurements of cognitive functions and neuroimaging techniques.

-Study design: All clinical trials published in English from January 2007 to November 2017 were included.

4.2.2 Search strategy

Studies were identified by a systematic literature search in the following databases: PubMed, Web of Science, Science Direct, MEDLINE, and PsycINFO. A search was performed combining all the chosen keywords across the above databases. The keywords and the search strategy are presented in Table 4.1. A hand search was also performed to identify relevant studies.

Search Strategy	**Database**	**Articles Yielded**
1. aged OR aging OR old adult OR old people OR old person OR aged OR aging/ageing OR elder OR geriatric	PubMed	2282878
	Web of science	20020579
	Science Direct	160098
	Medline	2215444
	PsycINFO	990595
2. mild cognitive impairment OR MCI OR subtle cognitive impairment OR mild dementia OR prodromal dementia	PubMed	39043
	Web of science	32402
	Science Direct	26522
	Medline	18949
	PsycINFO	13300

3. dementia OR Alzheimer's disease OR AD OR vascular dementia OR VD OR dementia with Lewy bodies OR DLB OR mixed dementia OR frontotemporal dementia	PubMed	680614
	Web of science	230907
	Science Direct	8365
	Medline	218682
	PsycINFO	67559
4. 1 AND 2 OR 3	PubMed	688964
	Web of science	234611
	Science Direct	1936
	Medline	221967
	PsycINFO	69699
5. cognition OR executive function OR attention OR memory or working memory OR cognitive training OR cognitive intervention OR cognitive stimulation OR cognitive rehabilitation OR cognitive remediation OR brain training OR mental training OR memory training OR mnemonic training OR executive function training OR attention training or working memory training	PubMed	688598
	Web of science	934342
	Science Direct	24133
	Medline	462185
	PsycINFO	815917

6. transcranial direct-current stimulation OR tDCS OR direct-current stimulation OR TES OR DC stimulation OR electrical stimulation OR transcranial stimulation OR non-invasive brain stimulation OR NIBS OR neuromodulation	PubMed	65155
	Web of science	60269
	Science Direct	11106
	Medline	44985
	PsycINFO	36695
7. 4 AND 5 AND 6	PubMed	1135
	Web of science	601
	Science Direct	43
	Medline	460
	PsycINFO	333
8. randomized control trials OR clinical trial OR crossover studies OR case control studies OR case series OR case report OR placebos OR sham OR control	PubMed	3021385
	Web of science	3889523
	Science Direct	231043
	Medline	2521985
	PsycINFO	744877
9. 7 AND 8	PubMed	434
	Web of science	317
	Science Direct	31
	Medline	235
	PsycINFO	181

Table 4.1. Sample search strategy and databases.

4.2.3 Selection criteria

After removing duplicates, the abstracts of the articles retrieved were screened to make a final decision for further review. Two investigators realized the search and the selection of studies to be included. Any disagreements were resolved by a third reviewer.

4.2.4 Data extraction

The data extracted from the selected studies were conducted by two investigators using a standardized data extraction sheet which included study design, study population, number of participants, mean participant age, gender ratio, general cognitive level, number of intervention sessions, experimental/sham tDCS parameters, combination of tDCS with other interventions, outcome measures, neuroimaging techniques, assessment sequence, FU, effect(s) of the intervention, and intervention safety reports.

4.2.5 Methodological quality

The studies selected for review were categorized and leveled according to their design based on the hierarchy level of evidence ("Oxford Centre for Evidence-based Medicine Levels of Evidence," 2009). All RCTs were then rated by the first two authors using the Risk of Bias Tool in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019).

4.2.6 Data analysis

Only RCTs, excluding crossover designs, were considered for meta-analysis. In some cases, authors were contacted to obtain data from their studies. After the review of the clinical methodology's heterogeneity of each study, the selected papers were further assessed for statistical heterogeneity, using the I-squared and Chi-squared statistics of the outcome measures.

Data of pooled memory outcomes comparing: (1) Short-term effects of tDCS treatments versus sham tDCS that targeted the DLPFC were calculated based on the differences between post-intervention evaluations relative to the baseline to assess the immediate effects of tDCS; (2) Long-term effects of tDCS treatments versus sham tDCS that targeted the DLPFC; were assessed according to the differences between FU evaluations relative to the baseline.

All outcomes were analyzed as continuous variables with the mean change, the largest standard deviation, and the sample size in each group. The standardized mean difference and 95% confidence intervals were calculated for all meta-analyses using the fixed-effect model. The effect size was considered to be small between 0.2–0.49, moderate (0.5–0.79), and a value of 0.8 or above was considered to be large (Cohen, 1992). If I^2 was below 40%, it was considered to not represent statistical heterogeneity. Otherwise, the random-effect model was used instead. Significance was set at $p = 0.05$ and both meta-analyses were conducted using Review Manager Software 5.3.

4.3 Results

4.3.1 Study selection

The search strategy identified 1,198 published articles from the selected databases: PubMed (n = 434), Web of Science (n = 317), Science Direct (n = 31), Medline (n = 235), and PsycINFO (n = 181) (Table 4.1). Sixteen articles met the eligibility criteria (Figure 4.1).

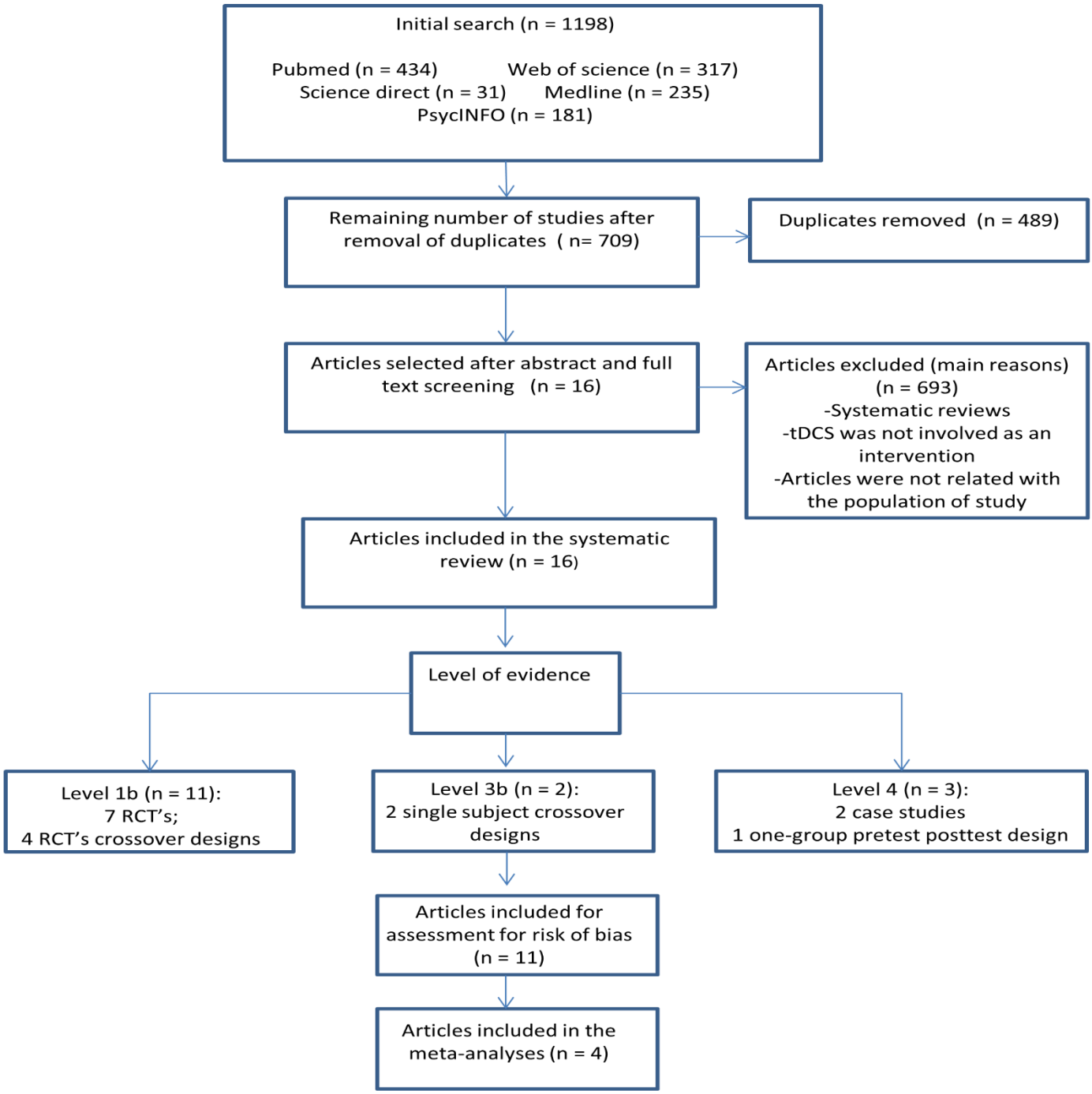


Figure 4.1. Flowchart of the study selection and level of evidence.

4.3.2 Study characteristics

Eleven studies (André et al., 2016; Boggio et al., 2012; Boggio et al., 2009; Bystad, Grønli, et al., 2016; Bystad, Rasmussen, Abeler, & Aslaksen, 2016; Bystad, Rasmussen, Grønli, & Aslaksen, 2017; Costa, Brighina, Piccoli, Realmuto, & Fierro, 2017; Cotelli et al., 2014; Ferrucci et al., 2008; Khedr et al., 2014; Penolazzi et al., 2015; Suemoto et al., 2014) involved the application of tDCS on PwD. These articles included three randomized crossover studies (Boggio et al., 2012; Boggio et al., 2009; Ferrucci et al., 2008), five RCTs (André et al., 2016; Bystad, Grønli, et al., 2016; Cotelli et al., 2014; Khedr et al., 2014; Suemoto et al., 2014), two single-subject pretest-posttest case studies (Bystad, Rasmussen, et al., 2016; Bystad et al., 2017), and two single-subject crossover-design studies (Costa et al., 2017; Penolazzi et al., 2015). Four articles (Ladenbauer et al., 2017; Meinzer et al., 2015; Murugaraja, Shivakumar, Sivakumar, Sinha, & Venkatasubramanian, 2017; Yun, Song, & Chung, 2016) exposed persons with MCI (PwMCI) to the application of tDCS. These four studies each used a different design: a randomized crossover (Meinzer et al., 2015), a RCT (Yun et al., 2016), a group pretest-posttest (Murugaraja et al., 2017), and a balanced crossover (Ladenbauer et al., 2017).

These studies included a total of 195 participants with dementia and 53 participants with MCI. Eleven studies applied tDCS “alone” (André et al., 2016; Boggio et al., 2012; Bystad, Grønli, et al., 2016; Bystad, Rasmussen, et al., 2016; Bystad et al., 2017; Ferrucci et al., 2008; Khedr et al., 2014; Ladenbauer et al., 2017; Murugaraja et al., 2017; Suemoto et al., 2014; Yun et al., 2016) and five paired tDCS with CT (Boggio et

al., 2009; Costa et al., 2017; Cotelli et al., 2014; Meinzer et al., 2015; Penolazzi et al., 2015) The details of the studies' characteristics and protocols are set out in Table 4.2.

Study and design	Participants	tDCS montage	Sham tDCS montage	Number of sessions	Combination with other intervention	Outcomes	Assessment sequence	Effect of intervention
i) AD/MD								
Ferrucci et al., 2008 Randomized crossover design	N= 10 (3 groups) AD participants MMSE= 22.7±1.8 Age= 75.2±7.3 70% Females	1.5 mA 15 mins (1) Anode (P3-T5) Cathode (right deltoids) (2) Cathode (P6-T4) Anode (right deltoids)	10 sec Same tDCS montage	1	No	Assessments: WRT (modified from ADAS-cog), VAT (exogenous cue version of the Posner paradigm) Imaging: No	At baseline, 30 mins after tDCS 1 week wash out period FUP: No	Accuracy in WRT increased significantly after anodal tDCS but decreased after cathodal tDCS Safety: Itching sensation
Boggio et al., 2009 Randomized crossover design	N= 10 (3 groups) AD participants MMSE= 17±4.9 Age= 79.1±8.8 60% Females	2 mA 30 mins 35 cm^2 (1) Anode (LDPFC) Cathode (Fp2) (2) Anode (T7) Cathode (FP2)	30 sec Same tDCS montage	1	VRT with faces (IBV software) ; Stroop test; DST (starting 10 minutes after the onset of the stimulation)	Assessments: VRT, Stroop test, DST Imaging: No	10 minutes after tDCS onset 2 days wash out period FUP: No	A significant effect of both tDCS experimental conditions on VRT, as compared with sham tDCS Safety: No adverse effects
	N= 15 (2 groups)	2 mA	30 sec		No	Assessments:	At baseline, right after the	VRT improved significantly after

Boggio et al., 2012 Randomized crossover design	AD participants MMSE= 20±3 Age= 79.05±8.2 46.6% Females	30 mins Anode (T3 and T4) 35 cm^2 Cathode (right deltoids) 64 cm^2	Same tDCS montage	5 (in a row)		MMSE, Adas-Cog, VRT (IBV software), VAT (using endogenous cue version of the Posner task) Imaging: No	last tDCS session, 1 week and 1 month FUP Average wash out period 71.1 days	anodal tDCS than after sham tDCS VRT performance kept improving in tDCS group at 1 month FUP Safety: No adverse effects
Cotelli et al., 2014 RCT	N= 36 (3 groups) AD participants MMSE; expC= 20.1±2.4 expM= 22.1±2.3 sham= 20.8±2.1 Age; expC= 76.6±4.6; expM= 78.2±5.2 sham= 74.7±6.1 Female proportion; expC= 83.3% expM= 83.3% sham= 75%	2 mA 25 mins Anode (LDLPFC) 25 cm^2 Cathode (right deltoids) 50 cm^2	40 sec (20 sec at first, 20s at the end) Same tDCS montage	10 (5 per week for 2 weeks)	Memory training (based on the performance of the, FNAT, at the baseline) or motor training Both interventions started at the same time as the onset of tDCS	Assessments: FNAT, MMSE, ADL, IADL, Tinetti scale, NPIT, Picture naming task, BADA, RBMT, Rey auditory verbal learning test, Complex figure-copy, TMT Imaging: No	At baseline, post-intervention, 3 and 6 months FUP	tDCS plus memory training and sham tDCS plus memory training showed significantly improved performance on FNAT compared with the tDCS plus motor training group after the intervention and at 12 weeks FUP Safety: No adverse effects
	N= 40 (2 groups)	2 mA	20 sec		No			No significant effects

Suemoto et al., 2014 RCT	AD participants MMSE; exp= 15.0±3.1 sham= 15.4±2.6 Age; exp= 79.4±7.1 sham= 81.6±8.0 Female proportion; exp= 37.5% sham= 32.5% N= 34;	20 mins 35 cm^2 Anode (LDLPFC) 25 cm2 Cathode (Fp2)	Same tDCS montage	6 (during 2 weeks)			Assessments: Apathy Scale; ADAS-Cog (word list learning, word recognition and digit cancellation) Imaging: No	At baseline, post-intervention, 1 week FUP	Safety: Tingling , sking redenss, scalp burning
Khedr et al., 2014 RCT	NexpA= 11 NexpC= 12 Nsham= 11 AD participants MMSE; expA= 18.4±3.9 expC= 18.8±2.9 sham= 16.9±2.9 Age;	2 mA 25 mins (1) Anode (LDPFC) 24 cm^2 Cathode (Fp2) 100 cm^2 (2) Cathode (LDPFC) 24 cm2	40 sec (20sec at first, 20s at the end) Same tDCS montage	10 (in a row)	No		Assessments: MMSE, WAIS-III Imaging: ERP, resting motor threshold, cortical silent periods.	At baseline, post-intervention, 1 and 2 months FUP	WAIS IQ performance significantly improved after cathodal tDCS, MMSE improved and reduced P300 latency occurred after both anodal and cathodal tDCS Safety: Itching, headache and dizziness

	expA= 68.5±7.2 expC= 70.7±5.4 sham= 67.3±5.9 Female proportion; expA= 45.4% expC= 33.3% sham= 54.5%	Anode (Fp2) 100 cm2						
Bystad et al., 2016 RCT	N= 25; Nexp= 12 Nsham= 13 AD participants MMSE; exp= 20.5±8.0; sham= 22.1±13.0 Age; exp= 70.25±21.0; sham= 75.0 ± 30.0 Female proportion; exp= 42% sham= 47%	2mA 30 mins 35 cm2 Anode (T3) Cathode (Fp2)	60 sec (30sec at first, 30s at the end) Same tDCS montage	6 (in 10 days)	No	Assessments: CVLT-II, MMSE, clock-drawing test; TMT, WAIS (Abbreviated version) Imaging: No	At baseline, post-intervention FUP: No	No significant effects Safety: No adverse effects
Bystad et al., 2016	N= 1 AD case	2mA 30 mins	No sham	12 (during a 6-day	No	Assessments: CVLT-II, MMSE	At baseline, two days after the last	Significantly improvement on MMSE. CVLT-II

Case study	MMSE= 23.2 Age= 59 0% Females	35 cm^2 Anode (T3) Cathode (Fp2)		period, twice a day)		Imaging: EEG	session, 2 months FUP EEG at baseline and 2 months FUP	delayed recall test was clinically significant No changes in EEG Safety: No adverse effects
Bystad et al., 2017 Case study	N=1 AD case MMSE= 20 Age= 60 0% Females	2mA 30 mins 35 cm2 Anode (T3) Cathode (Fp2)	No sham	Daily (for 8 months)	No	Assessments: RBANS Imaging: NO	Baseline, at 5 months, at 8 months FUP: No	The patient's cognitive functions were stabilized except for visuospatial functioning. At 8 months, immediate recall and delayed recall improved Safety: Tingling and itchy sensation
Penolazzi et al., 2015 Single subject crossover design	N= 1 (2 groups) AD case MMSE= 23.2 Age= 60 0% Females	2 mA 20 mins Anode (LDPFC) 35 cm2 Cathode (Fp2) 100 cm2	10 sec Same tDCS montage	10 (in 2 weeks)	WRT; VWMT; PFT; CPT (All these activities were administered right after the tDCS administration for 45 minutes)	Assessments: WRT, VWMT, PFT, CPT, DST, TMT, overlapping figures, clock drawing Imaging: No	At baseline, post-intervention,2 weeks FUP 2 month wash out period	A significant accuracy improvement in WMT for tDCS+CT Safety: No adverse effects

Costa et al., 2017 Single subject crossover design	N= 1 (2 groups) AD case MMSE= 14.27 Age= 67 100% Females	2 mA 30 mins 35 cm^2 Anode (Broca's area) Cathode (Fp2)	30 sec Same tDCS montage	5	Linguistic exercises; as writing-to-dictation, reading aloud, and repetition of words and pseudowords. (exercise were administered 7 minutes after the onset of tDCS)	Assessments: Naming, auditory, comprehension of nouns and verbs tasks Imaging: No	At baseline, immediately after end of intervention , 2 weeks FUP 2 week wash out period	Significant improvement of comprehension of verbs Safety: No adverse effects
Andre et al., 2016 RCT	N= 21; Nexp =19 Nsham= 9 VD/MD participants MMSE; exp= 24.5±1.8 sham= 22.4 ±2.6 Age; exp= 80.3±5.8 sham= 75.8±7.4 Females -	2 mA 20 mins 35 cm2 Anode (LDPFC) Cathode (Fp2)	8 sec Same tDCS montage	4 (in a row)	No	Assessments: ADAS, picture-naming task, 2-back task, Go/no-go task Imaging: No	Baseline, after intervention, 2 weeks FUP	2-back task and the go/no-go test improved. Picture naming task increased the number of memorized words after intervention Safety: No adverse effects

ii) MCI

Meinzer et al., 2015 Randomized crossover design	N= 18 (2 groups) MCI participants MMSE= 27.17±1.34 Age= 67.44± 7.27 Females 38.8%	1 mA 20 mins Anode (IFG) Cathode (Fp2)	30 sec Same tDCS montage	1	Overt semantic word-retrieval task	Assessments: Overt semantic word-retrieval task Imaging: fMRI	Anodal tDCS vs sham tDCS with concurrent fMRI recording during a word-retrieval task and resting state. One week wash out period FUP: No	Significant improvement of the semantic word-retrieval task to the level of healthy controls. Reduced task-related prefrontal hyperactivity during resting-state fMRI Safety: No adverse effects
Yun et al., 2016 RCT	N= 16 MCI participants MMSE;	2 mA 20 mins 25 cm^2	20 sec Same tDCS montage	9 (3 times per week for 3 weeks)	No	Assessments: Modified MMQ Imaging: PET	Baseline, post-intervention FUP: No	Subjective memory satisfaction and memory strategies

	exp= 26.75± 1.58; sham= 25.12 ± 2.74 Age; exp= 74.75± 7.47 sham= 73.12± 4.25 Female distribution; exp= 37.5% sham= 25%	Anode (LDPFC) Cathode (RDPFC)						significantly improved. Increased regional cerebral metabolism Safety: No adverse effects
Murugaraja et al., 2017 One group pretest-posttest	N= 11 MCI participants MMSE= 28 Age= 59.6±4.3 Females 54.5%	2 mA 30 mins 35 cm^2 Anode (IFG) Cathode (Fp2)	No sham	5 (in a row)	No	Assessments: PMIT Imaging: No	Baseline and 1 hour after end of the intervention 1 month FUP	Immediate and delayed recall performance improved, persisting at 1 month FUP Safety: Pricking, burning sensation

Ladenbauer et al., 2017 Randomized crossover design	N= 8 (2 groups) MCI participants MMSE= 28.3 ± 1.4 Mean age= 71±9 Females 43.7 %	so-tDCS frequency of 0.75 Hz (0-262.5 uA) 5 minutes blocks(3-5 blocks in total) 8mm Anodes (F3 and F4) Cathodes (mastoids)	Same tDCS montage tDCS device remained off	1	No	Assessments: Visuospatial memory task, verbal memory task, sequential finger tapping task Imaging: EEG	Cognitive test at baseline and after tDCS and EEG during tDCS. 2 weeks wash-out period. FUP: No	Visual declarative memory improved so-tDCS significantly increased overall SO and spindle power Safety: Tingling sensation

Table 4.2. Study characteristics.
Abbreviations: ADAS-cog: Alzheimer's disease assessment scale-Cog; BADA: battery for analysis of aphasic deficits; CVLT-II: California verbal learning Test; CPT: continuous performance task; expC: cognitive experimental group; exp: experimental group; expA: anodal experimental group; expC: cathodal experimental group; expM: motor experimental group; FNAT: face-name memory association task; FUP: Follow-up; I/ADL: instrumental/activities of daily living; IFG: inferior frontal gyrus; L/RDFPC: left/right dorsolateral prefrontal cortex; MD: Mixed dementia; MCI: mild cognitive impairment; MMQ: metamemory questionnaire for older adults; MMSE: Mini-mental state examination; N: sample size; PFT: phonemic fluency task; PMIT: picture memory impairment test; RBANS: assessment of neuropsychological status; RBMT: Rivermead behavioral memory test; so-tDCS: slow oscillatory tDCS; TMT: Trail making test; VAT: visual attention task; VD: Vascular dementia; VRT: visual recognition task; VWMT: verbal working memory task ; RCT: randomized control trial; WAIS-III: Weschler abbreviated scale of intelligence; WRT: word recognition task.
Note: Values are means ± SD or as otherwise.

4.3.3 tDCS parameters

Two studies randomly assigned participants to anodal, cathodal, and sham groups (Ferrucci et al., 2008; Khedr et al., 2014). The majority of the studies involved anodal and sham groups (André et al., 2016; Boggio et al., 2012; Boggio et al., 2009; Bystad, Grønli, et al., 2016; Costa et al., 2017; Cotelli et al., 2014; Ladenbauer et al., 2017; Meinzer et al., 2015; Murugaraja et al., 2017; Penolazzi et al., 2015; Suemoto et al., 2014; Yun et al., 2016). In contrast, three studies focused on anodal stimulation lacking sham tDCS (Bystad, Rasmussen, et al., 2016; Bystad et al., 2017; Murugaraja et al., 2017). Regarding the dose, we found a high level of heterogeneity among experiments. Only four studies were single-session (Boggio et al., 2009; Ferrucci et al., 2008; Ladenbauer et al., 2017; Meinzer et al., 2015) whereas the number of sessions for the rest of studies ranged from 4 to 10 (André et al., 2016; Bystad, Grønli, et al., 2016; Cotelli et al., 2014; Khedr et al., 2014; Penolazzi et al., 2015; Suemoto et al., 2014; Yun et al., 2016). Bystad carried out two case studies adopting unusual approaches, the first study with a daily dose of tDCS for a duration of eight months (Bystad et al., 2017) and the second study using tDCS twice daily consecutively for six days (Bystad, Rasmussen, et al., 2016). With respect to the electric fields, more homogeneous parameters were chosen among studies. The majority of the studies applied 2mA of intensity and the targeted region for the active electrode was the DLPFC and the right supraorbital region for the cathode (Figure 4.2).

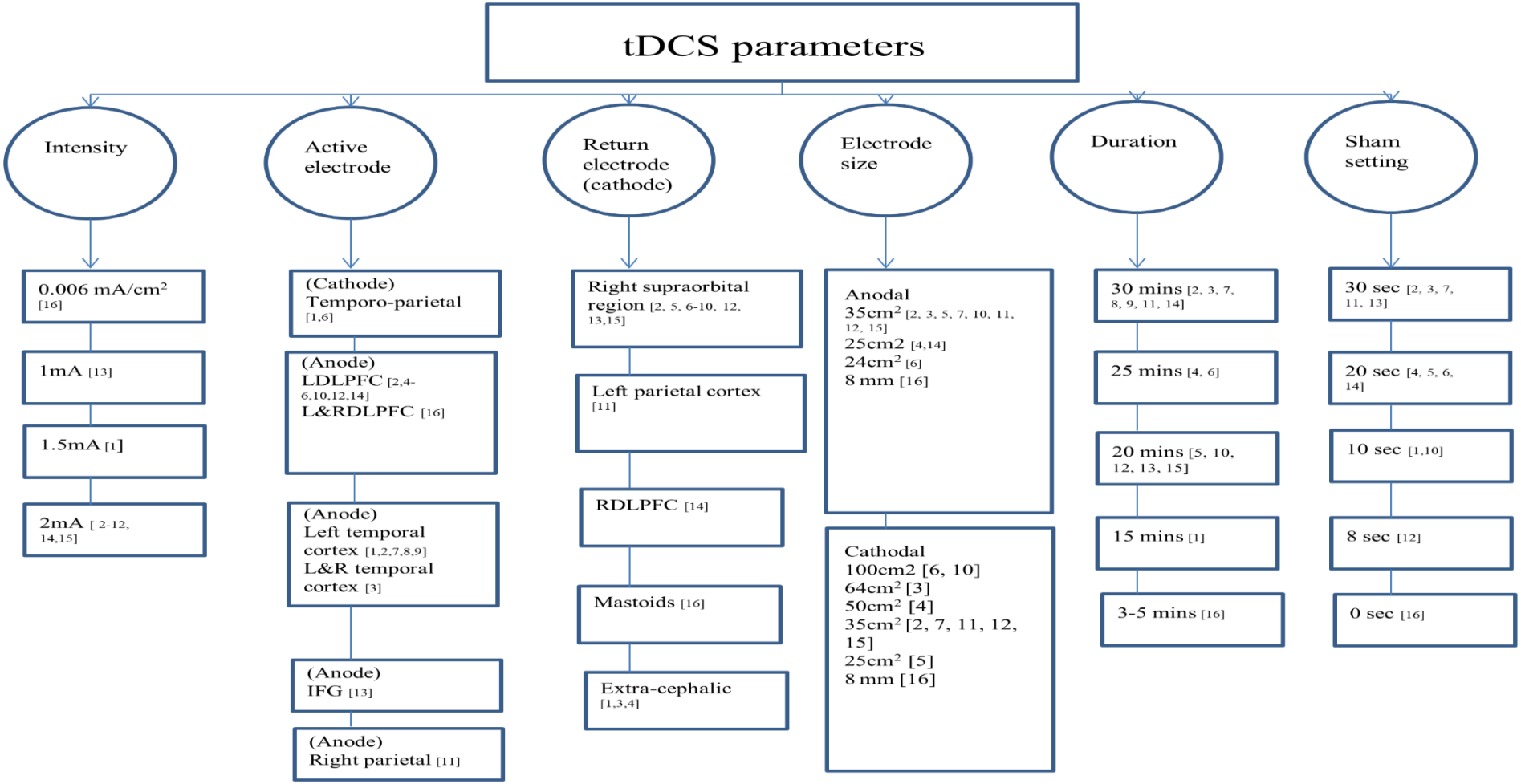


Figure 4.2. tDCS parameters used across the studies included.
Abbreviations: 1: Ferrucci et al., 2008; 2: Boggio et al., 2009; 3: Boggio et al., 2012; 4: Cotelli et al., 2014; 5: Suemoto et al., 2014; 6: Khedr et al., 2014; 7: Bystad et al., 2016a; 8: Bystad et al., 2016b; 9: Bystad et al., 2017; 10: Penolazzi et al., 2015; 11: Costa et al.,2017; 12: Andre et al., 2016; 13: Meinzer et al., 2015; 14: Yun et al., 2016; 15: Murugaraja et al., 2017; 16: Ladenbauer et al., 2017; IFG: inferior frontal gyrus; L/DLPFCT: left/right dorsolateral prefrontal cortex; L&R: left and right.

Six studies reported mild adverse reactions such as itchy and tingling sensations, redness in the area of electrode application, burning scalp, headache, dizziness and pricking (Bystad et al., 2017; Ferrucci et al., 2008; Khedr et al., 2014; Ladenbauer et al., 2017; Murugaraja et al., 2017; Suemoto et al., 2014).

4.3.4 Effectiveness of tDCS "alone"

Seven studies on the dementia population reported positive effects of anodal (André et al., 2016; Boggio et al., 2012; Bystad, Rasmussen, et al., 2016; Bystad et al., 2017; Ferrucci et al., 2008; Khedr et al., 2014) and cathodal tDCS (Khedr et al., 2014) on cognition. All these cognitive improvements were associated with memory and global cognition. All outcomes but two (Boggio et al., 2012; Bystad et al., 2017) were statistically significant. However, two of these studies failed to report positive effects in the attention domain (Boggio et al., 2012; Ferrucci et al., 2008). Two others did not report any positive effects of anodal tDCS on cognition (Bystad, Grønli, et al., 2016; Suemoto et al., 2014).

Four studies (Boggio et al., 2012; Bystad, Rasmussen, et al., 2016; Cotelli et al., 2014; Khedr et al., 2014) assessed the long-term effects of tDCS. Three of these reported significant changes: one showed that the improvement caused by anodal tDCS persisted four weeks after the end of stimulation (Boggio et al., 2012), another indicated that either anodal or cathodal tDCS improved mean MMSE score at one- and two-month FU (Khedr et al., 2014), and the third study revealed that two months after the end of the intervention, anodal tDCS was clinically significant.

Only two studies performed neuroimaging tests. In the first, an ERP experiment confirmed significant effects reducing P300 latency after both anodal and cathodal tDCS (Khedr et al., 2014). The second used EEG, although it did not prove changes from baseline (Bystad, Rasmussen, et al., 2016).

Three studies evaluated the efficacy of anodal tDCS on PwMCI. Overall, anodal tDCS achieved significant improvement in memory (Murugaraja et al., 2017; Yun et al., 2016). Furthermore, two of these studies investigated the neural effects of anodal tDCS. Yun (2016) utilized PET to demonstrate a significantly increased metabolism in cortical regions. In the same way, the work of Ladebauer (2017) made clear, through the use of concurrent EEG, that slow oscillatory tDCS significantly increased overall slow oscillations (SO) and spindle power (Ladenbauer et al., 2017).

4.3.5 Effectiveness of tDCS combined with CT

Details and methods about the CT operated among studies are shown in Table 4.2. All the studies involving PwD showed significant benefits after receipt of anodal tDCS paired with a CT. Boggio (2009) applied tDCS while participants completed cognitive assessments, enhancing memory in a visual recognition memory task, but there were no effects on attention. The work of Cotelli (2014) combining memory training with tDCS and sham tDCS resulted in improved memory performance illustrated in a face-name association memory task, as compared to a group which received tDCS paired with motor training; this improvement persisted significantly after twelve weeks. However, it failed to produce significant effects on standardized cognitive tests. In one single-

subject crossover study, the CT associated with memory components was started right after the end of tDCS administration and the findings revealed a significant accuracy improvement in a verbal working memory task. In contrast, there is no indication of amelioration in other cognitive assessments (Penolazzi et al., 2015). Alternatively, one case study that focused on stimulating the production and comprehension of language through a combination of anodal tDCS and linguistic training found a significant effect in an auditory comprehension task (Costa et al., 2017).

The work of Meizner (2015) targeting PwMCI revealed that during exposure to anodal tDCS, participants performed significantly better in a semantic word-retrieval task than those who received sham tDCS, achieving the level of healthy elderly subjects. Furthermore, the application of anodal tDCS led to reduced task-related prefrontal hyperactivity shown by resting-state fMRI.

4.3.6 Study quality

The level of evidence of all the trials is displayed in Figure 4.1. Details can be found in Table 4.3. Most of the studies reported a risk of bias describing the method used to conceal the allocation sequence (André et al., 2016; Boggio et al., 2012; Bystad, Grønli, et al., 2016; Ferrucci et al., 2008; Ladenbauer et al., 2017; Meinzer et al., 2015; Yun et al., 2016). The most common methodological limitation of these studies was the issue of the blinding of the personnel due to the nature of most tDCS devices.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Ferrucci et al., 2008	Unclear	High	High	Low	Low	Low	Low
Boggio et al., 2009	Unclear	Low	High	High	Low	Low	Low
Boggio et al., 2012	Unclear	High	Low	High	Low	Low	Low
Cotelli et al., 2014	Unclear	Unclear	High	Low	High	Low	Low
Suemoto et al., 2014	Low	Low	High	Low	Low	Low	Low
Khedr et al., 2014	Low	Low	Low	Low	Low	Low	Low
Bystad et al., 2016a	Low	High	Low	Low	Low	Low	Low
Andre et al., 2016	Unclear	High	High	High	Low	Low	Low
Meinzer et al., 2015	Unclear	High	High	Low	Low	Low	Low
Yun et al., 2016	Low	High	Low	Low	Low	Low	Low
Ladenbauer et al., 2017	Unclear	High	High	High	Low	Low	Low

Table 4.3. Methodological quality (Cochrane Risk of Bias Tool).

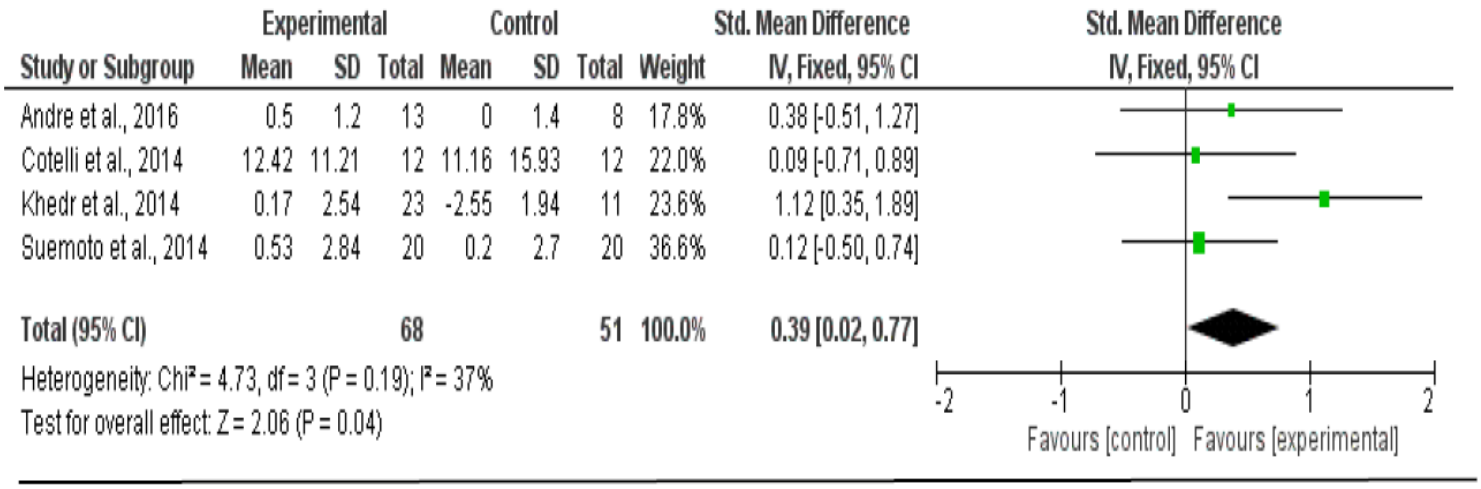
4.3.7 Meta-analysis

Four studies (André et al., 2016; Cotelli et al., 2014; Khedr et al., 2014; Suemoto et al., 2014) involving 119 PwD in total were included in the meta-analysis. One RCT study was excluded because the region of stimulation was the temporal region (Bystad, Grønli, et al., 2016) details can be seen in Table 4.4. The results revealed a statistically significant mean effect size of 0.39 [95% CI, 0.02, 0.74] (p = 0.04) that favored real tDCS over sham stimulation for immediate effects. There was no evidence of heterogeneity across studies (Q = 4.73, I^2 = 37%, p = 0.19). An overall small non-significant effect of 0.15 [95% CI, -0.023, 0.52] (p = 0.44) was noted in long-term effects of tDCS in comparison with sham tDCS. Heterogeneity was not found (Q = 2.18, I^2 = 0%, p = 0.53) (Figure 4.3).

Study	**Stimulated region**	**Intensity**	**Sessions**	**Duration**
Andre et al., 2016	Left DLPFC	2mA	4	20 mins
Cotelli et al., 2014	Left DLPFC	2mA	10	25 mins
Khedr et al., 2014	Left DLPFC	2mA	10	25 mins
Suemoto et al., 2014	Left DLPFC	2mA	6	20 mins
Bystad et al., 2016	Temporal cortex (T3)	2mA	6	30 mins

Table 4.4. Methodology's heterogeneity assessment of RCTs.

A) Short term effects of tDCS on memory



B) Long term effects of tDCS on memory

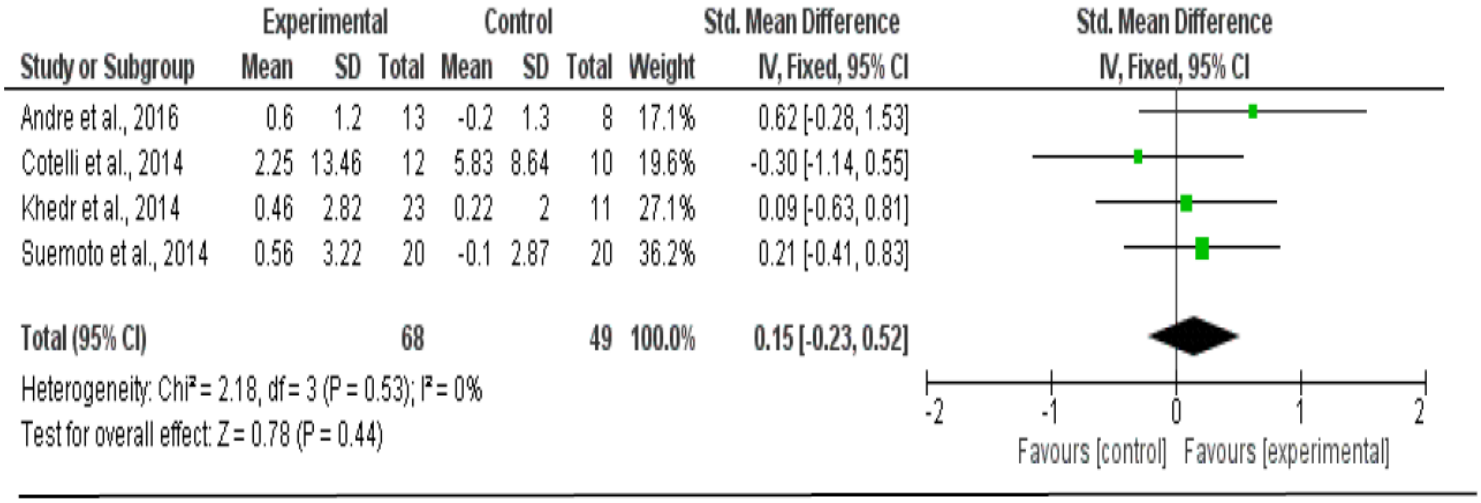


Figure 4.3. Meta-analyses forest plot.

A) Short term effects of tDCS on memory. Data derived from a fixed effect model. Each line represents an individual effect size of each study. The diamond at the bottom shows the standardized effect size (0.39). Relative weight for each trial is illustrated by the sized of the corresponding square.

B) Long term effects of tDCS on memory. Data derived from a fixed effect model. Each line represents an individual effect size of each study. The diamond at the bottom shows the standardized effect size (0.15). Relative weight for each trial is illustrated by the sized of the corresponding square.

4.4. Discussion

All the 11 articles (RCTs) whose evidence was ranked as level 1b presented a commendable methodological quality with a general presence of low risk of bias. From the MMSE admission scores in the AD studies that ranged from 15 to 24.5 and MCI studies from 26.75 to 28.3, we noticed that the effects of tDCS benefits on cognition were significantly better for patients with mild to moderate cognitive decline.

When comparing the effectiveness of tDCS, in single and multisession interventions, positive changes occurred in both behavioral and neural systems. In this systematic review, we aimed to reveal robust interventions by identifying similar elements across studies. One main concern when designing interventions in NIBS is the treatment duration in multisession trials. There is similarity in terms of the number of sessions across the selected studies: four to ten sessions, staggered over one to two weeks. These short interventions can provide valuable data that allow tDCS to be proposed as a potential option in CR. However, the benefit is rather short-term with a medium effect size of 0.39. This also contrasts with other long intervention frameworks for clinical use in which more time is needed to evaluate whether the changes have a real benefit in reversible conditions such as MCI (Portet et al., 2006) or have an impact in long-term neurodegenerative processes such as dementia. For example, an alternative was proposed by Bystad (Bystad et al., 2017) that adopted an eight-month protocol of daily tDCS use in a person with AD to stabilize cognitive decline. The long-term outcome probably requires prolonged periods of intervention.

Although six studies reported side effects (Bystad et al., 2017; Ferrucci et al., 2008; Khedr et al., 2014; Ladenbauer et al., 2017; Murugaraja et al., 2017; Suemoto et al., 2014), all participants tolerated the therapies well and the sensations experienced were mild. This suggests that the parameters employed are sufficiently safe (up to 30 mins, 2mA). Another concern is that the range of the parameters for intensity and duration stimulation and the size of the electrodes were highly diverse, making it difficult to draw conclusions in order to select a specific protocol for future research.

Another view is that when selecting a region of interest for stimulation, most of the studies targeted the temporal regions (Boggio et al., 2012; Bystad, Grønli, et al., 2016; Bystad, Rasmussen, et al., 2016; Bystad et al., 2017; Ferrucci et al., 2008), for the role this area plays in certain memory processes (Brown, Wilson, & Riches, 1987; Kaye et al., 1997) as well as language (Nguyen et al., 2018). Another common region of interest is the DLPFC because of its importance in high-order cognitive mechanisms (Tremblay et al., 2014). Language-oriented work has targeted the inferior frontal gyrus and DLPFC as well, successfully achieving better performance in semantic word retrieval (Meinzer et al., 2015) and comprehension of language (Costa et al., 2017). In the same way, studies that applied tDCS combined with CT operated a CT related with a cognitive domain associated with the brain area targeted by tDCS. Although this approach is reasonable and consistent, the studies failed to assess if other cognitive domains associated with other brain regions were affected. Due to the lack of focality of tDCS and the variability of the current flow direction, there is a possibility that other neural networks, not directly targeted by tDCS, could have been affected (Woods et al., 2016).

Three studies used an extracephalic cathodal montage (Boggio et al., 2012; Cotelli et al., 2014; Ferrucci et al., 2008) but the majority of the studies selected a cephalic montage by placing the cathode on the supraorbital region (Fp2) (André et al., 2016; Boggio et al., 2009; Bystad, Grønli, et al., 2016; Bystad, Rasmussen, et al., 2016; Bystad et al., 2017; Costa et al., 2017; Khedr et al., 2014; Meinzer et al., 2015; Murugaraja et al., 2017; Penolazzi et al., 2015; Suemoto et al., 2014).

Overall, these studies have selected predominantly global cognition and memory domain as experimental evaluators. Despite the fact that these constructs are similar in nature, there is great variability in terms of assessment and CT chosen. All the studies but two (Bystad, Grønli, et al., 2016; Suemoto et al., 2014) report positive effects of the application of tDCS. Against this trend, among the other articles, we must emphasize that only six studies translated these improvements into standardized cognitive assessments (André et al., 2016; Bystad, Rasmussen, et al., 2016; Ferrucci et al., 2008; Khedr et al., 2014; Ladenbauer et al., 2017; Yun et al., 2016) while other studies reporting improvements in non-standardized CT to prove the effects of tDCS. Yet it must be acknowledged that certain cognitive functions are mediated by networks of various brain sites and might be difficult to be influenced by targeting only a subset of their brain regions (Reinhart, Cosman, Fukuda, & Woodman, 2017), besides the short length of the intervention might have contributed to these changes being insufficient to translate into standardized test results.

It is hypothesized that targeting a neural circuit with tDCS paired with a CT may produce stronger therapeutic effects than stimulating the same brain area without cognitive

stimuli (Birba et al., 2017; Cruz Gonzalez et al., 2018). The evidence on whether using tDCS alone or in combination with other CT yields identical results seems to be inconclusive in both PwD or PwMCI. Recently, a single-subject design study using CS practice across sessions in combination with simultaneous anodal tDCS showed significantly stronger effects on planning ability, processing speed, and attention of CS practice than both sham tDCS and the application of CS practice alone in PwMCI (Cruz Gonzalez et al., 2018). This finding prompts the plausible speculation that tDCS, combined with CT, might have synergic effects. A recent review of CR or CT interventions with control conditions for PwD shows that RCTs on the effect of CT on PwD are limited and there is no indication of any significant benefits from CT (Bahar-Fuchs, Clare, & Woods, 2013). Following this line of thought, future studies would carry more weight if they considered combining both interventions in comparison with control groups receiving tDCS or CT alone, and would report not just benefits in the trained CT but also generalization to the trained cognitive domains and daily functioning.

Only five studies reported the use of brain imaging as an outcome demonstrating the neuromodulatory effects of tDCS (Bystad, Rasmussen, et al., 2016; Khedr et al., 2014; Ladenbauer et al., 2017; Meinzer et al., 2015; Yun et al., 2016). In the absence of imaging techniques, we can only speculate on the results of behavioral tests without examining the underlying neural mechanism of tDCS in MCI or dementia.

This is the first meta-analysis to explore the short- and long-term effects of tDCS in the memory domain, targeting the DLPFC in PwD. We have found evidence that tDCS has a significant immediate effect but that it is not significantly sustained with the passage of

time. We suggest that future research address the need to evaluate the long-lasting effects of tDCS on the cognitive domain, implementing both behavioral and imaging FU evaluations.

This study has several limitations. For instance, although the pooled outcomes for meta-analysis were all memory-based, the selected studies used different tests. In addition, only four studies could be included, this may have contributed in making the meta-analyses somewhat underpowered and thus the findings should be interpreted with caution. Another striking example is the AD stage, which varied among the studies. Moreover, we have not included the most recent work published since November 2017 (Cruz Gonzalez et al., 2018), because of the time eligibility criteria. This systematic review included all tDCS trials carried out in dementia and MCI populations, and subsequently reported a few papers that did not use a comparison group (sham tDCS), which weakens the conclusions somewhat.

4.5. Conclusion

Our meta-analysis suggests that there is modest evidence supporting tDCS on the DLPFC ameliorates memory in PwD, however, the benefits are not long-term. Our review shows that tDCS alone seems to have a positive effect on cognition particularly for memory and language in PwD, with mild to moderate cognitive decline, and MCI. Whether tDCS might produce better outcomes on PwMCI and PwD in coupling with another CT than when administered alone remains unclear.

Although all these findings are promising, the administration of tDCS might not yet be a valid option for clinical intervention for dementia or MCI. Some of the results come from non-RCT studies, and the heterogeneity of the clinical trials does not allow one to define a clear protocol with optimal parameters. Furthermore, the interventions were too short to determine the real effects on cognitive functions and none of the studies assessed the impact of treatments on everyday cognition in daily functioning, which is an essential domain to be considered due to the functional consequences of dementia. We recommend that future studies include prolonged periods of intervention, neuroimaging techniques, and consider more robust, standardized methodology of tDCS in order to establish whether tDCS can serve as an evidence-based clinical intervention for PwMCI and PwD.

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CHAPTER 5: THE EFFECTS OF TRANSCRANIAL DIRECT CURRENT STIMULATION ON THE COGNITIVE FUNCTIONS IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT: A PILOT STUDY

This chapter reports on the first experiment carried out after reviewing the evidence for the fundamentals and operation of tDCS and CT and understanding the characteristics of both the ageing and cognitively impaired population, all as explained in the previous chapters. This section of the thesis helps to put into practice these theoretical concepts and set a new focus through which to integrate the ideas that have been formulated into the experimental research.

The chapter starts by briefly explaining the concept of MCI and NPT and their potential use in persons who are on the cognitive impairment spectrum, with particular reference to tDCS and computerized CS. The pilot study adopted a single-subject design in which five older adults with MCI underwent four different phases in the pattern A-B-C-A (baseline of CS practice, sham tDCS combined with CS practice, tDCS combined with CS practice, and baseline again). The outcomes consisted of accuracy performance measures from the CS practice, which were visually compared across phases in the form of charts. Standardized cognitive assessments were also recorded between phases and tabulated. The chapter concludes with a discussion of the performance trends identified, a comparison with the literature, the conclusions of the pilot and suggestions for future research.

The overall aim of the chapter is to provide the reader with research alternatives to study the potential combination of tDCS and CT and set out a basis for developing future large-scale RCTs in this field.

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5.1 Introduction

MCI is a syndrome of cognitive decline below the typically expected age norm in an individual. It is commonly referred to as an intermediate phase between the expected cognitive decline of normal aging and the pathological cognitive decline linked to dementia and usually does not interfere with daily activities (Petersen et al., 1999). There is a difference between MCI and a formal diagnosis of dementia: the latter represents a more severe cognitive decline and has a substantial negative impact on daily functioning (Gauthier et al., 2006). In some cases, MCI will revert to normal cognition or remain stable. Only an insignificant proportion of people presenting with known MCI, 12–15% per year, will gradually worsen and develop dementia, compared to 1-2% of the general population; approximately, 40–65% of patients with MCI will eventually progress to AD (Petersen et al., 1999).

Regarding possible interventions to tackle MCI, there is a lack of evidence for pharmacological interventions that can prevent cognitive decline or conversion to dementia. To date, drugs have proved to have no positive impact in MCI trials (Langa & Levine, 2014). As a form of non-pharmacological intervention, CR is defined as:

> "The therapeutic process of increasing or improving an individual's capacity to process and use incoming information so as to allow increased functioning in everyday life. This includes methods to train and restore cognitive function and compensatory techniques" (Sohlberg & Mateer, 1989, p. 871).

One type of CR is CS which has been used as a potential intervention to slow down

the deterioration of cognitive functions in people presenting with known MCI. According to the largest RCT of cognitive intervention carried out with older adults to date, the experimental treatment approaches used in this study support the improvement of targeted cognitive areas in different groups in comparison to the control group, which did not receive any kind of intervention (Ball et al., 2002). Contrary to conventional cognitive tasks that are performed with paper-and-pencil with a lack of simultaneous feedback, computerized CS is designed to be more enjoyable and engaging based on human-computer interaction (Faria, Andrade, Soares, & Badia, 2016; Hill et al., 2017). These CS strategies have also been shown to improve performance after repetition of computerized CT tasks in older adults presenting with known MCI (Finn & McDonald, 2011). A systematic review found evidence of memory and executive function enhancement while analyzing the effects of non-pharmacological interventions on cognitive functions in older people presenting with known MCI (Olazarán et al., 2010). However, the appropriate protocol and optimal frequency for inducing benefits in the cognitive functioning of this population remain unknown.

tDCS is another type of non-pharmacological intervention that uses direct electrical currents to stimulate specific parts of the brain. It involves delivering a noninvasive weak direct current (1-2 mA) through at least two electrodes, at least one of which is placed on the scalp for a period of a few seconds to 20–30 minutes, which modulates neuronal activity. There are two types of stimulation: anodal stimulation acts to excite neuronal activity and cathodal stimulation has hyperpolarizing effects, inhibiting neuronal activity (Nasseri, Nitsche, & Ekhtiari, 2015; Nitsche et al., 2008). As soon as tDCS is

administered, the current travels in an anode-cathode circuit which is likely to cause neurons to fire in stimulated areas (Nitsche et al., 2008).

Priming is the change in repetitive behavior due to implicit learning based on previous stimuli (Hauptmann & Karni, 2002), and it has recently been used for inducing neuroplasticity and enhancing the effects of conventional rehabilitation as combined approaches (Stoykov & Madhavan, 2015). The excitability modulation induced by tDCS is considered a potential intervention to modulate the learning processes (Nitsche et al., 2007). tDCS boosts subthreshold neuronal action potentials beyond their unaugmented state, thus, may achieve stronger firing patterns than would occur in the absence of tDCS. Although, repeated practice with cognitive stimuli in CS may elicit unintentional learning, mechanisms that circumvent cognitive impairments, targeting a neural circuit with tDCS whereas it is simultaneously engaged by a CS task, may produce better therapeutic effects than stimulating the same cortical area in the absence of cognitive stimuli (Birba et al., 2017; Miniussi, Harris, & Ruzzoli, 2013). tDCS may augment the strength of transmission across synaptic circuits in pathways that are stimulated by cognitive practice, and thus it may also strengthen the circuits that are formed through unintentional, practice-related learning and maximize the possibility of enduring behavior change through such implicit learning. Given that CS and tDCS can enhance plastic changes, the combination of both techniques could cause a better synergistic positive effect on behavior (Birba et al., 2017; Ditye, Jacobson, Walsh, & Lavidor, 2012). Indeed, it has been shown that anodal stimulation of the left DLPFC increases the performance of a sequential-letter working memory task in healthy young adults (Fregni

et al., 2005). Recent research also indicates that healthy older adults can benefit from tDCS, enhancing retention skills of object-location learning a week after completion of the object-location task compared to participants who took part in a tDCS sham condition (Flöel et al., 2012). There is growing evidence that tDCS coupled with CS improves cognitive performance. After ten sessions of a working memory CS in combination with tDCS, healthy adults experience an enhanced effect and perform CS tasks more accurately than those who received sham tDCS (Martin et al., 2013).

The impact of tDCS has also been explored for AD, fronto-temporal dementia, and mild vascular dementia. Positive effects were found in visual recognition memory tasks in persons with AD when applying anodal tDCS to the left temporal cortex (Boggio et al., 2009). Results after five consecutive sessions over five days in which anodal tDCS was applied over both hemispheres of the temporal cortex and an extracephalic cathodal tDCS (for a 30-minute period using 2 mA) showed significant improvement in the performance of a visual recognition memory test (Boggio et al., 2012). In a more recent study that involved participants presenting with mild vascular dementia, four consecutive day sessions of anodal tDCS (for a 20-minute period using 2 mA) on the left DLPFC generated positive additional effects on visual short-term memory, verbal working memory, and executive control (André et al., 2016).

The beneficial effects of tDCS on cognition in people presenting with known MCI have been demonstrated (Meinzer et al., 2015); however, the literature on using tDCS on people presenting with known MCI is still very limited. The frequency and targeted areas are not the only significant issues that remain unknown. To optimize the positive and

therapeutic benefits of NIBS, it is also worth investigating the uncertainty of combining tDCS with conventional behavioral treatments such as a CS that might also yield more information and understanding about the impact of tDCS effects for people at risk of MCI.

Based on the above background information, we considered the use of anodal tDCS on the left DLPFC (30 minutes 2 mA) with an extracephalic return electrode to be a promising and safe intervention approach to optimize the impact of CS on tablet PCs for older adults at risk of MCI. The current study aimed to compare the impact of anodal and sham tDCS applied to the left DLPFC on the cognitive performance of people at risk of MCI engaging in CS interventions on tablet PCs. We hypothesized that there would be a significant improvement in cognitive task performance after the use of tDCS, which would subsequently generalize to other cognitive domains; short-term memory, planning ability, working memory, attention, and processing speed skills. We also aim to determine the optimal frequency of tDCS application with the same dosage to improve the cognitive skills of older adults with MCI.

5.2 Material and methods

5.2.1 Participants

Five older adults with MCI were recruited by convenience sampling from community center groups in Hong Kong. The inclusion criteria followed the modified Petersen's criteria (Portet et al., 2006) (given by the MCI Working Group of the European

Consortium on Alzheimer's Disease, Brescia Meeting, Italy, June 2005). Participants had to (a) be aged between 60 and 85; (b) obtain a score between 19 and 26 on the MoCA (Nasreddine et al., 2005); (c) achieve a score of 0.5 or below on the CDR (Morris, 1991); (d) self-report cognitive decline; (e) be independent in daily living activities; and (f) have completed three or more years of primary education.

Regarding exclusion criteria, the following were excluded: (a) individuals presenting with a diagnosis of dementia or any other neurological disease and mental disorders; (b) individuals with depression, determined by a score of 5 or above on the GDS-15 (Lim et al., 2000); and (c) individuals who had metallic fixtures around the cephalon.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the human subject ethics committee of The Hong Kong Polytechnic University (ref. number: HSEARS20160415002). All participants gave informed written consent before the intervention began.

5.2.2 Design

This study utilized a prospective, single-subject design (SSD) with multiple nonconcurrent treatments; anodal tDCS + CS, sham tDCS + CS, and CS only. A four-phase A-B-C-A SSD was employed. After the baseline with the administration of CS (phase A), a sham tDCS with CS was applied (B). Following the withdrawal of this sham treatment, a tDCS treatment was introduced in combination with CS (C). Finally, phase A was replicated to provide the control needed to document the differences between the sham and tDCS phases (Figure 5.1).

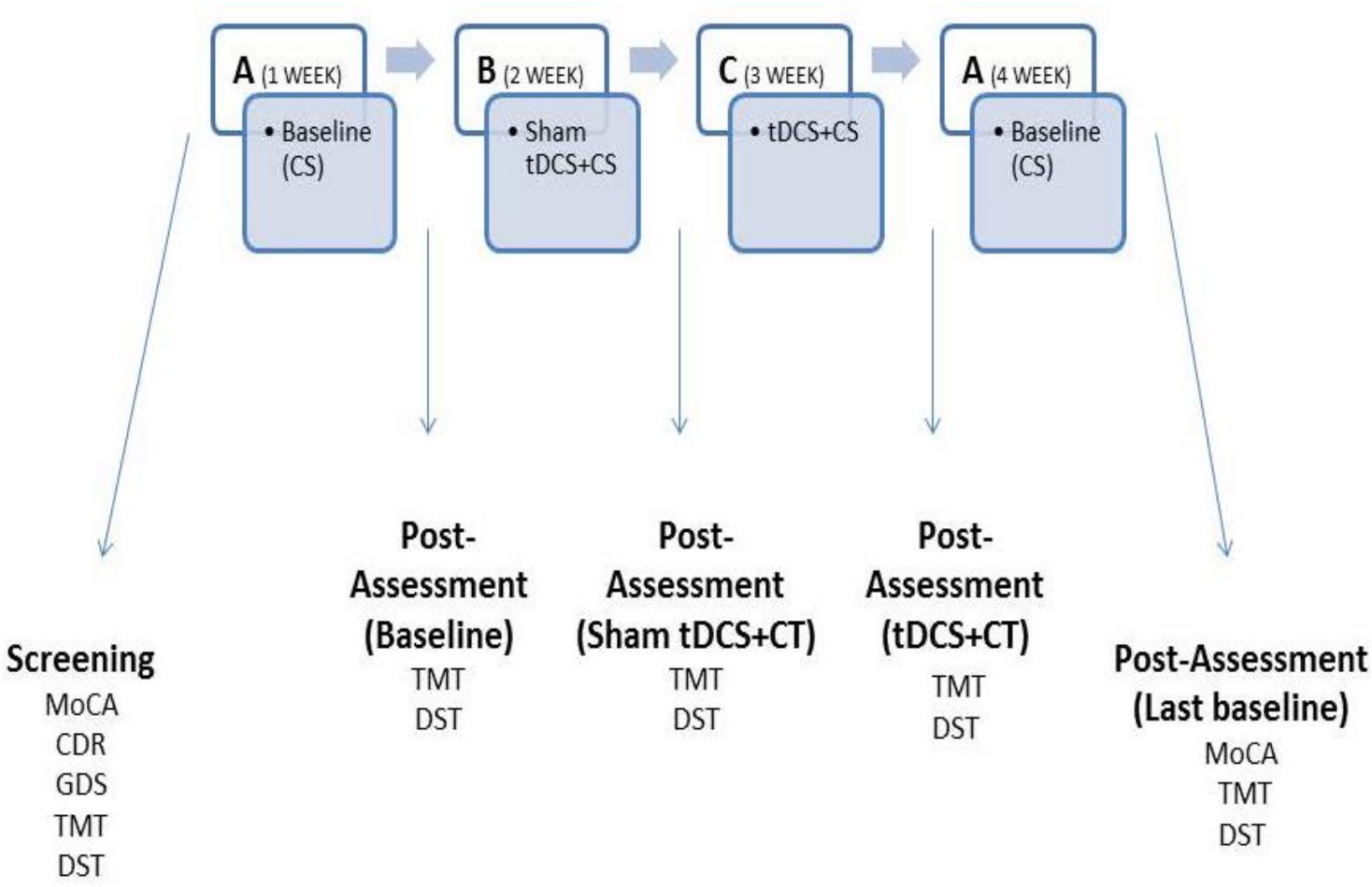

Figure 5.1. Intervention sequence. A-B-C-A design.

In this design, it is assumed that both treatments B and C have differential and independent effects. Differences in the target responses are expected across the four phases of the study. The sham phase (B) was the first treatment intervention to be used to avoid possible carryover effects due to the tDCS stimulation treatment (i.e., phase C), thereby eliminating this potential treatment effect, which can be analyzed during the last

baseline (A).

5.2.3 Cognitive training

“Neuron Up” was the computerized CT and CS system administered to participants. It is a web platform (https://www.neuronup.com/) designed to serve as a fundamental support for professionals involved in CR and CS (de Piérola, 2015). The display format was full screen in a 9.7-inch screen iPad situated on a desk approximately 35 centimeters in front of the participant. Participants’ individualized level was identified through two training sessions that were conducted for all the participants prior to the implementation. Five cognitive activities associated with different cognitive domains were selected:

Sorting bugs: This task is associated with planning ability and divided attention. Participants are asked to move a bar located in the middle of the screen either to block the movement of bugs which are moving in different directions or to let them pass from one side to the other. The final goal is to keep the green bugs on the green side and the red bugs on the red side. Participants are allowed seven minutes to complete the task, and the completion time is measured. This task also trains sustained and selective attention.

The last light on: This task is associated with processing speed and selective attention. Participants are asked to pay attention to the windows in a building that light up. They have to touch the window which is the last to light up. This task is repeated five times per session, and the number of correct answers and completion time are measured.

Illuminated windows: This activity is associated with short-term memory. Participants are asked to remember which windows are illuminated in a building in an open memorization period. Then, all the lights are turned off and participants must identify the windows that had been lit. This activity is repeated five times. The number of correct answers, number of errors, memorization time, and completion time are measured.

Addition and subtraction questions. Both tasks are associated with calculation and working memory. Participants are given three addition operations involving four numbers of six digits each and six subtraction operations with two numbers of six digits each to solve. The number of errors and the completion time are measured.

These five cognitive activities were presented as a CS practice with one-to-one supervision from an occupational therapist in which all participants were exposed to repetitive testing via the computer system across sessions.

5.2.4 Transcranial direct current stimulation

The Soterix Medical 1 × 1 low-intensity tDCS stimulator was the device used to provide the stimulation. The two rubber electrodes employed for tDCS in this study were introduced in saline-soaked synthetic sponges (7 × 5 cm, 35 cm2). Anodal tDCS was delivered to the left DLPFC, and the cathode electrode was placed over the contralateral deltoid muscle as extracephalic cathode. The scalp electrode was positioned over F3 according to the 10–20 EEG international system. The left DLPFC was targeted as the stimulation site because of its role in high-order cognitive processes (Tremblay et al., 2014) and due to the existence of functional disconnection of the

DLPFC in persons with MCI (Liang, Wang, Yang, Jia, & Li, 2011). A constant current of 2 mA was applied for 30 minutes. For sham tDCS, the 2 mA intensity was only given for 30 seconds at the beginning and the end of the stimulation.

5.2.5 Experimental protocol and procedures

Each interval (A, B, C, and A) was staggered by a week at a time. During the baseline phases, three sessions of CS were implemented for all the participants. Both interventions, sham tDCS and anodal tDCS, were combined with the same CS that was performed for the baseline phases. However, the treatment phases varied from one to five sessions. The sessions per phase were distributed over five days. Participants were randomly assigned to combinations of intervention each of which had a different time span to compare the treatment frequency effect (Table 5.1).

The experimental sessions were 30 minutes in length. In this way, tDCS was administered for 30 minutes and the CS was begun five minutes after the tDCS began, thus running for 25 minutes. For the sham phase, the administration of the sham tDCS lasted 30 minutes too, with the difference that a ramping current of 2 mA was applied during the first and last 30 seconds. The participants remained blinded for both stimulation conditions.

Participant	Demographics			Inclusion assessment scores					Number of sessions conducted in every interval by week			
	Age	Gender	Medical history	MoCA pre-intervention	MoCA post-intervention	MoCA gain (%)	CDR	GDS	1st week (A) CT alone	2nd week (B) sham tDCS+CT	3rd week (C) anodal tDCS+CT	4th week (A) CT alone
1	79	Female	Heart disease	24	26	6.66	0.5	3	3	1	1	3
2	68	Female	NA	24	25	3.33	0.5	1	3	2	2	3
3	67	Male	NA	24	29	16.6	0.5	1	3	3	3	3
4	69	Male	Diabetes	25	26	3.3	0.5	1	3	4	4	2
5	81	Male	Diabetes	26	27	3.3	0.5	2	3	5	5	3

Table 5.1. Demographics, inclusion criteria scores and number of sessions conducted in every interval by week.

5.2.6 Cognitive measures

CS data were recorded for each task of each cognitive activity during the sessions. Data such as completion time and performance in terms of correct answers or number of errors were collected.

The standardized cognitive assessments used in this study for screening were the CDR (Hong Kong Version), and the scale was found to have good reliability with internal consistency ranging from 0.7 to 0.9 (Chan, Choi, Chiu, & Lam, 2003), the GDS-15 item which has a satisfactory reliability with Cronbach alpha = 0.82 (Lam & Boey, 2005), and the MoCA (Hong Kong Version) with a sensitivity of 90% to detect MCI (Nasreddine et al., 2005; Wong et al., 2009). The standardized cognitive measures to assess the study phases included the MoCA (Hong Kong version) (Wong et al., 2009), the digit span test (DST) (Wechsler & De Lemos), and the Trail Making Test ((TMT) Chinese version) which normative data has provided evidence that the part B (Chinese version) may be equivalent to the standard part B (Lu & Bigler, 2002).

The participants were assessed in five phases: screening (pre-A), after baseline (post-A), after first intervention (post-B), after second intervention (post-C), and after final baseline (post-A).

To summarize, DST and TMT were conducted before the initial baseline and after each interval. However, the MoCA was only administered before the first baseline and after the last for a general comparison of the whole sequence and to avoid learning effect due to repeated testing (Figure 5.1).

5.2.7 Data analysis

To study the effects of tDCS on the “Neuron Up” computerized CS program across the design phases, visual analysis and two standard deviation procedures were used as analytical methods.

Visual analysis was based on observing the visual patterns presented in the graphs where the target parameter changed once the treatment was introduced or withdrawn. Difference in means among phases was also compared.

In the two standard deviation procedure, the levels of the baseline are compared to those of the intervention data points. The procedure assumes that if we are to extend the baseline, then ultimately 95 percent of our observations would be less than two standard deviations away from the baseline mean. The two standard deviations were calculated manually following the guidelines set out by Rubin and Babbie (Rubin & Babbie, 2005). Data analyses of the cognitive assessments administered before the commencement of the baseline and after every single interval were compared.

5.3 Results

Although all five participants did well in the tDCS intervention, redness in the area was observed after removing the electrodes in one participant, and he also complained of having a mild headache a few hours after receiving the therapy. The remaining participants reported a tingling sensation in the DLPFC region during the stimulation

phase which faded away after a few minutes of the onset of the stimulation. They completed all sessions as scheduled, with the exception of one participant who was not available to complete the last session of the last baseline.

5.3.1 Cognitive training outcomes

The results are presented in graphs in the sequence in which the CS tasks were performed and following the order from fewer to more treatment sessions received. The x-axis corresponds to the observation points (the number of tasks) per day. The y-axis represents either the performance or the time taken to complete the task. The blue line is the measurement of the targeted problem across observation points. There were four intervals for each condition: (A) baseline, (B) sham tDCS intervention, (C) tDCS intervention, and (A) baseline. Every single black line which crosses every interval is the mean of the performance, and the two standard deviations are marked by a black dotted line starting at the corresponding interval.

Sorting bugs (Figure 5.2): All participants demonstrated fluctuating times of completion during the first baseline phase. There are positive effects for those subjects who received three or more tDCS sessions (participants 3, 4, and 5) with a general slight increase in time required to complete the task after withdrawal of the tDCS intervention, and a difference by more than two standard deviations was observed at the last baseline phase of participant 3.

The last light on (Figure 5.3): Figure 5.3 shows that there were differences by more than two standard deviations in participants 1, 3, and 5. With respect to the baselines and

sham phases, all participants exhibited decreasing accuracy in the cognitive task in comparison with the experimental interval, except for participant 4, but no significant difference was found.

Illuminated windows (Figure 5.4): Despite all participants exhibiting similar outcomes in all phases, there is a slight general improvement in task performance across conditions, but no significant difference was found.

Addition question (Figure 5.5): Participants 1, 2, 3, and 4 demonstrated a clear intervention effect of tDCS administration, but no significant difference was found. Participants made fewer errors in operations when the tDCS was applied. However, participant 5 performed differently, reducing the number of errors after the sham tDCS intervention and especially achieved the best performance during the last baseline phase.

Subtraction question (Figure 5.6): The outcomes of these operations were similar to the addition questions, but the change in level was not very pronounced. Participants 2, 3, and 5 were more accurate, solving the operations during the tDCS treatment, and the tendency during the baseline and sham phases was associated with a larger number of errors, but no significant difference was found. For participants 1 and 4, the results were almost identical across conditions.

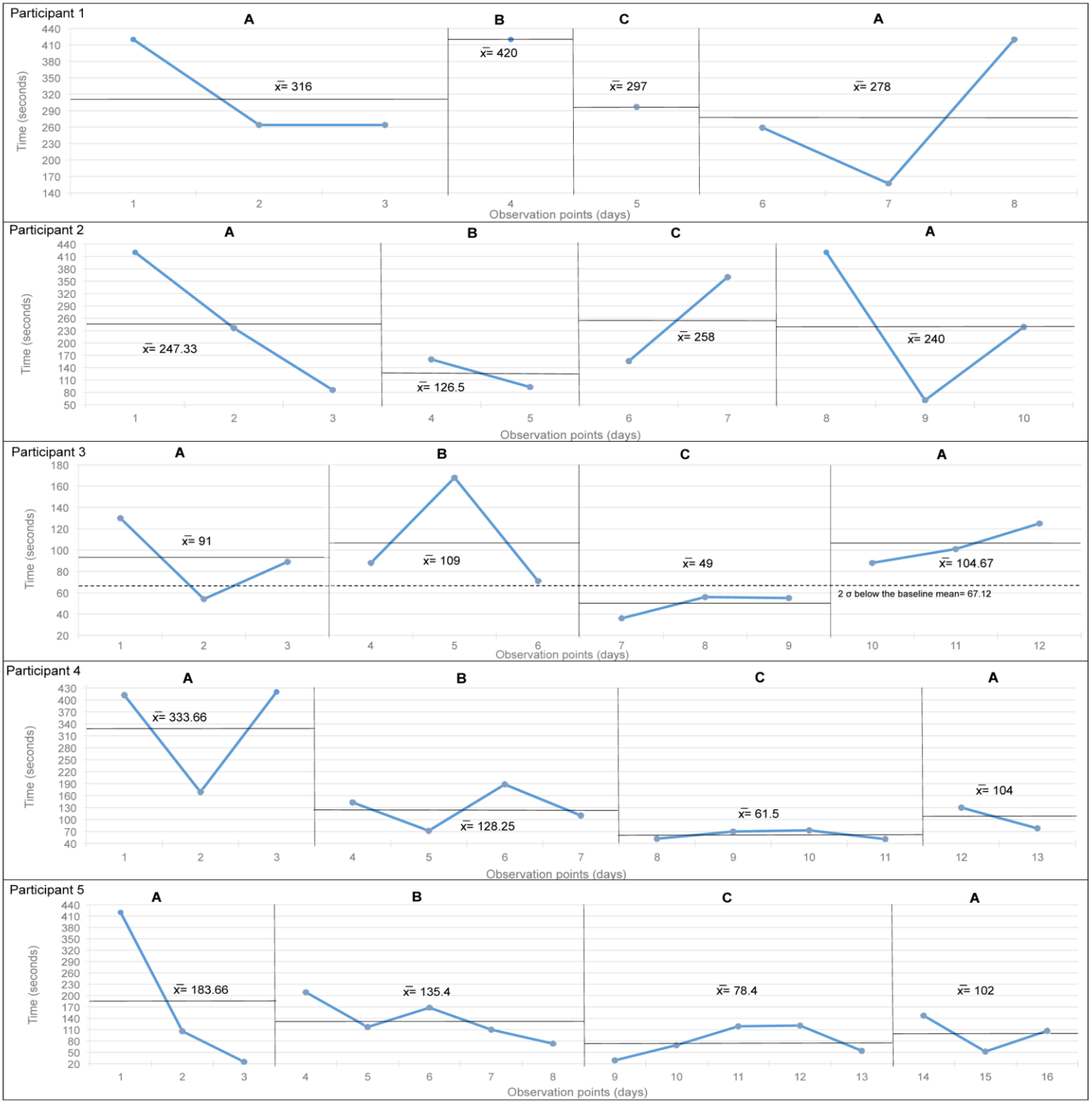

Figure 5.2. Sorting bugs. Note: A: baseline; B: sham tDCS; C: tDCS; x-axis: observation points in days; y-axis: completion time in seconds. Scores are shown, along with black lines marking the average of each phase and with a black dotted line starting at the corresponding baseline marking 2-standard deviation (2 σ) when there is statistically significant difference (participant 3).

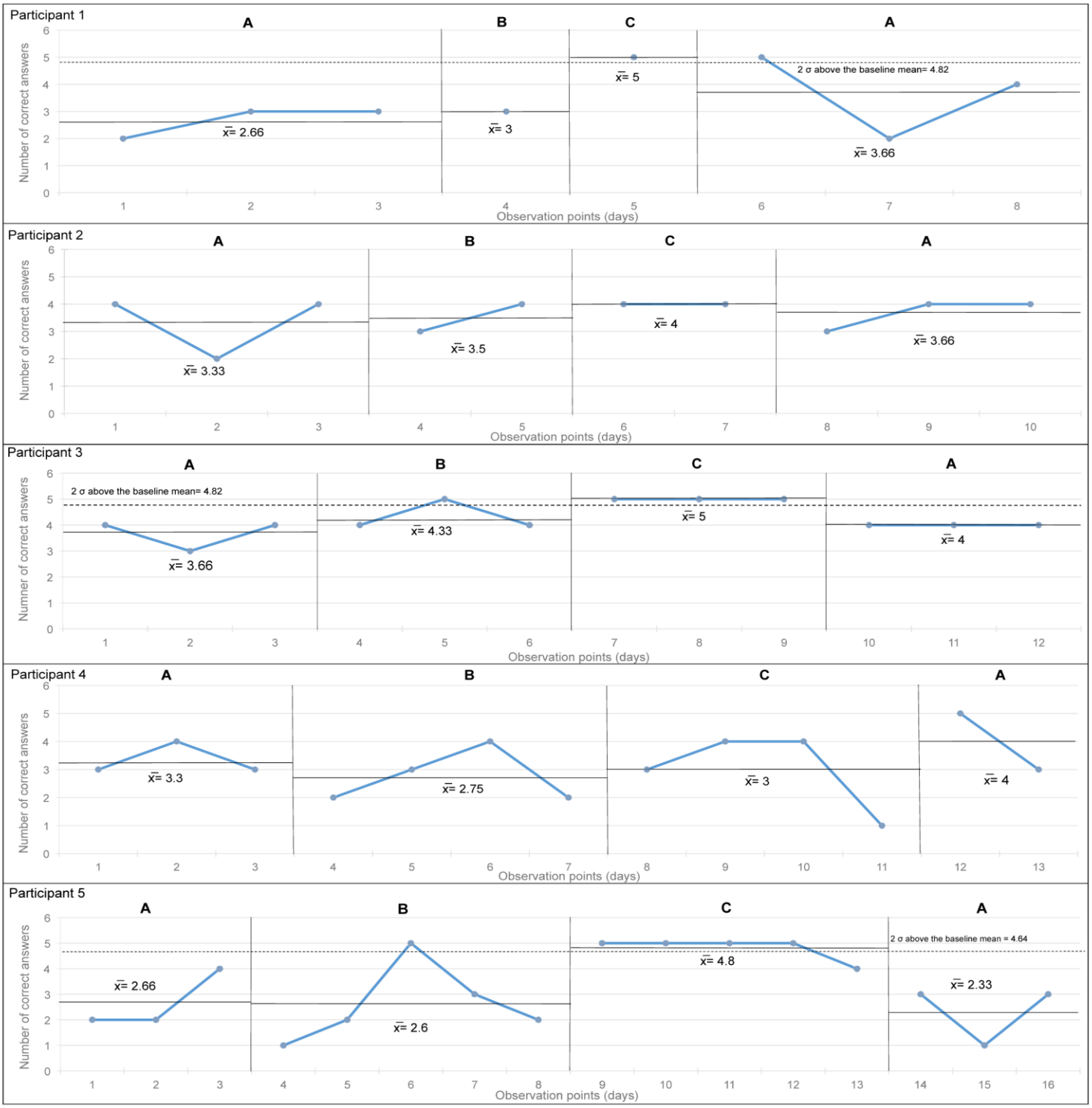

Figure 5.3. The last light on. Note: A: baseline; B: sham tDCS; C: tDCS; x-axis: observation points in days; y-axis: number of correct answers. Scores are shown, along with black lines marking the average of each phase and with a black dotted line starting at the corresponding baseline marking 2-standard deviation (2 σ) when there is statistically significant difference (participants 1, 3, and 5).

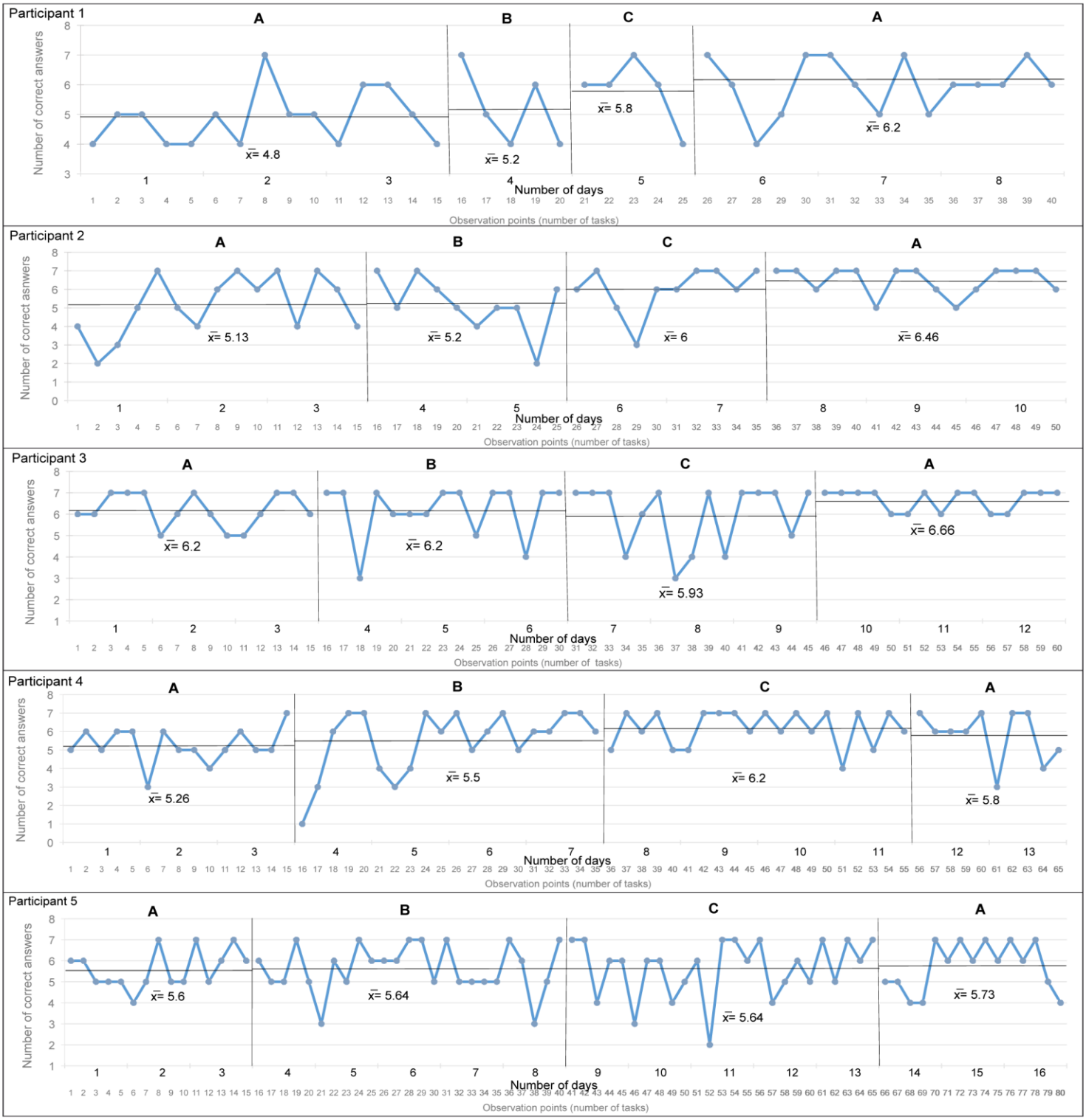

Figure 5.4. Illuminated windows. Note: A: baseline; B: sham tDCS; C: tDCS; x-axis: observation points in number of tasks performed within days; y-axis: number of correct answers. Scores are shown, along with black lines marking the average of each phase.

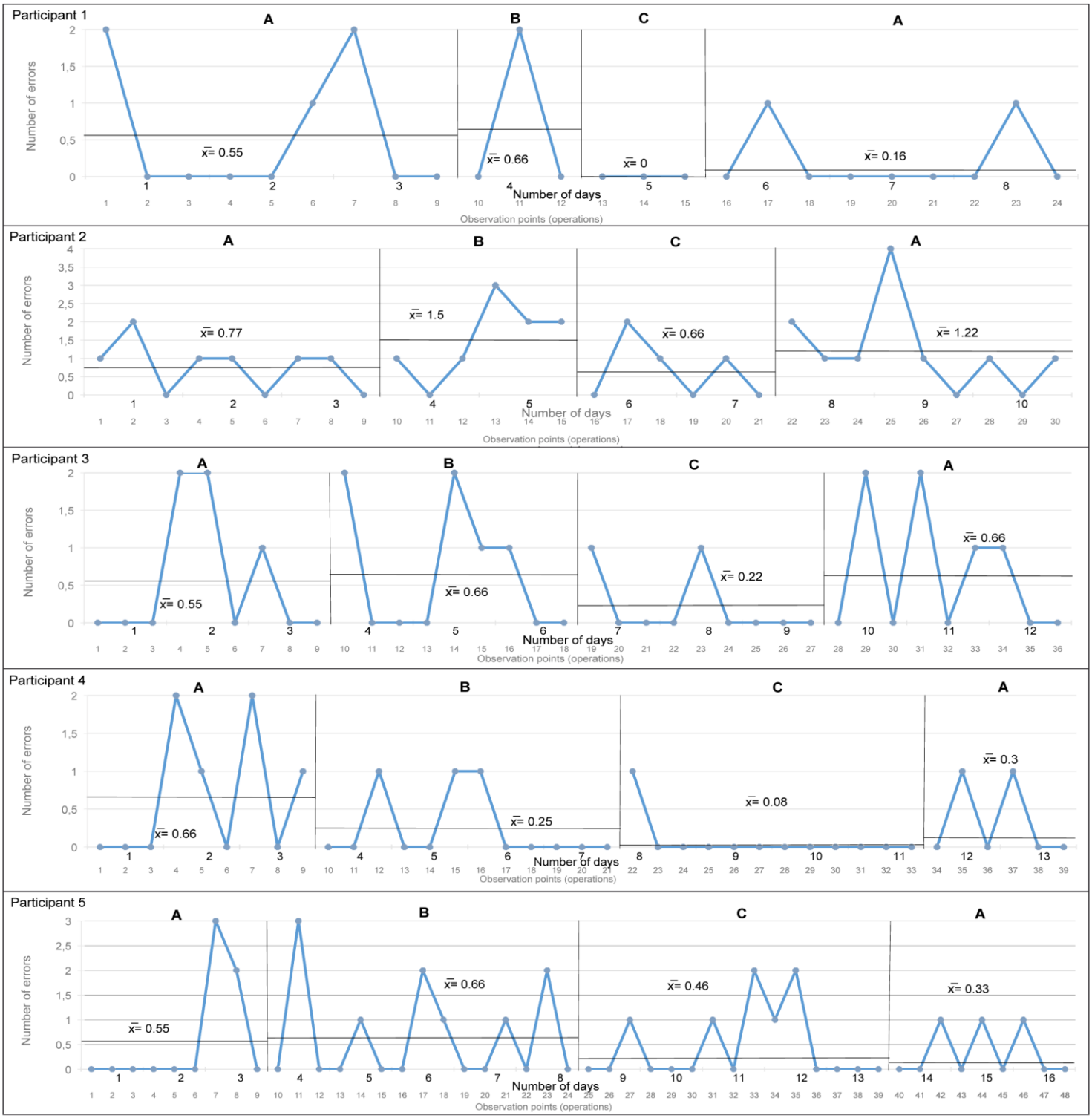

Figure 5.5. Addition question. Note: A: baseline; B: sham tDCS; C: tDCS; x-axis: observation points in number of tasks performed within days; y-axis: number of errors. Scores are shown, along with black lines marking the average of each phase.

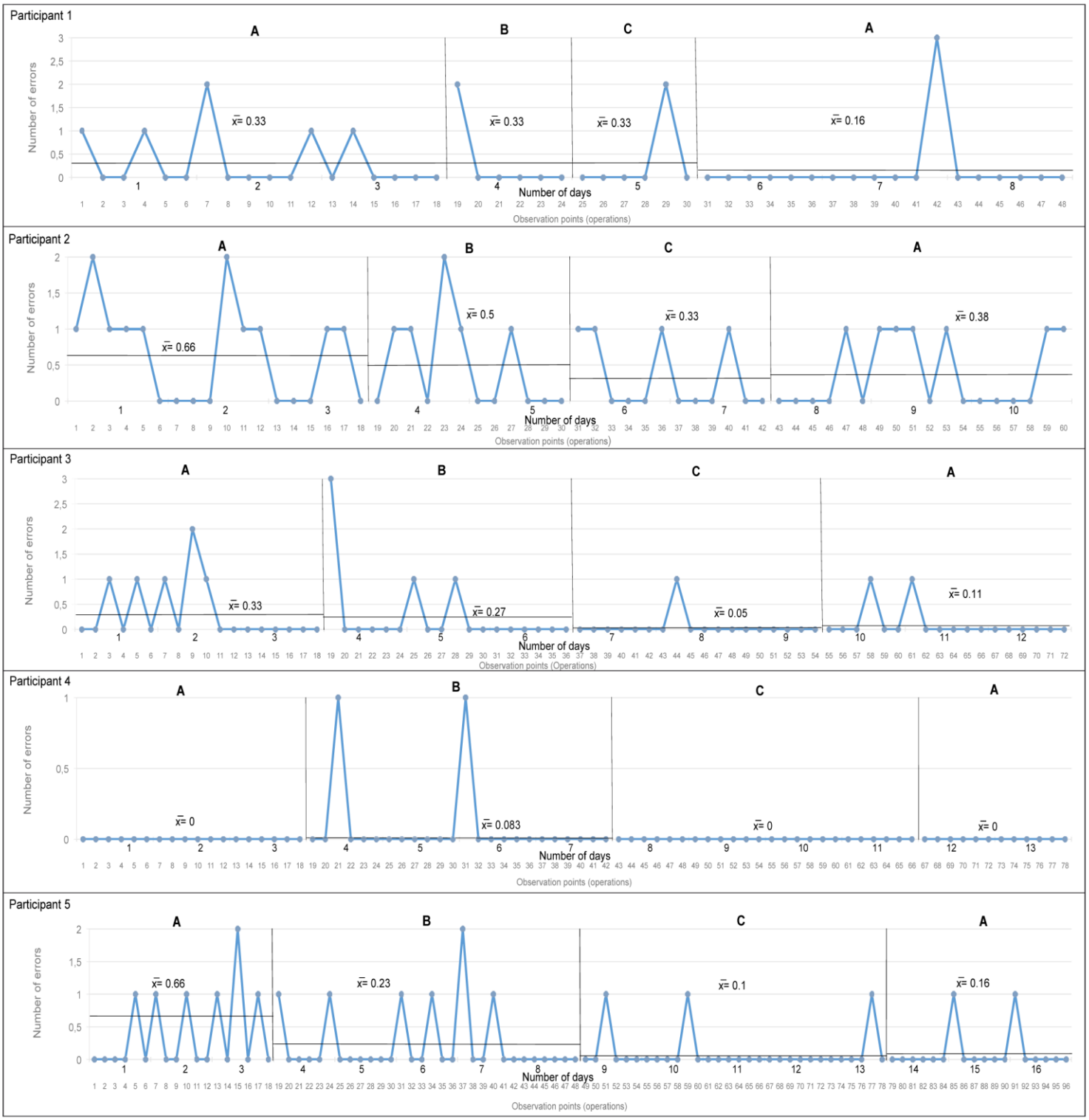

Figure 5.6. Subtraction question. Note: A: baseline; B: sham tDCS; C: tDCS; *x*-axis: observation points in number of tasks performed within days; *y*-axis: number of errors. Scores are shown, along with black lines marking the average of each phase.

5.3.2 Behavioral assessment outcomes

All participants showed an improvement in MoCA scores. Participant 3 showed the largest improvement (Table 5.1).

Participants 1 and 4 demonstrated the greatest impact of the tDCS as revealed by the shortest completion time in the TMT (parts A and B) right after the last session of the tDCS intervention. The negative ratio shown in Table 5.2 indicates a shorter time taken to complete the task after tDCS relative to sham tDCS. Participant 3 also improved during phase B and participant 5 during phase A (Table 5.2).

Participant	Trial Making Test	Baseline	After first baseline (A1)	After sham tDCS (B)	After tDCS (C)	After last baseline (A2)	Immediate effect (seconds) (C vs. Baseline)	After-effect (seconds) (A2 vs. C)	tDCS vs. Sham tDCS (seconds) (C vs. B)
1	Part A	58.82	58.45	51.53	44.48	55.69	-14.34	10.81	-6.82
	Part B	109.74	87.22	67.7	60.52	67.45	-49.22	6.93	-7.18
2	Part A	38.46	38.4	32.92	41.34	28.03	2.88	-13.31	8.42
	Part B	55.45	83.04	75.73	56.55	64.77	1.1	8.22	-7.31
3	Part A	26.35	22.68	22.91	20.86	15.53	-5.49	-5.53	-2.05

	Part B	42	44.92	29.68	26.73	27.13	-15.87	0.4	-3.25
4	Part A	32.48	40.16	56.12	28.08	51.93	-4.4	23.85	-28.04
	Part B	51.6	56.23	51.5	42.35	56.74	-9.25	14.39	-9.15
5	Part A	37.58	50.4	43.76	38.48	46.55	-0.9	8.07	-5.28
	Part B	57.42	40.55	71.42	52.65	50.15	-4.77	-2.5	-18.77

Table 5.2. Trail making test score. Note: Immediate effect (C versus baseline) is the gain in seconds after the application of tDCS compared with the baseline; after-effect (A2 versus C) is the maintenance or gain in seconds after tDCS withdrawal in phase C; tDCS versus sham tDCS (C versus B) is the comparison between tDCS and sham tDCS. A positive ratio implies decrement, a neutral ratio implies maintenance, and a negative ratio implies improvement in terms of time of completion.

All participants improved in their DST scores when comparing the baseline to the last assessment. The trend shows that improvement follows a general and steady progressive pattern without obvious significant changes (Table 5.3).

Participant	Digit Span Test	Baseline	After first baseline (A1)	After sham tDCS (B)	After tDCS (C)	After last baseline (A2)	Immediate effect (%) (C vs. Baseline)	After-effect (%) (A2 vs. C)	tDCS vs. Sham tDCS (C vs. B)
1	Forward Score	15	16	16	15	16	0	3.33	-3.33
	Backward Score	6	8	10	8	9	6.66	3.33	-6.66
	Total Score	21	24	26	23	25	6.66	6.66	-9.99
2	Forward Score	14	15	14	15	16	3.33	3.33	3.33
	Backward Score	5	5	7	6	8	3.33	6.66	-3.33
	Total Score	19	19	21	21	24	6.66	9.99	0
3	Forward Score	14	16	16	16	16	6.66	0	0
	Backward Score	9	9	9	9	13	0	13.32	0

	Total Score	23	25	25	25	29	6.66	13.32	0
4	Forward Score	16	16	16	16	16	0	0	0
	Backward Score	7	8	5	8	8	3.33	0	9.99
	Total Score	23	24	21	24	24	3.33	0	9.99
5	Forward Score	13	16	16	16	16	9.99	0	0
	Backward Score	4	4	5	7	5	9.99	-6.66	6.66
	Total Score	17	20	21	23	22	19.98	-3.33	6.66

Table 5.3. Digit span test score. Note: Immediate effect (C versus baseline) is the gain (%) after the application of tDCS compared with the baseline; after-effect (A2 versus C) is the maintenance or gain (%) after tDCS withdrawal in phase C; tDCS versus sham tDCS (C versus B) is the comparison in terms of gain (%) between tDCS and sham tDCS. A positive ratio implies improvement, a neutral ratio implies maintenance, and a negative ratio implies decrement in terms of accuracy.

5.4 Discussion

This pilot study combined anodal tDCS with CS to investigate their impact on the cognitive performance of older adults with MCI. The result shows that application of anodal tDCS to the left DLPFC and cathodal tDCS to the right deltoid muscle helps to enhance cognitive performance in processing speed, selective attention, and working memory activities, as well as the completion time in planning ability and divided attention tasks. One of the objectives of this study was to compare anodal tDCS and sham tDCS. Although the data generated with CS fluctuated and were variable, the participants did not show significantly better outcomes in the sham intervention than the baseline CS alone.

This was the first study of its kind to show mild benefits in multiple domains of cognition in older adults with MCI as other studies have focused on the possible benefits of tDCS in a single cognitive domain, usually working memory (Fregni et al., 2005; Ohn et al., 2008; Stoykov & Madhavan, 2015).

Placement of an anodal tDCS on the left DLPFC and a cathodal tDCS on the right deltoid muscle did not increase participants' performance in the short-term memory CS task. This agrees with previous studies that applied the same montage as the current study in combination with memory training in persons suffering from AD and which also observed no significant additional effect of tDCS on memory performance beyond that of sham tDCS with the same memory training (Cotelli et al., 2014).

Our study adopted extracephalic cathodal tDCS, which eliminated the confounding

effect of a monocephalic cathode electrode placed on the scalp. Our findings are also in line with the study conducted by Boggio and colleagues (Boggio et al., 2012) in which the return electrode was extracephalic and placed over the right deltoid muscle in people presenting with AD. The use of a monocephalic cathode setup has been controversial because:

> "Current flow direction/electrical field orientation relative to neuronal orientation might determine the effects of tDCS and it might be that the effects of an extracephalic electrode differs relevantly from that of a bipolar electrode arrangement" (Brunoni et al., 2012, p.179).

Monocephalic cathodes are also common in studies, but that does not mean that the return electrode is physiologically inert, since its positioning does have a critical impact on the electrical field orientation (Stoykov & Madhavan, 2015). Notwithstanding, we are confident that the electrical current passes through the stimulated brain area, the left DLPFC, when applying tDCS. With the same cathode montage, both our study and that of Boggio and colleagues (Boggio et al., 2012) indicate a significant improvement in visual recognition after the administration of multisession tDCS.

It is disappointing that all these positive CT findings are somewhat inconsistent with the results of standardized cognitive assessments, except for the TMT, in which most of the participants showed their best score of the tDCS intervention in all phases. Interestingly, TMT could be an indicator of processing speed (Salthouse, 2011) and visual selective attention domains (Spikman, Kiers, Deelman, & van Zomeren, 2001), which might also

correspond to the CS task improvement associated with these domains.

Despite our aim to determine the optimal frequency of tDCS application with the same dosage by modifying the number of sham tDCS and tDCS sessions among participants, the findings appear to be inconclusive. In some occasions, just one session of tDCS was sufficient to produce positive changes in performance while other participants who had up to five sessions of tDCS showed no evidence of benefiting from exposure to the tDCS intervention. Comparison of participants' individual performance of all the CS tasks indicates that the most beneficial dose of tDCS seems to be three sessions per week. However, conclusions cannot be gleaned from the session's variability due to the small sample of this study. This should be addressed in the future as it remains unclear.

Although this study has produced encouraging results, it also has several limitations. First, an A-B-C-A SSD was used without randomization among experimental conditions. The same order was used for all the participants because if tDCS was administered in phase B right after the baseline, then it could have affected the outcomes under the sham tDCS phase due to possible carryover effects of tDCS stimulation; therefore, it could have also disguised the sham effect we originally aimed to compare with real tDCS. This could have given rise to a second limitation during the last baseline A, either due to a training effect of the CS or a carryover effect of the tDCS administration in phase C, which cannot be separated for interpretation. This is a disadvantage of using an SSD in cognitive studies. We intended to monitor daily response in behavioral terms to different treatments, but the frequency of the application of CS in some of the participants in such a short period made it problematic to decouple what participants

might have achieved by continued testing from what was changed by tDCS.

For the same reason, our original intention was to observe whether the CS outcomes could match the cognitive assessment score in every condition. To check this possibility, we administered a battery of assessments five times over a four-week interval, which might provide a learning effect and reduce overinterpreting the CS task outcomes by making a linkage with the standardized cognitive evaluations, and alternative forms of cognitive assessments to measure changes over time should be used.

Despite the limitations of this pilot study, it is essential to conduct pilot studies with NIBS techniques before the implementation of larger trials. The strength of this study allow us to monitor the daily cognitive response of single or coupling therapies gathering valuable data that can shape a future robust intervention. The ultimate purpose of using NIBS is to prove if it can be used as a feasible NPT in couple with conventional treatment, in this case computer CS, for older adults with MCI. The emerging application of tDCS as a therapeutic intervention gives us the obligation of conducting studies to develop treatment programs which can support evidence base and determine the future use of these innovative techniques in the field of CR.

5.5 Conclusion

The current study investigated the effects of anodal tDCS on CS in older adults with

MCI and found mild beneficial effects on processing speed, selective attention, planning ability, and working memory which were better than those achieved by CS alone or by sham tDCS. The optimal frequency of tDCS administration remains unclear.

Further research is required to improve understanding of the neuromechanism and to determine the behavioral effects of tDCS on CS in a larger multicentered, randomized controlled study to determine the possibility of transferability to everyday cognition.

5.6 References

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CHAPTER 6: TRANSCRANIAL DIRECT CURRENT STIMULATION AS AN ADJUNCT TO COGNITIVE TRAINING FOR OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT: A RANDOMIZED CONTROLLED TRIAL

This chapter reports on the main research study conducted for this thesis. It starts by setting out the theory of why adding tDCS to CT may increase effectiveness and enhance therapeutic benefits in persons with MCI in along two different dimensions; standardized cognitive outcomes and task-specific cognitive outcomes of CT tasks.

It goes on to describe a double-blinded RCT design with three intervention groups composed of persons with MCI. All three groups received the same intervention. The first received CT in combination with tDCS, the second in combination with sham tDCS, and the third CT only. The outcome measures were based on global cognition, working memory, attention, and everyday memory as standardized cognitive outcomes. Findings on the performance of the CT tasks are presented in the form of charts. The chapter concludes with a discussion of the findings, draws a comparison with similar studies and sets out recommendations for future studies in this area.

The overall aim is implementing the theories set out in previous chapters by means of a clinical trial and test the study hypotheses.

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Cruz Gonzalez, P., Fong, K. N. K., & Brown, T. (2021) Transcranial direct current stimulation as an adjunct to cognitive training for older adults with mild cognitive impairment: A randomized controlled trial. *Annals of Physical and Rehabilitation Medicine*, 64. https://doi.org/10.1016/j.rehab.2021.101536.

Preliminary data from this study with a smaller sample size was presented at the 3rd International Brain Stimulation Conference: Vancouver, Canada; 2019, the abstract of which has been published. The reference for this abstract is as follows:

Gonzalez, P. C., Fong, K., and Brown, T. (2019). Is transcranial direct current stimulation (tDCS) an effective adjunct to cognitive training for older adults presenting with mild cognitive impairment (MCI)? Brain Stimulation, 12(2): 448-9. (Abstract)

Access to the scientific paper: https://doi.org/10.1016/j.brs.2018.12.456

6.1 Introduction

MCI is considered the frontier between the natural cognitive decline from ageing and the very early stages of dementia (Petersen, 2016). Although MCI can be classified as a cognitive disorder in non-demented persons, it is indeed an age-related condition with a probable degenerative aetiology associated with the onset of (AD) (Okello et al., 2009; Petersen, 2016). Cognitive compensatory mechanisms may activate in the ageing brain. For instance, when healthy older adults face difficulties in executive tasks, there is an over-activation of bilateral prefrontal cortex areas, whereas non-impaired young adults display this over-activation in one hemisphere (Reuter-Lorenz et al., 2000). This brain response might be explained in terms of cognitive restructuring in older adults because they are likely having a lower level of attention and working memory capacity (Kirova, Bays, & Lagalwar, 2015; Reuter-Lorenz et al., 2000). The decline of executive functioning is exacerbated during MCI, which has been shown to cause deficits in working memory and attention (Kochan et al., 2010; Saunders & Summers, 2011). There is evidence that one or more cognitive domains can be impaired in people with MCI without affecting their preservation of independence in functional abilities or causing their ADL to be performed in a less efficient manner (Langa & Levine, 2014). Furthermore, people with MCI often report cognitive subjective complaints (Albert et al., 2011; Langa & Levine, 2014).

CR is described as:

> 'The therapeutic process of increasing or improving an individual's capacity to process and use incoming information so as to allow increased functioning in everyday life. This includes methods to train and restore cognitive functioning' (Sohlberg & Mateer, 1989, p.871) such as CT.

Changes in neural activity in persons with MCI suggest that CT can have restorative effects, improving the impaired brain area or function, as well as compensatory effects, engaging other intact neural networks (Strobach & Karbach, 2016). In point of fact, memory training increased activation in areas associated with memory encoding before CT and also generated new activations in areas that were not active before the administration of CT (Belleville et al., 2011; Strobach & Karbach, 2016). CT improved cognitive performance in the domains trained in healthy older adults. However, there is insufficient evidence regarding the effects of CT on populations with MCI reporting gains in training performance (Butler et al., 2018). Similar conclusions were drawn in a systematic review when appraising the therapeutic benefits of CT in RCTs, which showed positive effects on various domains of cognitive functioning in healthy older adults, but not in persons with MCI (Reijnders, van Heugten, & van Boxtel, 2013). It appears that CT induces changes in neural activity that may not be translated into cognitive gains in individuals with known MCI.

The application of CT itself as an intervention for persons with MCI may not always be sufficient to produce tangible benefits to cognitive functioning (Reijnders et al., 2013). A

complementary solution would involve pairing CT with another intervention, thus creating synergistic effects (Andrews, Hoy, Enticott, Daskalakis, & Fitzgerald, 2011; Ohn et al., 2008). tDCS is a NIBS technique that modulates brain excitability. tDCS delivers direct current to the brain cortex, travelling from the anode to the cathode electrode. The former has depolarizing properties that excite neural activity, whereas the latter has hyperpolarizing effects that inhibit neural activity (Nasseri, Nitsche, & Ekhtiari, 2015; Nitsche et al., 2008). As a result, 'tDCS causes a shift in the membrane potential threshold which is likely to change the probability that an incoming action potential will result in post-synaptic firing during and after its administration' (Cruz Gonzalez, Fong, Chung, et al., 2018, p. 2; Prehn & Flöel, 2015). According to a recent systematic review, the application of tDCS alone has exhibited promising improvements in various cognitive domains for different types of dementia and MCI, however, whether tDCS combined with CT concurrently might produce optimal therapeutic outcomes than when administered alone remains unclear yet (Cruz Gonzalez, Fong, Chung, et al., 2018).

Based on this background, we hypothesize that tDCS may augment the strength of transmission across synaptic circuits in pathways that are stimulated by CT. Hence using tDCS to target a brain region or function that could be impaired in persons with MCI during a CT may be more efficient than not using tDCS (Birba et al., 2017). Consequently, it could produce more tangible benefits in cognitive functioning outcomes. The aim of the present study was to investigate whether the application of tDCS combined with CT would lead to superior domain-specific outcomes – both

standardized cognitive outcomes and task-specific outcomes – of CT tasks in older adults with MCI compared to the application of sham tDCS and CT or of CT alone.

6.2 Material and Methods

6.2.1 Participants

Participants were older adults presenting with suspected MCI recruited by convenience sampling from community center groups and by research recruitment posters in Hong Kong. The enrolment started in July 2017 and ended in July 2019. All included participants met the modified Petersen's criteria (Portet et al., 2006) (given by the MCI Working Group of the European Consortium on Alzheimer's Disease, Brescia Meeting, Italy, June 2005) and were required to: (a) be aged between 60 and 85 years old; (b) obtain a score on the MoCA (Nasreddine et al., 2005) between 19 and 26; (c) achieve a score on the CDR of 0.5 or below (Morris, 1993); (d) self-report cognitive decline; (e) self-report independence in daily living activities; and (f) have completed at least three years of primary education. Participants were excluded if they presented any of the following conditions: (a) individuals presenting with any neurological disease, except for suspected MCI; (b) individuals with suspected depression determined by a score on the GDS-15 > 4 (Yesavage et al., 1982); and (c) history of drug abuse. All participants were screened to detect any contraindications to tDCS (metallic implants, epilepsy, etc.).

A description of the study was explained to all participants and informed written consent was obtained before the intervention began. The study was conducted in accordance

with the Declaration of Helsinki and was approved by the human subject ethics committee of The Hong Kong Polytechnic University (ref. number: HSEARS20170526001) and registered at ClinicalTrials.gov (NCT03441152).

6.2.2 Trial design

The trial utilized a double-blinded sham-controlled design with 3 intervention groups. Interested participants underwent a screening assessment, after which all eligible participants were invited to receive a three-week computerized CT. Once recruited, the participants were randomly assigned to receive CT, either with tDCS (tDCS+CT group), with sham tDCS (sham tDCS+CT group), or only CT (CT group). Randomization was assigned following a random sequence generated by an online platform 'Qminim' (1:1:1 ratio) and the random allocation sequence was implemented based on the recruitment order by the therapist who administered the interventions and who did not get involved in the assessment of the participants. All groups completed three sessions per week, undertaking a total of nine sessions in three weeks. Participants were assessed at baseline, post-treatment, and at six-weeks FU. This study follows the Non-pharmacological Consolidated Standards for Reporting Trials (CONSORT) (Boutron, Altman, Moher, Schulz, & Ravaud, 2017) for RCT (Figure 6.1).

6.2.3 Intervention

The intervention sessions were carried out at the research facilities of the university. All participants were exposed to the same computerized CT content. Only the experimental group performed the CT with tDCS (tDCS+CT group). The participants in the sham

tDCS+CT group served to provide a placebo effect, while the participants in the CT group served as the control for documenting differences among both tDCS modalities. Although the type of intervention was unknown to the assessors conducting the cognitive assessments as well as the participants (i.e. they were blind), the tDCS and CT administrator responsible for delivering the treatment remained unblinded.

6.2.3.1 tDCS

Stimulation was delivered by the Soterix Medical 1 X 1 low-intensity tDCS stimulator. The electricity was conducted via two rubber electrodes inserted in saline-soaked sponges (5 X 3 cm, 15 cm^2). The anode electrode was placed over the left DPFC corresponding to the F3 region based on the 10/20 EEG international system. The LDPFC was selected because it had been extensively used as a target in studies using tDCS in older adults with MCI and dementia (Cruz Gonzalez, Fong, Chung, et al., 2018). In addition, the prefrontal cortex in older adults was selected for stimulation because it might influence the executive functional performance that are impaired in MCI (Harada, Love, & Triebel, 2013; Traykov et al., 2007). The cathode electrode was positioned, as an extra-cephalic reference, on the contralateral brachioradialis muscle in order to avoid the confounding effects of two electrodes with different polarities over the brain (Nitsche et al., 2008). The sponges were attached to the abovementioned areas with a head and an arm elastic band, respectively. The application of tDCS for the tDCS+CT group included an initial ramp-up over 30 seconds, followed by a constant current at 1.5 mA for 30 minutes, and ended with a ramp-down for other 30 seconds. In the sham condition, the whole process and parameters were mimicked excluding the

delivery of constant current at 1.5 mA for 30 mins. However, the ramp-up and ramp-down procedures were maintained to replicate the physical sensations produced by tDCS. The CT was applied concurrently with the onset of tDCS and sham tDCS, respectively. The participants from the CT group did not receive any tDCS at all, so technically it was not possible to mask these participants to the type of intervention.

6.2.3.2 Computerized CT

The computerized CT used for the intervention was 'Neuron Up' (Fdz de Piérola & Sastre, 2015), an online platform (https://www.neuronup.com/) which consists of customizable training materials to enable CR. This CT was selected because it has been shown to improve various cognitive outcomes in persons with MCI (Mendoza Laiz, Del Valle Diaz, Rioja Collado, Gomez-Pilar, & Hornero, 2018) and has been previously used for pairing with tDCS, showing mild cognitive gains (Cruz Gonzalez, Fong, & Brown, 2018).

The CT was administered for 30 mins to all groups and included the following content with a focus on executive function: one adaptive task associated with working memory delivered as a warm-up during the first five minutes, this activity consisted of remembering the order in which a set of buildings placed on different locations lighted up and later the participants were asked to reproduce that exact same order in reverse. The challenge of the task was that the more accurate the participants were, the more times the buildings lighted up in the following trials, hence, the difficulty of the task increased. The adaptive task was followed by the administration of six non-adaptive

tasks related to arithmetic math (additions and subtractions) working memory, short-term memory, and attention, presented in counterbalanced order across nine sessions. The reason why the CT was based on working memory and attention was that both are components of executive functions (Diamond, 2013).

The CT sessions were conducted individually and the participants were supervised by the investigator when performing the CT tasks to ensure that they understood how to realize the tasks and that they complied with the course of the intervention. The display format was a touchscreen 13.30-inch HP Spectre x360 laptop placed on a table approximately 35 cm in front of the participant.

6.2.4 Outcome measures

All primary outcome measures were conducted at baseline, post-assessment, and FU. They were domain-specific cognitive outcome measures, which included: MoCA (Hong Kong non-parallel version) to evaluate global cognitive functioning; the DST for working memory, consisting of two parts in which sequences of digits are presented and must be verbally recalled in forward and reverse order (DST-f and DST-b), respectively (Blackburn & Benton, 1957); and the TMT, encompassing attention skills, processing speed, and mental flexibility. In part A (TMT-a), a set of 25 numbered dots must be accurately connected in sequential order. The Chinese version was used in part B (TMT-b) (L. Lu & Bigler, 2002), alternating dots with Chinese numerals. TMT is administrated with paper and pencil and performance time is measured as the main outcome.

The secondary outcome measures included: The Rivermead Behavioral Memory Test (3rd edition) (RBMT-3) – Hong Kong version (Fong et al., 2019), which assesses everyday memory skills and was administered following the same timeline as the primary outcome measures. Alternate forms of the parallel versions of the RBMT-3 were used in order to avoid any testing effect. Task-specific outcomes derived from the CT tasks were recorded for all non-adaptive tasks across time. Depending on the nature of the CT task, data such as the number of errors, completion time, and reaction time was collected.

6.2.5 Sample size

The sample size of the study was not estimated according to our previous pilot study (Cruz Gonzalez, Fong, & Brown, 2018), as the parameters needed to determine the sample size were somewhat insufficient. Furthermore, no previous similar research was available on which to ground the sample size estimation. Therefore, we based the sample size estimation using a conservative approach (Cohen, 1992), assuming 80% power at 5% Type I error, sample size estimates indicated that to detect a correlation among repeated measures of 0.325 with an effect size of 0.3, 54 participants (e.g., 3 groups x 18 participants) would be adequate to detect significance. By adding a 20% drop-out rate, a total of 65 participants were targeted to be recruited (G*power, Version 3.1.3, University of Kiel, Germany, 2010).

6.2.6 Statistical analysis

Differences at baseline among groups in demographics, primary outcome measures, and the total scores of RBMT-3 were tested employing Chi-square tests and One-way ANOVA, for categorical and continuous variables, respectively. A two-way repeated-measures ANOVA (time x intervention) was used to examine changes of the interventions applied in primary and secondary outcomes measures. If the time or interaction effect was significant in the primary outcomes and in the RBMT-3, *post-hoc* multiple comparisons were conducted to investigate the within-group differences for each group. Cohen's d was used to calculate the effect size (Cohen, 1992) for the general outcome measures within groups. Multiple Independent t-tests were conducted for the grand average of the CT outcomes in every single session so that it could be explored at which endpoint the three groups started to show significant changes. Statistical significance was set at $p = 0.05$. Significance values for *post-hoc* tests were adjusted by the Bonferroni correction, $p = 0.017$. Data analyses were performed using IBM SPSS statistics 22.0. Last observation carried forward was the method chosen to deal with missing data for participants who dropped out.

6.3 Results

One hundred fifty participants were screened for eligibility and 67 of them were recruited to commence the study. Twenty-two participants were allocated to receive tDCS combined with CT, 24 participants to receive sham tDCS combined with CT, and 21 participants to receive CT alone. Two participants, 1 receiving tDCS+CT and 1 receiving

sham tDCS+CT, dropped out during the intervention due to uncomfortable sensations with the current delivered (see Figure 6.1). There were no differences in demographic data and the baselines of outcomes across groups (see Table 6.1). None of the participants reported severe side effects.

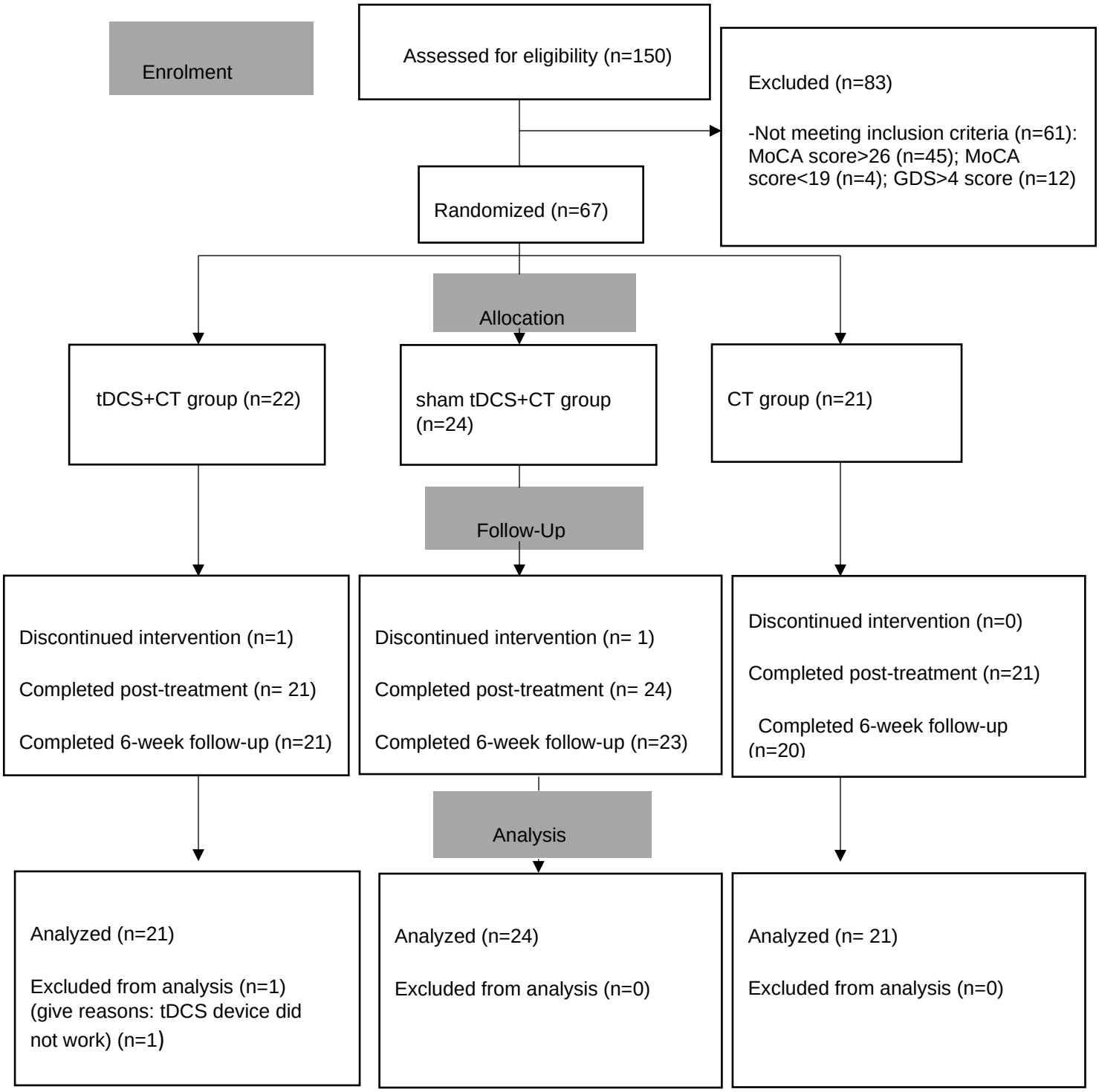


Figure 6.1. CONSORT flow diagram.

Variable	tDCS+CT group (n = 21) Mean (SD)	Sham tDCS+CT group (n = 24) Mean (SD)	CT group (n =21) Mean (SD)	F/x^2	*p*
Gender (Male/Female)	6/15	8/16	4/17	1.17 x^2	0.555
Age	69.86 (5.33)	71.00 (6.22)	70.67 (5.42)	0.23	0.792
Years of education	9.76 (3.61)	9.75 (3.69)	11.95 (4.98)	2.02	0.140
MoCA	23.71 (1.73)	24.17 (2.44)	24.33 (1.71)	0.48	0.617
TMT-a	54.96 (17.97)	50.11 (24.21)	47.60 (16.75)	0.69	0.505
TMT-b	77.70 (32.55)	73.08 (24.24)	76.23 (37.40)	0.11	0.888
DST-f	13.62 (1.71)	13.67 (2.05)	13.67 (1.93)	0.00	0.996
DST-b	6.67 (2.65)	6.04 (2.44)	6.19 (2.52)	0.36	0.697
RBMT-3	123.47 (16.99)	124.58 (14.14)	126.80 (18.97)	0.21	0.805

Table 6.1. Demographic and clinical data at baseline.
Abbreviatures: X2, Chi-square.
Note: p-value was between groups.

6.3.1 Primary outcomes

Significant main effects of time were found for all groups in MoCA after intervention with larger effect sizes in the tDCS+CT group (tDCS+CT group: $p = 0.001$, Cohen's d = 0.9; sham tDCS+CT group: $p = 0.001$, $d = 0.66$; CT group: $p = 0.005$, $d = 0.58$). This improvement was also noted from baseline to six-weeks FU (tDCS+CT group: $p = 0.001$, $d = 1.27$; sham tDCS+CT group: $p = 0.001$, $d = 0.9$; CT group: $p = 0.001$, $d = 1.16$).

In the TMT-a, the tDCS+CT showed marginally significant improvement from baseline to six-weeks FU (p = 0.019, d = -0.51). This gain was not evidenced in either the sham tDCS+CT group (p = 0.640, d = 0.06) or the CT group (p = 0.267, d = -0.23).

Regarding the DST-b, a better performance was observed in the CT group after the intervention (tDCS+CT group: p = 0.297, d = 0.16; sham tDCS+CT group: p = 0.040, d = 0.47; CT group: p = 0.005, d = 0.53), and six-weeks FU (tDCS+CT group: p = 0.050, d = 0.28; sham tDCS+CT group: p = 0.159, d = 0.22; CT group: p = 0.005, d = 0.58). However, no significant interactions (time x intervention) were found in any of the primary outcomes, as shown in Table 6.2.

6.3.2 Secondary outcomes

All groups showed significant improvements in RBMT-3 after the intervention (tDCS+CT group: p = 0.001, d = 0.95; sham tDCS+CT group: p = 0.001, d = 0.72; CT group: p = 0.004, d = 0.56) and at six-weeks FU relative to the baseline (tDCS+CT group: p = 0.000, d = 0.95; sham tDCS+CT group: p = 0.000, d = 0.89; CT group: p = 0.005, d = 0.67). Significant large effect sizes in everyday memory were evidenced, particularly in the tDCS+CT group. Nevertheless, two-way repeated-measures ANOVA showed no significant interaction effect in the total score (see Table 6.2). Regarding the subscores of RBMT-3, there was significant time vs intervention interaction in the orientation/date domain between post-intervention and baseline in favor of the sham tDCS+CT group (p = 0.004). The improvement was significantly reversed between post-intervention and FU

(p = 0.016), there were also significant differences between groups at FU relative to the baseline in favor of the CT group (p = 0.001).

	tDCS+CT (n = 21)			Sham tDCS+CT (n = 24)			CT alone (n = 21)			Within group		Time x Intervention	
	Baseline	**Post**	**6-week FU**	**Baseline**	**Post**	**6-week FU**	**Baseline**	**Post**	**6-week FU**	**F**	***p***	**F**	***p***
MoCA	23.71 (1.73)	25.76 (2.48)**	26.29 (20)**	24.17 (2.44)	25.83 (2.58)**	26.46 (2.63)**	24.33 (1.71)	25.71 (2.84)**	26.71 (2.32)**/***	49.82	0.000	0.34	0.851
TMT-a	54.96 (17.97)	52.5(29.70)	45.59 (18.17)*	50.11 (24.21)	50.54(25.32)	48.45(26.03)	47.60 (16.75)	48.35(16.86)	44.00(14.29)	3.39	0.037	0.64	0.628
TMT-b	77.70 (32.55)	79.84(41.22)	72.54 (34.18)	73.08 (24.24)	73.08 (23.42)	66.02(24.5)	76.23 (37.40)	73.82 (35.58)	68.58 (26.37)	2.67	0.073	0.08	0.988
DST-f	13.62(1.71)	12.76(2.02)	13.33(1.85)	13.67(2.05)	13.92(1.99)	14.04(2.19)	13.67 (1.93)	13.62(2.17)	13.57(2.22)	1.03	0.359	1.99	0.099
DST-b	6.19(2.52)	6.62(2.72)	6.95(2.85)*	6.04(2.44)	7.33(2.92)*	6.88(2.96)	6.67(2.65)	8.10(2.70)**	8.38(3.21)**	10.52	0.000	1.15	0.333
RBMT-3	123.47 (16.99)	137.14 (10.94)**	138.00 (13.20)**	124.58 (14.14)	136.45 (18.23)**	137.79 (15.46)**	126.80 (18.97)	137.71 (19.53)**	140.81 (22.50)**	39.02	0.000	0.13	0.967
Names-DR	8.61(2.33)	9.47(2.46)	10.19 (2.54)**	8.50(2.16)	9.79(2.5)*	10.41 (2.37)**	7.85(2.72)	9.33(3.05)*	9.66(2.79)**	15.36	0.000	0.17	0.951
Belongings-DR	8.00 (2.64)	9.28(2.36)	9.00(2.23)	9.33 (2.42)	10.41(2.7)	9.62(2.82)	7.90 (3.12)	10.14(2.88)**	9.71(3.03)*	7.449	0.001	0.70	0.593
Appointments-DR	8.47 (2.58)	10.23(1.91)	9.42(1.83)	8.04 (2.27)	9.45(2.43)	9.95(1.92)*	8.28 (2.39)	9.57(2.58)*	9.90(2.16)**	13.78	0.000	0.83	0.496
Picture Recognition-DR	10.09 (2.18)	9.71(2.32)	9.71(2.17)	8.87 (2.64)	9.45(2.3)	9.25(2.90)	9.80 (2.33)	9.76(2.36)	10.33(2.28)	0.11	0.892	0.51	0.724
Story-IR	9.85(2.43)	10.04(2.29)*	10.38(3.36)	8.95 (2.38)	9.83(2.94)	10.83 (2.31)**	9.52 (3.14)	11.71(1.97)**	11.28(2.07)**	9.36	0.000	2.02	0.095

Story-DR	8.80(2.87)	9.66(2.85)	9.76(3.06)	9.04(2.54)	9.37(3.14)**	10.41(2.39)	8.95(2.85)	10.33(2.28)*	10.42(2.99)*	6.96	0.001	0.61	0.651
Face Recognition-DR	8.76(2.77)	9.33(3.19)	10.38 (3.18)**	7.33 (2.54)	9.79(3.1)**	8.75(3.09)*	8.71 (2.95)	8.90(1.78)	9.76(3.34)	6.603	0.002	2.148	0.079
Route-IR	8.85(3.19)	10.90(1.92)*	10.33 (2.72)***	10.33 (3.08)	10.62(3.39)	11.37(1.95)	10.85 (2.74)	10.23(2.40)	11.52(1.96)	3.46	0.039	1.90	0.120
Route-DR	9.00(3.03)	10.28(2.36)	10.42(2.24)	10.83 (1.99)	10.58(2.87)	10.70(2.01)	9.90 (2.40)	9.61(3.23)	10.23(2.77)	1.08	0.333	1.21	0.308
Messages-IR	9.85(1.93)	10.42(1.46)	10.57(1.07)	9.58 (2.68)	9.91(2.18)	9.58(2.37)	10.19 (1.77)	9.80(2.01)	9.28(2.62)	0.25	0.773	0.92	0.452
Messages- DR	9.23(2.68)	10.28(1.55)	10.42(1.20)	9.58 (2.08)	9.50(2.24)	10.16(2.05)	9.90 (1.84)	9.66(2.22)	9.19(2.40)	0.59	0.553	1.74	0.144
Orientation and Date	7.95(2.51)	8.00(2.04)	7.95(2.43)	7.37 (2.39)	9.12(2.50)**	7.95 (2.21)***	7.61(2.03)	7.85(2.93)*	9.19(2.42)**	4.03	0.020	4.28	0.003
Novel Task-IR	7.76(2.75)	10.23 (2.77)**	9.57 (2.50)**	8.25 (2.65)	9.50(2.9)	9.91(2.50)	8.57 (2.29)	10.57(3.32)*	10.38(2.87)*	14.15	0.000	0.49	0.742
Novel Task-DR	8.23(2.70)	9.23(2.36)	9.85 (2.10)**	8.54 (2.26)	9.08(2.68)	8.83(2.89)	8.71 (2.72)	10.19(2.48)	9.90(2.07)	4.99	0.008	0.76	0.550

Table 6.2. Comparison of standardized cognitive outcome variables across and within groups (Raw means, SD).

Abbreviatures: DR, delayed recall; IR, immediate recall.

Note: * *P* < 0.05; ** *P* < 0.017. The *P*-values were within-group comparisons versus baseline. *** P < 0.05; The P-values were within-group comparisons, follow-up assessment versus post-intervention assessment. / represents the separation of results.

Regarding the CT outcomes, in the 'additions' task, all groups maintained an average of less than one error per operation. The tDCS+CT group committed fewer errors during the first four sessions and then the performance equalized across groups for the remaining sessions, reverting to the initial pattern in the last session. All these differences were minimal in terms of score and not statistically significant (see Figure 6.2a). However, the tDCS+CT group took less time to complete the operations in every single session than the sham tDCS+CT and CT groups. In the first session, a marginally significant difference was found between the tDCS+CT group and the sham tDCS+CT group (p = 0.037). The difference between these groups was also significant (p = 0.013) in the last session (see Figure 6.2b). Regarding the task-specific outcomes, two-way repeated-measures ANOVA showed no significant differences between groups in any of the tasks, although there were significant within-group changes in all the outcomes related to the completion time variable as shown in Table 6.3.

CT task	**Within group**		**Time x Intervention**	
	F	***p***	**F**	***p***
Additions (errors)	0.31	0.940	0.55	0.888
Additions (completion time)	5.29	0.000	0.68	0.756
Working memory (completion time)	12.14	0.000	0.82	0.585
Working memory (reaction time)	2.37	0.032	0.62	0.814
Attention (completion time)	11.09	0.000	1.38	0.196
Attention (reaction time)	8.57	0.000	1.27	0.260

Table 6.3. Comparison of task-specific outcomes across and within groups.

Multiple independent t-test showed that in the working memory task, except for the first session, the tDCS+CT group completed the task successfully faster than the other two groups in all sessions. In sessions 4, 6, and 8, marginally significant performance differences were observed relative to the sham tDCS+CT group ($p = 0.041$, $p = 0.045$, $p = 0.029$). Furthermore, in session 9 the difference between these two groups was significant ($p = 0.007$) (see Figure 6.3a). In terms of reaction time, the tDCS+CT group showed significantly and marginally significantly faster scores than the CT group in sessions 2 and 3 respectively ($p = 0.013$, $p = 0.025$) (see Figure 6.3b).

Figure 6.4a shows that the tDCS+CT group performed the visual attention task successfully and significantly faster than the CT group in session 4 ($p = 0.012$). Marginally significant differences were also found versus the CT group in session 3 ($p = 0.028$) and versus the sham tDCS+CT group in session 5 ($p = 0.021$). In terms of reaction time, the tDCS+CT group evidenced significantly faster responses than the CT group in session 4 ($p = 0.017$) and marginally significant differences relative to the sham tDCS+CT group in sessions 4, 5, and 6 ($p = 0.020$, $p = 0.039$, $p = 0.036$) (see Figure 6.4b). No significant differences were observed in the remaining CT tasks (subtractions, short-term memory tasks, and an additional attention task).

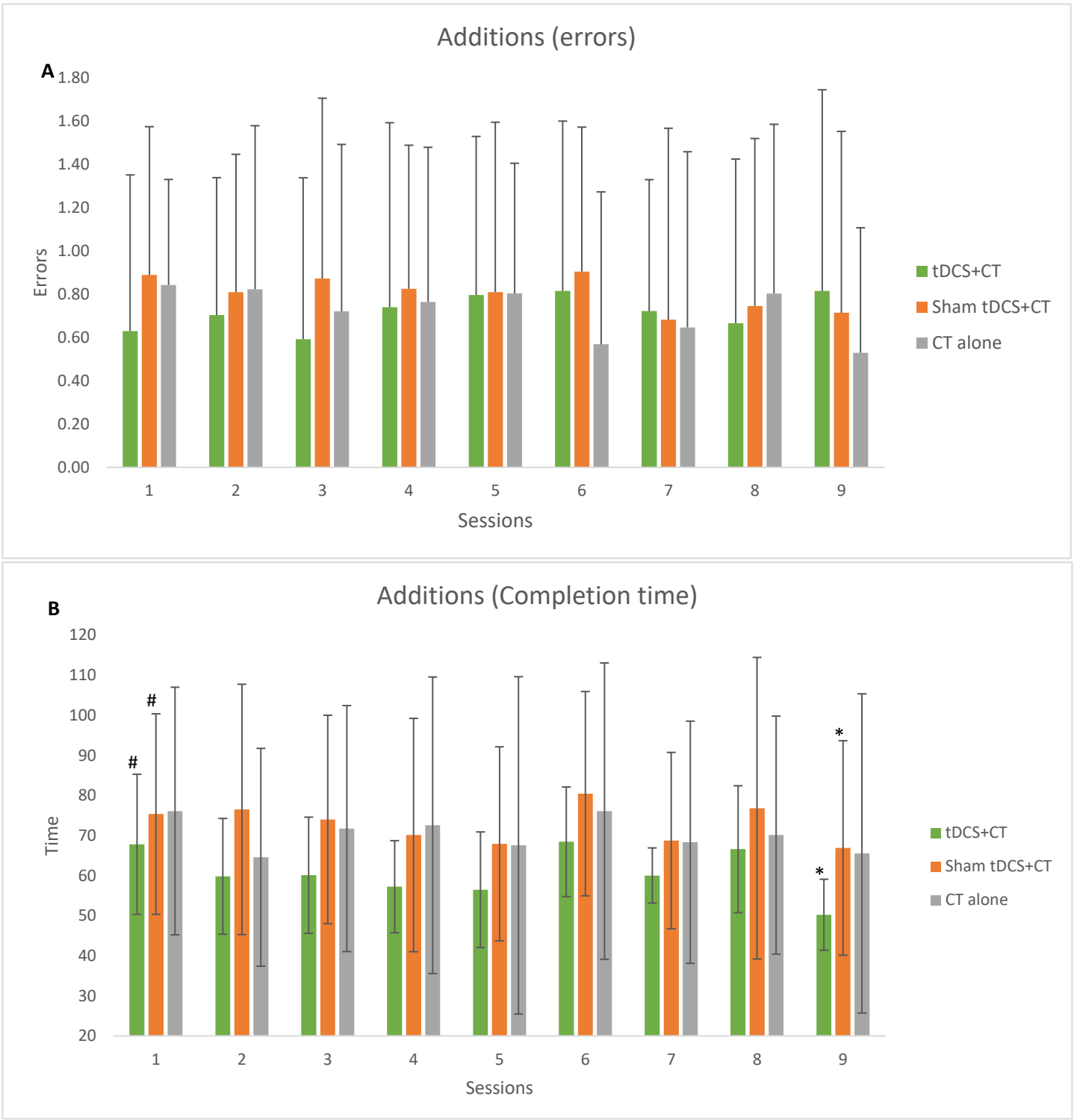


Figure 6.2. CT task, additions. Note: 6.2A represents the mean performance of the three groups across nine sessions in terms of accuracy. Errors bars with plus caps represent the standard deviation. Figure 6.2B represents the mean performance of the three groups across nine sessions in terms of time. Errors bars with both caps represent the standard deviation. # shows marginal significant differences across groups $P < 0.05$.

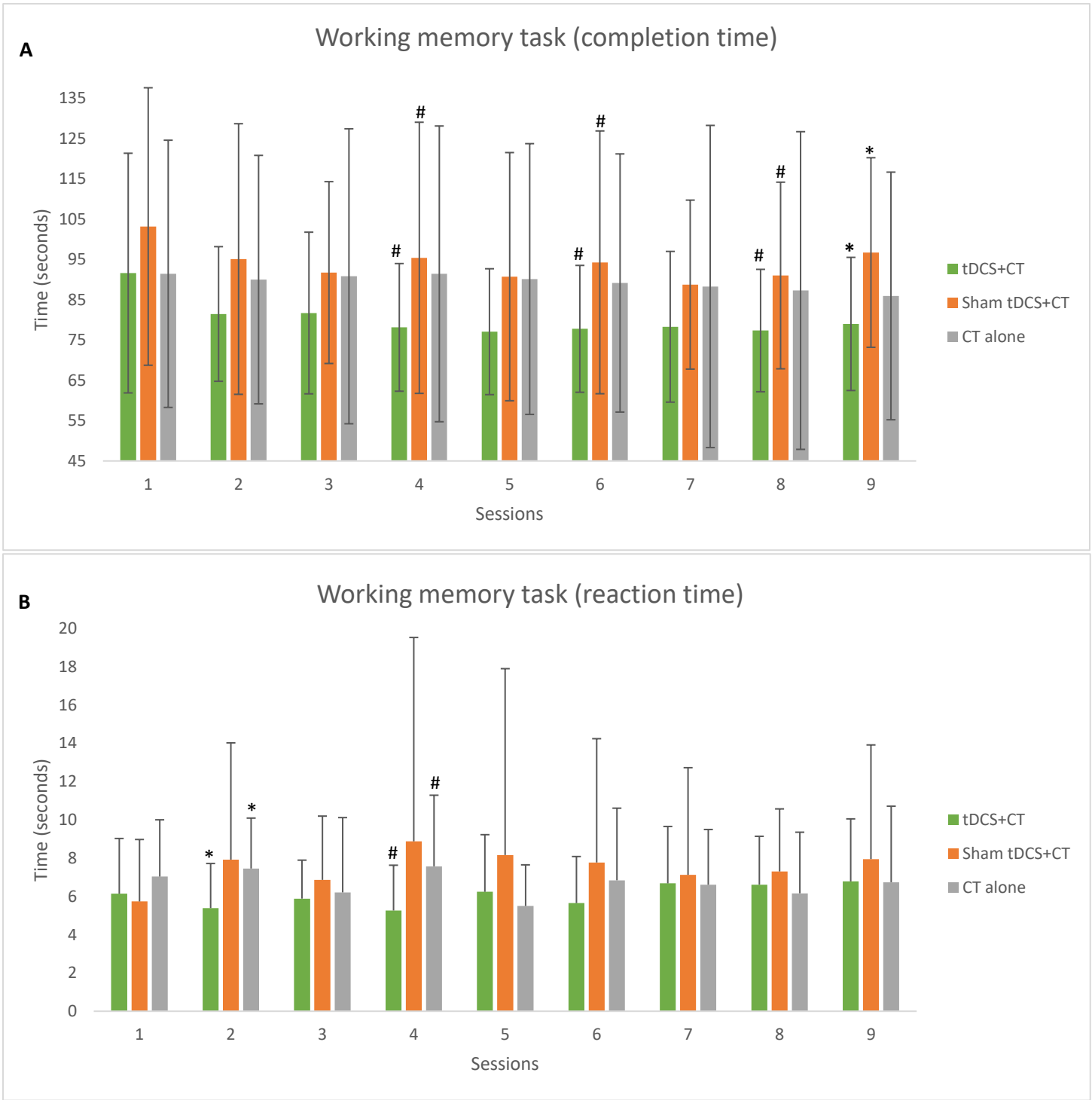
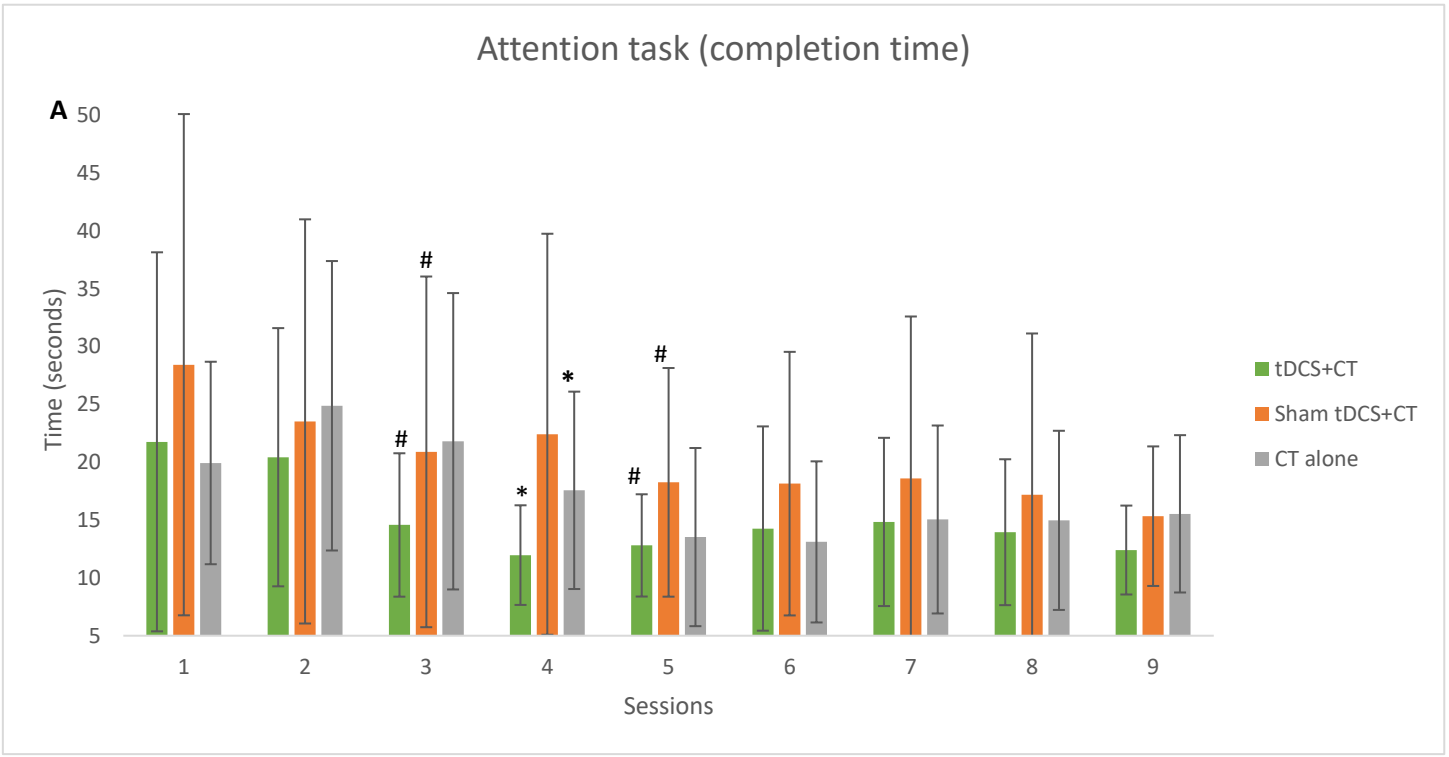


Figure 6.3. CT task, working memory. Note: Figure 6.3A represents the mean performance of the three groups across nine sessions in terms of time. Errors bars with both caps represent the standard deviation. Figure 6.3B represents the mean performance of the three groups across nine sessions in terms of reaction time. Errors bars with plus caps represent the standard deviation. # shows marginal significant differences across groups $P < 0.05$. * shows marginal significant differences across groups $P < 0.017$.



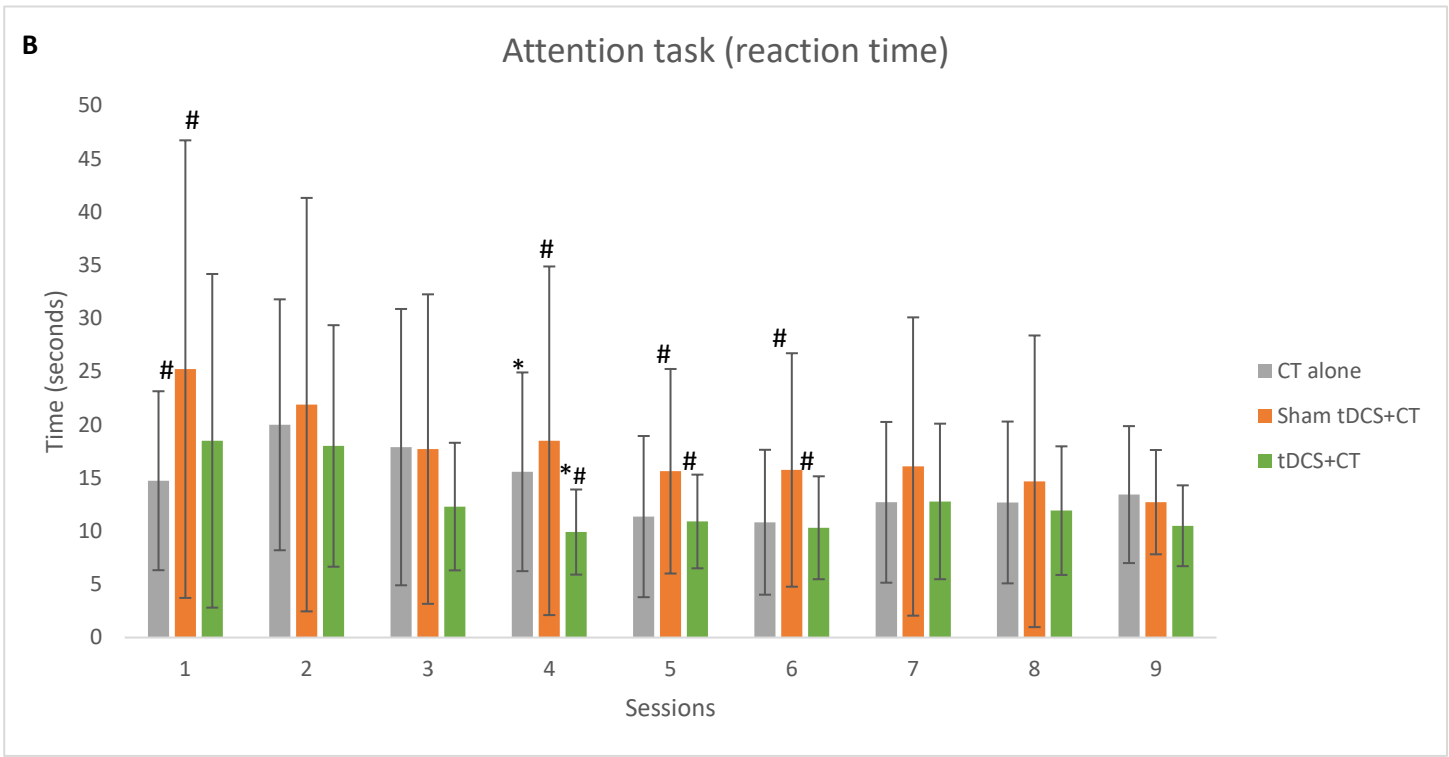


Figure 6.4. CT task, attention. Note: Figure 6.4A represents the mean performance of the three groups across nine sessions in terms of time. Figure 6.4B represents the mean performance of the three groups across nine sessions in terms of reaction time. Errors bars with both caps represent the standard deviation. # shows marginal significant differences across groups $P < 0.05$. * shows marginal significant differences across groups $P < 0.017$.

6.4. Discussion

The purpose of this study was to investigate whether a multisession intervention of anodal tDCS on the left DLPFC, combined with a computerized CT consisting of working memory and attention tasks, would improve cognitive functioning and whether the improvement would be superior to that from computerized CT alone. To answer this question, we compared the effects of anodal tDCS+CT with both sham tDCS+CT and CT alone, thus rigorously eliminating bias. Our statistical analysis confirmed that tDCS+CT was not superior to sham tDCS+CT and CT alone as the cognitive domain outcomes failed to exhibit significant differences among groups after the intervention and at FU. There are few possible reasons for these disappointing results. First, both the experimental and comparison groups were effective in enhancing global cognition and everyday memory as indicated by the MoCA and RBMT-3 respectively. This finding is similar to that of a recent meta-analysis of the effects of computerized CT with 17 RCTs, that CT is a viable intervention for enhancing various cognitive domains including but not limited to global cognition and memory (Hill et al., 2017).

The results from the study we are presenting are in line with an RCT carried out by Martin et al. (Martin et al., 2019) in which participants with MCI received either CT with tDCS or sham tDCS on the left DLPFC as well. Both groups reported significant improvements at post-intervention in different domains of cognition, although there was no significant difference among groups. The largest RCT study to date on tDCS paired with working memory training for individuals with mild neurocognitive disorder due to AD (Lu et al., 2019) indicated that all participants regardless of group allocation

(tDCS+working memory training, sham tDCS+working memory training, tDCS+CT) enhanced global cognition and memory function, which is consistent with our findings. On the other hand, Lu et al targeted the lateral temporal cortex whereas we selected the LDPFC as the area of stimulation for anodal tDCS. The DPFC plays a crucial role in functional connectivity and in high-order cognitive functions (Tremblay et al., 2014) such as attentional processes, decision making, and working memory. Moreover, several studies have reported deficits in working memory, irrespective of the MCI subtype (Kochan et al., 2010), and in attention (Saunders & Summers, 2011), as well as functional disconnection of the LDPFC (Liang, Wang, Yang, Jia, & Li, 2011).

Following this rationale, we prepared a specific CT based mainly on working memory and attention modules. Regarding this aspect, only the tDCS+CT group appeared to show significant within-group improvements in attention and processing speed as revealed by TMT-a score. However, this pattern was reversed for the DST-b score, since the greatest improvements were seen in the group that received CT alone. These mixed results are difficult to explain, given that it has been previously shown that tDCS combined with CT resulted in a greater subsequent improvement in working memory outcomes in healthy adults (Andrews et al., 2011; Park, Seo, Kim, & Ko, 2014). Interestingly, Park et al. targeted both the right and left DPFC, yielding significant improvements in the DST-f, although none of the cited studies reported significant improvements in DST-b.

It was unexpected to find the within group and interaction effects in the orientation/date subtest of the RBMT-3. Since the Orientation and Date subtest does not fit in the

everyday memory construct of the RBMT-3 (Fong et al., 2019), the significant results were probably due to the testing effect or by chance.

In order to track the participants' performances in CT tasks simultaneously with tDCS, this study lacked the presence of a condition with the application of tDCS alone. The reason to applying tDCS with a CT task was that the efficacy of tDCS improves when applied with a cognitive task instead of rest (Park, Seo, Kim, & Ko, 2014), and the advantages of tDCS modulation could only be seen explicitly through a task-specific training. For this reason, our novel design allowed us to track the participants' performance on the computerized CT tasks in every single session across the whole intervention. It is noteworthy that these computerized CT task-specific scores have generated substantial valuable data, given the fact that the majority of the studies that combine NIBS with CT rely on scores of standardized cognitive domain outcomes acquired solely after the completion of interventions. The CT task results elucidated clearer performance during the training process in the tDCS+CT group. For example, when the participants realized additions, all groups had the tendency to make few errors each session. Moreover, in terms of completion time, the tDCS+CT group finished the operations much faster than the sham tDCS+CT and CT groups, particularly in the last session. This behavior was repeated in the tasks related to working memory and attention (Figure 3 and Figure 4) in which the performance of the task was rated by the time it took to finish the task successfully. Faster responses in terms of reaction time were also evident for the tDCS+CT group. Processing speed is linked to the efficient use of other cognitive abilities (Drozdick, Holdnack, Weiss, & Zhou, 2013) that affect the

speed with which one processes information and completes tasks (Beal, Holdnack, Saklofske, & Weiss, 2016). Processing speed deficits have been associated with ageing and are emphasized in pathological conditions such as dementia and MCI (Haworth et al., 2016). Following this line of thought, we can speculate that tDCS could enhance the efficacy of CT activities in terms of processing speed. Our hypothesis would be in consonance with previous research studies that have shown that tDCS applied to the LDPFC as compared to sham tDCS enhanced processing speed as measured by the Paced Auditory Serial Addition Task in young adults (Plewnia, Schroeder, Kunze, Faehling, & Wolkenstein, 2015). The findings are consistent with our pilot study using a single subject-design for 5 older adults with MCI (Cruz Gonzalez, Fong, & Brown, 2018). Our findings regarding processing speed could be explained by the mechanism of LTP, in which:

> ‘A brief episode of strong synaptic activation leads to a persistent strengthening of synaptic transmission’. Therefore, tDCS in combination with CT may boost the effects of training via LTP (Andrews et al., 2011, p. 87).

Another interesting observation when analyzing the data of the CT task is that the tDCS+CT group yielded lower standard deviations as compared with the sham tDCS+CT and CT groups, which tended to exhibit greater variability. This suggests that the application of tDCS provides more stable and less variable responses to the performance of the CT task that could also be attributed to the constant strengthening of synaptic transmission. However, the interpretation of task-specific outcomes we are

presenting must be taken with caution, because of the multiple statistical comparisons conducted for each CT task over 9 time points.

There are limitations to the current study. For instance, a question that remains unanswered in the literature is how many tDCS sessions are needed to induce behavioral changes. Some studies have stated that a single session is sufficient while other studies suggest various numbers of sessions, making it difficult to draw adequate conclusions (Cruz Gonzalez, Fong, Chung, et al., 2018). In our study, significant differences were registered across sessions in different CT tasks, adding more uncertainty regarding the optimal frequency of tDCS application. It would be useful for future studies to focus on contributing to this area as it could have an impact on the length of interventions in clinical settings. Although the participants included in this study met the modified Petersen's criteria (Portet et al., 2006) with regards to the diagnosis of MCI and the neuropsychological tests were conducted by experienced researchers, we lacked confirmed diagnoses of MCI (e.g. the presence of a physician to confirm the suspected diagnosis of MCI as well as to determine the subtype of MCI). In addition, we did not control the use of medications by the participants, this might be a factor to be considered in future studies involving the application of tDCS since medications may alter the excitability effects of tDCS (McLaren, Nissim, & Woods, 2018). Despite one of the strengths of this study was having both the sham and control groups, participant blinding was not assessed. We encourage researchers to control this variable after the end of the intervention as it could provide valuable information regarding participant blinding and tolerability (Kessler, Turkeltaub, Benson, & Hamilton, 2012).

It is also important to note that the CT administered to the participants was non-tailored. In other words, the cognitive tasks were not customized to the individuals' cognitive deficits (Lawrence, Gasson, Johnson, Booth, & Loftus, 2018). However, as it was our interest to monitor the participants' daily performance between groups, it was essential for them to all be exposed to the same content to enable us to compare the responses in a standardized manner. The common factor for all groups in this study was CT. Looking at the results, it is evident that all groups therapeutically benefited from receiving this intervention. However, our study did not include a waitlist control group, which would have supported this statement. For this reason, it could be argued whether the existence of a learning effect has favored all groups to improve their scores on the outcome measures. Another potential limitation was that the CT tasks that were recorded were non-adaptive, participants could have become unmotivated or performed at ceiling when proficient (Kwok et al., 2011). Finally, the fact that we did not have a robust reference on which to base our sample size estimation might have contributed to make our study underpowered.

6.5. Conclusions

CT with or without tDCS can enhance global cognitive functioning and everyday memory. The significance of this study was to determine if CT coupled with tDCS could be used as a NPT more efficiently than CT in the absence of tDCS for older adults with MCI. Whereas the combination of tDCS with CT did not create a superior effect as

compared with sham tDCS+CT or CT alone, the coupling improved the processing speed of CT tasks related to working memory and attention, in which tDCS appears to be a potential effective adjunct to CT exercises. Whether tDCS can be coupled with CT in clinical settings as a superior therapeutic intervention to CT alone warrants larger RCTs using persons with MCI.

6.6 References

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Transcranial direct current stimulation as an adjunct to cognitive training for older adults with mild cognitive impairment: A randomized controlled trial

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CHAPTER 7: EXPLORING THE EFFECTS OF COUPLING COGNITIVE TRAINING WITH TRANSCRANIAL DIRECT CURRENT STIMULATION ON EVERYDAY FUNCTIONING FOR OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

This section follows on from Chapter 6 and exclusively covers the impact of the tested interventions in terms of everyday functional outcomes. Most of the research done in the field of CT focuses more on the improvement or maintenance of cognitive functioning, as measured using well-established standardized cognitive tests associated with global cognition or specific cognitive domains. While these tests are good indicators of specific cognitive skills, it is often difficult to assess how well these skills are put into practice beyond this assessment process. In other words, it may be unclear how the benefits obtained in a therapeutic intervention, as shown by the results of a test, can be extrapolated to real-life situations. For example, if a patient with cognitive deficits improves his or her working memory after treatment, and this enhancement is expressed in a working memory test, will this translate to better performance in solving real-life problems, such as checking one has received the correct change after buying groceries in the supermarket? This real-life outcome is termed the transfer effects of the intervention, and should be the ultimate goal of CR.

Persons with MCI display cognitive deficits such as memory, attention, and so on. These lead to them performing ADL less efficiently. CT training has been proposed as a treatment to improve the affected cognitive skills. However, CT has not been proven to improve performance in real-life situations such as recognizing a face or recalling where one left a set of keys. The study described in the previous chapter therefore also

examined whether tDCS could work as a booster to CT so as to improve memory in a real-life context.

This chapter accordingly considers the potential implications of combining CT and tDCS concurrently in real-world situations. The manuscript has been slightly reformatted to fit the thesis requirements.

This study was presented at the 11th World Congress for Neurorehabilitation; Lyon, France: 2020. The abstract of which has been published. The reference for this abstract is as follows:

Cruz Gonzalez, P., Fong, K. N., & Brown, T. (2020). The impact of paired cognitive training with transcranial direct current stimulation on everyday functioning for older adults with mild cognitive impairment: Beyond conventional testing. Neurorehabilitation and Neural Repair (Abstract).

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7.1 Introduction

CT involves guided practice on a set of cognitive tasks with the purpose of slowing down cognitive deterioration or improving cognitive functioning (Kelly et al., 2014; Martin, Clare, Altgassen, Cameron, & Zehnder, 2011). CT has been widely used as form of NPT, especially in healthy older adults and those with medical conditions related to cognitive deficits such as MCI (Martin et al., 2011). A large number of RCTs have reported significant gains in composites of cognition in both populations (Hill et al., 2017; Kelly et al., 2014). However, most of these studies have also showed little evidence of generalizability to everyday cognitive tasks, either because CT failed to yield transfer benefits, or the researchers did not focus on investigating this area (Chandler, Parks, Marsiske, Rotblatt, & Smith, 2016; Kelly et al., 2014; Reijnders, van Heugten, & van Boxtel, 2013). This is the case even though it is well known that persons with MCI carry out everyday activities in a less efficient manner relative to cognitively normal older adults, due to their cognitive deficits (Langa & Levine, 2014). In spite of the lack of studies evaluating the impact of CT on everyday life, it appears that tailoring a CT with an executive functioning foundation improves the likelihood that everyday functioning will improve (Chandler et al., 2016; Ge, Zhu, Wu, & McConnell, 2018; Kelly et al., 2014; Reijnders et al., 2013).

CT induces neuroplasticity by strengthening synaptic circuits (Papp, Walsh, & Snyder, 2009). tDCS delivers weak direct currents to the brain, increasing the probability of transmission across neural circuitry (Nitsche et al., 2003), and subsequently alters behavior (Kuo & Nitsche, 2012; Prehn & Flöel, 2015). Combining these techniques

could therefore illustrate the principle of “mutualism”. Considering their effects when applied separately do not always surpass the threshold required (in terms of extended and functional cognitive benefits for CT (transfer effects in everyday functioning) or producing action potentials for tDCS), pairing them may be more efficient and represents an attempt to join forces to create synergy. Over the last decade, there has been a growth in research looking at such pairing of these interventions, although the evidence that this generates more therapeutic gains in MCI populations remains insufficient and inconclusive (Cruz Gonzalez et al., 2018).

Studies have shown that persons with MCI present with a wide-ranging impairment in everyday functioning, particularly in the everyday memory domain (Farias et al., 2006; Kazui et al., 2005; Niedźwieńska & Kvavilashvili, 2019). The Rivermead Behavioural Memory Test (RBMT) comprises tasks reflective of everyday situations that are associated with memory. Numerous research studies have reported the RBMT to have good ecological validity, in the sense of predicting everyday memory problems in the real world (Bolló-Gasol, Piñol-Ripoll, Cejudo-Bolivar, Llorente-Vizcaino, & Peraita-Adrados, 2014; Wilson, Cockburn, Baddeley, & Hiorns, 1989; Wilson, Zangwill, Baddeley, & Kopelman, 2004). In the present study, the RBMT was administered with the aim of investigating whether the combination of multiple sessions of tDCS with CT would produce transfer effects on everyday memory in older adults with MCI, compared to either CT alone or sham tDCS coupled with CT.

7.2 Methods

7.2.1 Trial design

The trial employed a randomized, double-blinded, sham-controlled design. The CONSORT flowchart is shown in Figure 7.1. The study was conducted in compliance with the Declaration of Helsinki and was approved by the human subject ethics committee of The Hong Kong Polytechnic University (ref. number: HSEARS20170526001) and registered at ClinicalTrials.gov (NCT03441152).

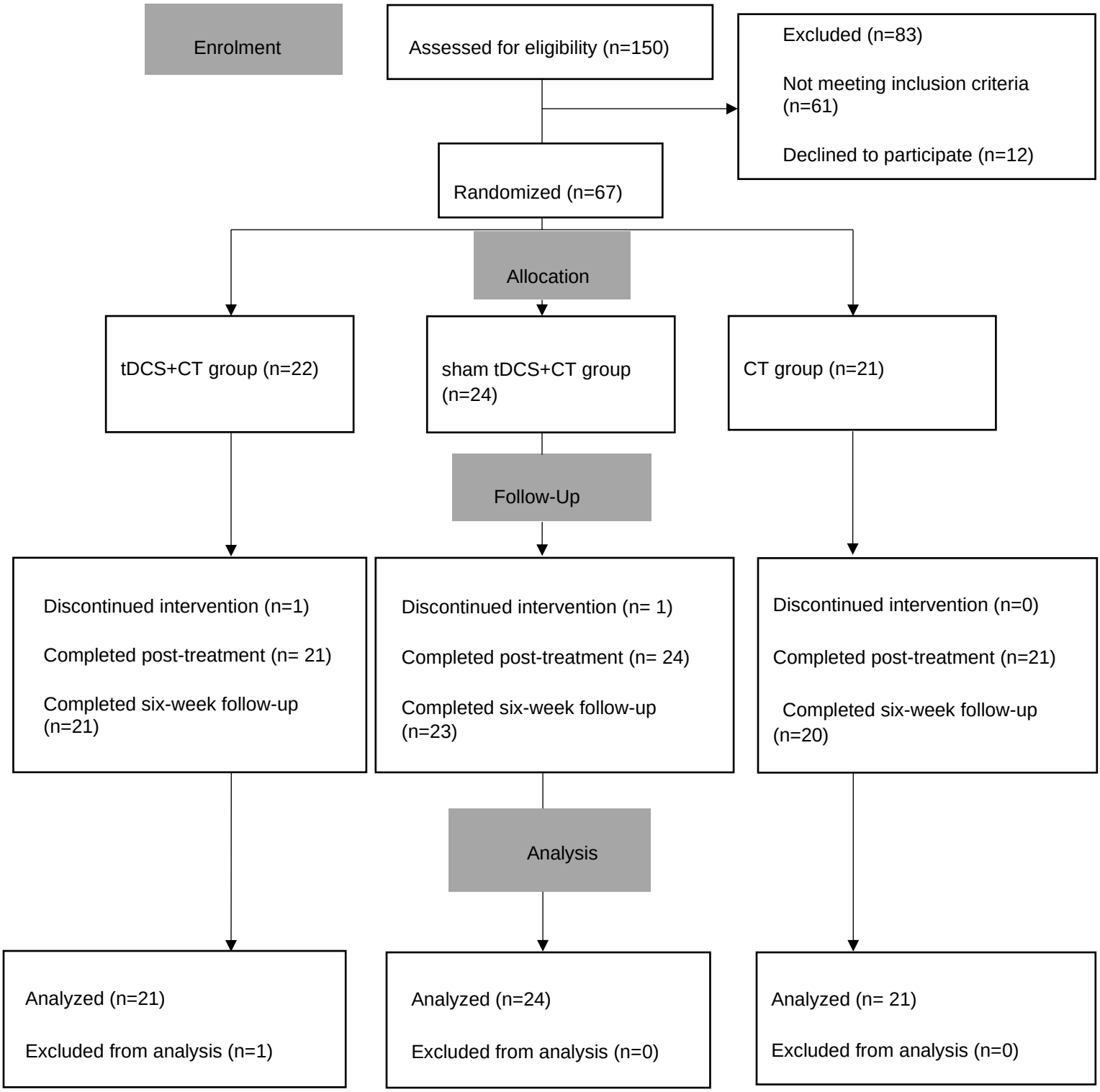

Figure 7.1. CONSORT flow diagram.

7.2.2 Participants

Participants were recruited by convenience sampling from community center groups and recruitment posters in Hong Kong. All participants met the modified Petersen's criteria for MCI (Portet et al., 2006) and were required to meet the following inclusion criteria: (a) be aged between 60 and 85 years; (b) achieve a score of 19-26 on the MoCA (Nasreddine et al., 2005); (c) achieve a score of 0 or 0.5 on the CDR (Morris, 1993); (d) self-report cognitive decline; (e) self-report independence in ADL; and (f) have completed at least three years of primary education. The exclusion criteria ruled out individuals who: (a) had been diagnosed with any neurological disease; (b) scored >4 on the GDS-15 (Yesavage et al., 1982); or (c) reported a history of drug abuse and/or contraindications to tDCS. Informed written consent was obtained before the intervention began.

7.2.3 Intervention and study settings

The intervention was conducted at the research facilities of the university. Three types of interventions were delivered to three independent groups as follows: (1) tDCS combined with CT (tDCS+CT group), (2) sham tDCS combined with CT (sham tDCS+CT), and (3) CT alone (CT group). All eligible participants were randomly assigned to one of the interventions and attended nine intervention sessions staggered over a three-week period.

7.2.3.1 CT

'Neuron Up,' was the computerized CT system used. This is a web platform administered by an occupational therapist and is designed to focus on cognitive functional deficits. The 'Neuron Up' system contains exercises and simulators related to cognitive functions and everyday activities (Fdz de Piérola & Sastre, 2015). All participants performed CT for 30 minutes. The CT content was executive functioning oriented and included tasks associated with arithmetical math, working memory, short-term memory, and attention.

7.2.3.2 tDCS

The device used to administer the current was the Soterix Medical 1 X 1 low-intensity tDCS stimulator. The targeted location for the anode electrode was the LDPFC equivalent to the F3 region according to the 10/20 EEG international system, while the cathode electrode was placed on the contralateral brachioradialis muscle. A constant current of 1.5 mA (current density 0.1 mA/cm^2) was delivered for 30 minutes. The same conditions were replicated for the sham tDCS+CT group, although the current was delivered only during the first and last 30 seconds. The CT was administered simultaneously with the application of the current. The whole process was supervised by an occupational therapist experienced in the use of tDCS.

7.2.4 Outcome measures

Certain areas of the RBMT-3 (Hong Kong version) were used to evaluate the impact of the intervention on everyday memory. These are the scales dealing with verbal, visual,

spatial, and prospective memory; orientation/date; and new learning. The RBMT-3 (Hong Kong version) has been shown to have excellent reliability with inter-rater (ICC [2, 1] = 0.997), intra-rater (ICC [3, 1] = 0), and parallel versions (ICC [3, 1] = 0.990). The internal consistency of the test is satisfactory (Cronbach's alpha: 0.643-0.832). The RBMT-3 (Hong Kong version) is believed to discriminate between PwD and PwMCI and healthy older adults with optimal cut-off scores of ≤ 102.5 and ≤ 131.5, respectively (Fong et al., 2019). Participants were assessed at pre-intervention, post-intervention and at six weeks FU.

7.2.5 Sample size and randomization

The sample size was calculated with 80% power at a 5% Type I error level with an effect size of 0.3, leading to a requirement for 54 participants. A 20% drop-out rate was incorporated, increasing the target sample size to 65 (calculations performed using G*power, Version 3.1.3, University of Kiel, Germany, 2010). Randomization of participants to groups was followed by a random sequence generated by the online platform Qminim (1:1:1 ratio).

7.2.6 Blinding

The assessors who conducted the cognitive assessments were blind to the type of treatment the participants received, but the occupational therapist administering the tDCS and the CT was unblinded during the whole process. The participants involved in the tDCS+CT and sham tDCS+CT group remained unblinded to the type of treatment they received. For obvious reasons, it was not possible to mask the type of intervention to the participants in the CT-only group.

7.2.7 Statistical analysis

Differences at baseline between groups in terms of demographic variables and outcome measures were tested using chi-square and one-way ANOVA tests for the categorical and continuous variables, respectively. A two-way repeated-measures ANOVA (time x intervention) was used to evaluate change. If the time or interaction effect was significant, *post-hoc* multiple comparisons were conducted to investigate within-group differences. Statistical significance was set at $p = 0.05$. Significance values for *post-hoc* tests were adjusted using the Bonferroni correction, $p = 0.017$. Cohen's d was used to calculate the effect size for the RBMT areas when significance was reached. All analyses were performed using IBM SPSS v22.0. An intention to treat analysis was applied to the missing data with the last observation carried forward.

7.3 Results

A total of 67 participants were recruited to be part of the study, of whom 22 were allocated to the tDCS+CT group, 24 to the sham tDCS+CT group, and 21 to the CT group, as set out in Figure 7.1. At baseline, there were no significant differences in any of the outcome measures and demographic data, as shown in Table 7.1.

Variable	tDCS+CT group (n = 21) Mean (SD)	Sham tDCS+CT group (n = 24) Mean (SD)	CT group (n =21) Mean (SD)	F/x^2	*p*
Gender (Male/Female)	6/15	8/16	4/17	1.17 x^2	0.555
Age	69.86 (5.33)	71.00 (6.22)	70.67 (5.42)	0.23	0.792
Years of education	9.76 (3.61)	9.75 (3.69)	11.95 (4.98)	2.02	0.140
MoCA	23.71 (1.73)	24.17 (2.44)	24.33 (1.71)	0.48	0.617
RBMT-3 total score	123.46 (16.99)	124.58 (14.14)	126.80 (18.97)	0.21	0.805
Orientation and Date	7.95 (2.51)	7.37 (2.39)	7.61 (2.03)	0.34	0.709
Verbal Memory	27.28 (6.32)	26.50 (4.96)	26.33 (7.44)	0.14	0.870
Visual Memory	18.85 (4.19)	16.20 (3.86)	18.52 (3.65)	3.11	0.510
Spatial Memory	17.85 (5.29)	21.16 (4.70)	20.76 (4.92)	2.86	0.065
Prospective Memory	35.57 (7.31)	36.54 (5.29)	36.28 (6.02)	0.14	0.867
New Learning	16.00 (5.10)	16.79 (4.42)	17.28 (4.47)	0.40	0.668

Table 7.1. Demographic and outcome measures at baseline.
Note: *p*-value was between groups.

Significant within-group differences were found for all groups in the sum of the scaled scores on the RBMT-3 (Post: tDCS+CT group: $p = 0.001$, $d = 0.95$; sham tDCS+CT group: $p = 0.001$, $d = 0.72$; CT group: p = 0.004, $d = 0.56$. FU: tDCS+CT group: $p = 0.000$, $d = 0.95$; sham tDCS+CT group: p = 0.000, $d = 0.89$; CT group: p = 0.005, $d = 0.67$). However, there were no significant differences between groups.

In terms of the RBMT-3 areas, there was an interaction effect of time-condition in the orientation/date area at post-intervention, compared to baseline, in favor of the sham tDCS+CT group (p = 0.004). The enhancement was significantly reversed at six weeks' FU relative to post-intervention (p = 0.016). There were also significant differences between groups at six weeks' FU as compared to the baseline in favor of the CT group (p = 0.001).

All groups significantly improved in the verbal memory area at six weeks' FU (tDCS+CT group: p = 0.013, d = 0.43; sham tDCS+CT group: p = 0.000, d = 0.99; CT group: p = 0.001, d = 0.74) but only the CT group had significantly improved at post-intervention (CT group: p = 0.001, d = 0.76). In the visual memory area, the sham tDCS+CT group significantly improved performance at post-intervention (sham tDCS+CT group: p = 0.003, d = 0.81). With regards to the prospective memory area, marginal significant differences were found in all groups at post-intervention (tDCS+CT group: p = 0.031, d = 0.76; sham tDCS+CT group: p = 0.031, d = 0.50; CT group: p = 0.027, d = 0.47) and significant differences in the sham tDCS group at six weeks' FU (sham tDCS+CT group: p = 0.017, d = 0.53; tDCS+CT group: p = 0.038, d = 0.66). Enhancement in the new learning area was noted to be statistically significant at post-intervention and six weeks' FU in the tDCS+CT group only (Post: tDCS+CT group: p = 0.004, d = 0.71; CT: p = 0.032, d = 0.69. FU: tDCS+CT group: p = 0.02, d = 0.74; CT group: p = 0.024, d = 0.66). All these results are shown in Table 7.2.

	tDCS+CT (n=21)			Sham tDCS+CT (n=24)			CT alone (n=21)			Within group		Time x Intervention	
	Baseline	Post	6-week FU	Baseline	Post	6-week FU	Baseline	Post-intervention	6-week FU	F	*p*	F	*p*
RBMT-3 total score	123.47 (16.99)	137.14 (10.94)**	138 (13.20)**	124.58 (14.14)	136.45 (18.23)**	137.79 (15.46)**	126.8 (18.97)	137.71 (19.53)**	140.81 (22.5)**	39.02	0.000	0.13	0.967
Orientation and Date	7.95(2.51)	8.00(2.04)	7.95(2.43)	7.37 (2.39)	9.12(2.50)**	7.95(2.21)***	7.61(2.03)	7.85(2.93)*	9.19(2.42)**	4.03	0.020	4.28	0.003
Verbal Memory	27.28(6.32)	29.19(5.49)	30.33 (7.52)**	26.5 (4.96)	29.00(6.64)	31.66(5.41)**	26.33 (7.44)	31.38(5.61)**	31.38 (5.97)**	20.86	0.000	1.32	0.263
Visual Memory	18.85(4.19)	19.04(4.97)	20.09(4.36)	16.20 (3.86)	19.25(3.61)**	18.00(4.09)	18.52 (3.65)	18.66(3.05)	20.09(4.52)	3.92	0.022	1.78	0.137
Spatial Memory	17.85 (5.29)	21.19(4.05)	20.76(4.62)	21.16 (4.70)	21.20(6.12)	22.08(3.48)	20.76 (4.92)	19.85(4.65)	21.76(4.10)	2.86	0.071	1.81	0.131
Prospective Memory	35.57 (7.31)	40.23(4.53)*	39.42 (3.66)*	36.54 (5.29)	39.29(5.57)*	39.33(5.12)**	36.28 (6.02)	39.19(6.30)*	38.09(8.14)	9.77	0.000	0.40	0.807
New Learning	16.00 (5.10)	19.47(4.63)**	19.42 (4.09)**	16.79 (4.42)	18.58(5.15)	18.75(5.16)	17.28 (4.47)	20.76(5.47)*	20.28(4.56)*	11.96	0.000	0.41	0.799

Table 7.2. Comparison of outcome measures across and within groups (Raw means, SD). Note: * P < 0.05; ** P < 0.017. The p-values were within-group comparisons versus baseline. *** P < 0.017; The P-values were within-group comparisons; follow-up assessment versus post-intervention assessment.

7.4 Discussion

The objective of this study was to investigate whether the combination of multisession tDCS with CT would yield transfer effects in everyday memory in older adults with MCI. It was hypothesized that tDCS could strengthen synaptic transmission in neuronal populations in circuits that would be active while engaged in CT practice. Thus, tDCS would provide a booster effect to CT that could translate in transfer effects on everyday memory. To test this hypothesis, three different interventions were compared; tDCS+CT with both sham tDCS+CT and CT alone. The treatments were evaluated using the RBMT-3.

All groups significantly improved in terms of the sum of the scaled scores on the RBMT-3 at all time points compared to baseline. In addition, large effect sizes were seen in the tDCS+CT group and these were larger relative to the other two groups. This finding is surprising because CT interventions are known to be effective in improving skills trained performance, but there is not enough robust evidence from RCTs for its impact on changes in daily functioning in healthy older adults (Papp et al., 2009) even from the largest trial to date (n = 2,832) (Ball et al., 2002). For persons with MCI, the latest evidence of the effectiveness of computerized CT has reported small to moderate positive effect sizes in global cognition function, memory, working memory, and executive function. However, there is no evidence of the improvement in cognitive test performance translating to clinically meaningful benefits in everyday functioning (Zhang et al., 2019). This is believed to be the first RCT involving persons with MCI to report

potential far transfer effects for computerized CT in standardized test performance that is associated with an improvement in real-life everyday memory situations as well.

Interestingly, in the results for the orientation/date area of the RBMT-3, the performance of the sham tDCS+CT group was significantly better at post-intervention compared to the other two groups. However, this improvement was significantly reversed at six week's FU, whereas the score for the CT group at this point was significantly higher, and the tDCS+CT group score remained stable across all time points. Given this unexpected outcome, the MoCA score related to the orientation domain was analyzed. These items are similar to those in orientation/date area of the RBMT-3. This score was obtained from a parallel research study conducted with the same participants (Chapter 6) and the results exhibited no significant interaction between groups ($F = 0.363$, $p = 0.834$). This demonstrates inconsistency with the orientation results reported here (see Table 7.3).

	tDCS+CT (n=21)			Sham tDCS+CT (n=24)			CT alone (n=21)			Within group		Time x Intervention	
	Baseline	**Post**	**6-week FU**	**Baseline**	**Post**	**6-week FU**	**Baseline**	**Post-intervention**	**6-week FU**	**F**	***p***	**F**	***p***
MoCA (Orientation)	5.86(0.35)	5.90(0.30)	5.90(0.30)	5.75 (0.44)	5.96(0.20)	5.88(0.33)	5.67(0.48)	5.76(0.53)	5.76(0.62)	2.21	0.118	0.36	0.817
RBMT-3 (Orientation/date)	7.95(2.51)	8.00(2.04)	7.95(2.43)	7.37 (2.39)	9.12 (2.50)**	7.95 (2.21)***	7.61(2.03)	7.85 (2.93)*	9.19(2.42)**	4.03	0.020	4.28	0.003

Table 7.3. Comparison of orientation outcome measures in MoCA and RBMT-3 across and within groups (Raw means, SD).
Note: * P < 0.05; ** P < 0.017. The P-values were within-group comparisons versus baseline. *** P < 0.017; The P-values were within-group comparisons; follow-up assessment versus post-intervention assessment.

The reason why the orientation/date score was significantly better in the sham tDCS+CT cannot be ascertained. While it may be speculated that a placebo effect was present (Dawood et al., 2019) this is undermined by the fact that the tDCS+CT group was also receiving a form of tDCS, although it is important to mention that the neurophysiological effects of tDCS are unpredictable (Horvath, Carter, & Forte, 2014); even the application of the anode electrode to the brain cortex does not always elicit action potentials and even if it does, it does not always yield behavioral gains (Prehn & Flöel, 2015). Finally, it is worth mentioning the high values for Cronbach's alpha in RBMT-3 which indicates how well the items of the test measures the same construct. Interestingly, when the orientation/date area scores were removed from the analysis for one group of older adults, the alpha value increased, suggesting this area does not fit well in the everyday memory construct (Fong et al., 2019).

Moreover, significant benefits have been evidenced in other areas of the test, such as verbal and prospective memory, in all groups. The sham tDCS+CT group improved in the visual memory area and the tDCS+CT group enhanced in the new learning area. These within-group far transfer effects on everyday memory raise the question of why this improvement has taken place in all groups, and why tDCS has not exerted a superior effect.

Older adults experience a volume reduction in gray matter, particularly in the frontal areas. This loss of tissue appears to cause decreased executive functioning and processing speed which ultimately results in everyday memory complaints (Denise & Helen, 2015; Harada, Love, & Triebel, 2013). These deficits seem to be exacerbated in

people with MCI (Traykov et al., 2007), who have been shown to impair working memory and attention (Kochan et al., 2010; Saunders & Summers, 2011), resulting in reduced efficiency when performing activities of daily living (Langa & Levine, 2014). Furthermore, people with MCI often report subjective cognitive complaints (Albert et al., 2011; Langa & Levine, 2014). Following this body of thought, and despite the lack of evidence on CT inducing transfer effects in everyday functioning, it is suggested that CT interventions based on executive functioning tasks are more likely to produce the desired outcomes (Kelly et al., 2014). For this reason, the computerized CT the participants received was based on core elements of executive functioning such as working memory and attention, and involved processes such as planning, reasoning, and response inhibition (Diamond, 2013; Harada et al., 2013). Furthermore, using computerized CT creates stronger effect sizes and improved generalization of benefits compared with nonspecific CT (Zhang et al., 2019). These two factors may have contributed to the overall improvement in everyday memory, since the same computerized CT intervention was delivered to all participants.

As mentioned above, the loss of brain tissue in the prefrontal areas of the brain seems to have a negative impact on executive functioning because of the relationship between this brain area and this type of cognitive function. This is why it was hypothesized that applying a direct current to the left prefrontal cortex could increase synaptic transmission among the neural networks activated when the participants were engaged in specific CT tasks (executive functioning based), thus producing a superior effect than if they completed these CT activities without additional stimulation. Unfortunately, this

superior effect was only manifested by the largest effect size exhibited in the total score of the RBMT-3 in the tDCS+CT group, although this is not enough to state that tDCS has emerged as a booster to the transfer effects of CT in everyday functioning. A similar study has discussed that significant behavioral effects could be attributed to practice effects from the nontrained cognitive tasks that may obscure any true between-group effects (D. M. Martin et al., 2019). The potential intersubject variability in tDCS application is also noteworthy, as anatomical characteristics such as head size, shape, and brain shrinkage associated with ageing all contribute to the physiological effects of tDCS (Horvath et al., 2014). This means that participants respond differently to tDCS, as shown in studies that have targeted the prefrontal cortex (Tremblay et al., 2014). All these factors compound, increasing the variability. One potential solution to this is to increase the sample size of studies as a counterbalance.

This study has some limitations. In order to conclude robustly that a computerized CT based on executive functions could produce transfer effects in everyday memory, it would have been necessary to include a fourth, no training, control group. As a matter of fact, there is a growing number of studies reporting beneficial effects on objective cognitive measures in MCI while disregarding the threat to internal validity arising from the lack of parallel forms of the tests used (Fong et al., 2019; Jean, Bergeron, Thivierge, & Simard, 2010). However, the RBMT-3 has a parallel version with excellent reliability that was administered here to compensate for the testing effect. This makes it possible to suggest there is a genuine transfer effect from computerized CT to everyday functioning (Fong et al., 2019). In addition, it would have been interesting to have

applied the Everyday Memory Questionnaire, a subjective measure of memory failure in everyday life, to evaluate its alignment with the RBMT results (Royle & Lincoln, 2018). For practical reasons, it was not possible to blind the occupational therapist who administered the tDCS and the CT and this could have introduced some bias in terms of their interaction with the participants. Regrettably, also, the post-intervention assessment was not conducted at the same time for all the participants. The intention was to perform the testing within a window of five days and the participants were encouraged to attend as soon as possible for this purpose, but ultimately the study relied on their availability. This could have influenced the results due to the unknown mechanism for the duration of the long-lasting effects of tDCS, thus diminishing its potential as a booster. Finally, the participants in this study did not have a formal diagnosis of MCI from a physician although they met the modified Petersen's criteria and the RBMT-3 values at baseline corresponded with the suggested MCI cut-off scores (Fong et al., 2019), the findings of this study must be interpreted with caution.

In summary, no tDCS specific effect was found between groups for the RBMT-3 total score but it did create a larger effect size in participants with MCI. Computerized CT focusing on executive functioning might produce a far transfer effect and enhance everyday memory, but concurrent tDCS provides no additional benefit.

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CHAPTER 8: NEURAL RESPONSE TO MULTISESSION TRANSCRANIAL DIRECT CURRENT STIMULATION COMBINED WITH CONCURRENT COGNITIVE TRAINING IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

This section is a subsequent chapter of the main study carried out in this thesis (chapter 6) that focuses exclusively on the effects of the randomized controlled interventions for older adults with MCI at the neurophysiological level by means of EEG. We have investigated the behavioural responses of multisession tDCS interventions in the last chapter. In this chapter, we investigated what occurs in the brain after multiple sessions of tDCS were delivered to the cortex when performing CT in older adults with MCI, comparing brain responses with control and placebo conditions.

In the last experimental section of this thesis, we aimed to understand more about the neural mechanism underpinning the application of tDCS.

8.1 Introduction

EEG is a non-invasive technique that studies the electrophysiological dynamics of the brain and enables researchers to look for associations between those dynamics and cognition. Therefore, EEG can help to provide physiological evidence about the neural mechanism underlying human cognition (Cohen, 2017). The capacity of tDCS to modulate brain activity extends to modulation of electrophysiological oscillations of the brain (Brunoni et al., 2012). Furthermore, modulating neural oscillations will likely alter subsequent behavior (Gandiga, Hummel, & Cohen, 2006). EEG would be a good option to measure the modifications of brain activity produced by tDCS since EEG can capture the fluctuation of local field potentials surging from the postsynaptic potentials of the cortical neurons due to the mechanism of action of tDCS. EEG can also track responses to tDCS in specific brain areas and circuits (Anna Mangia, Marco Pirini, & Angelo Cappello, 2014). Various studies have investigated electrophysiological changes in EEG oscillations after the application of tDCS (Anna Mangia et al., 2014), such as the effects of tDCS on motor skills (Baxter, Edelman, Sohrabpour, & He, 2017; Kasashima et al., 2012; Matsumoto et al., 2010) and on cognition (Martens et al., 2020; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011).

The ultimate goal when prescribing a CT intervention to older adults with MCI is to improve their cognitive functioning and prevent it from worsening with the passage of time which can have a critical impact on everyday functioning (Falkenstein & Gajewski, 2016). The effectiveness of CT interventions tends to be assessed in psychometric or neuropsychological tests. However, these tests present limitations, for instance, relying

on subjective judgements or variables such as age and education level. In addition, they can become time consuming (Cassani, Estarellas, San-Martin, Fraga, & Falk, 2018; Falkenstein & Gajewski, 2016; Farina et al., 2020; Parra, 2014). Alternatively, other measures based on brain imaging, namely MRI and fMRI, have been used in CT studies before. EEG is a potential technique for taking these measures of brain related activity. Interestingly, only a few studies have investigated the effects of CT with this technique despite the inexpensive nature of this method as compared to MRI and fMRI (Brehmer, Kalpouzos, Wenger, & Lövdén, 2014; Falkenstein & Gajewski, 2016). CT has neuroplastic properties - as the brain learns through taking part in new experiences, new neural networks are formed, even in medical conditions such as MCI where mental health is compromised (Berlucchi, 2011; Fernández-Ballesteros, Zamarrón, Tárraga, Moya, & Iñiguez, 2003). Neuroplasticity can be evidenced by functional changes in the brain as shown by increases or decrease in neuronal activity in brain regions associated with specific cognitive domains that can be influenced by the practice of cognitive tasks (Brehmer et al., 2011; Park & Bischof, 2013).

Taking into account that both interventions - tDCS and CT, can induce changes in brain activity that result in behavioral therapeutic benefits, we used a paradigm in which tDCS is delivered concurrently with CT in older adults with MCI. This paradigm seems to yield superior performance in the processing speed of task-specific domains of CT activities (see Chapter 6) as compared with the combination of sham tDCS paired with CT or CT alone. The rationale is that specific neural circuits are activated by a task (e.g. CT). Since these networks, but not others, had been activated, they become more receptive

to tDCS (Cruz Gonzalez, Fong, Chung, et al., 2018; Jackson et al., 2016; Kronberg, Bridi, Abel, Bikson, & Parra, 2017; Morya et al., 2019).

> "Only synapses already undergoing plasticity would be modulated by tDCS, while inert synapses would not be activated or modulated" (Morya et al., 2019, p.3)

We explored how the administration of multisession tDCS in combination with CT in persons with MCI could influence spectral analysis of absolute power relative to sham tDCS paired with CT and CT alone in the RCT. We investigated the offline effects of these three interventions to determine a change of power in delta, theta, alpha and beta frequency bands in brain regions targeted by tDCS.

8.2 Methods

8.2.1 Participants

Participants were recruited by convenience sampling using research recruitment posters advertised in The Hong Kong Polytechnic University and from community center groups in Hong Kong. All included participants were suspected to have MCI based on the modified Petersen's criteria (Portet et al., 2006) (given by the MCI Working Group of the European Consortium on Alzheimer's Disease, Brescia Meeting, Italy, June 2005) and had to meet the following conditions: (a) present a MoCA (Nasreddine et al., 2005) score between 19 and 26; (b) obtain a score on the CDR of 0.5 or below (Morris, 1993); self-report decline of cognitive function and independence in ADL; and (d) have

completed at least three years of primary education. Participants who met the following conditions were excluded: (a) diagnosis of a neurological disease except for MCI; (b) suspected depression defined by a score on the GDS-15 of greater than four (Yesavage et al., 1982); and (c) presented contraindications to tDCS treatment such as epilepsy and history of drug abuse. A description of the sequence, process, and content of the study was explained to all participants. Informed written consent was obtained before the intervention began.

The study was carried out in accordance with the Declaration of Helsinki and was approved by the human subject ethics committee of The Hong Kong Polytechnic University (ref. number: HSEARS20170526001) and registered at ClinicalTrials.gov (NCT03441152).

8.2.2 Trial design

The trial utilized a double-blinded sham-controlled design with three different treatment groups. After the screening and recruitment process, all participants who met the criteria and agreed to join the study were randomly assigned to receive either CT with tDCS (tDCS+CT group), CT with sham tDCS (sham tDCS+CT group), or only CT (CT group). Participants were assigned to a treatment group according to a random sequence generated by the web-based sequence generator ‘Qminim’ (1:1:1 ratio). The random allocation sequence was executed following the order of recruitment completed by a therapist who administered the interventions but was not involved in participant screening. All groups underwent three sessions per week for three weeks (nine

sessions in total). Participants were assessed at baseline and post-treatment. This study follows the CONSORT for RCT (Figure 8.1).

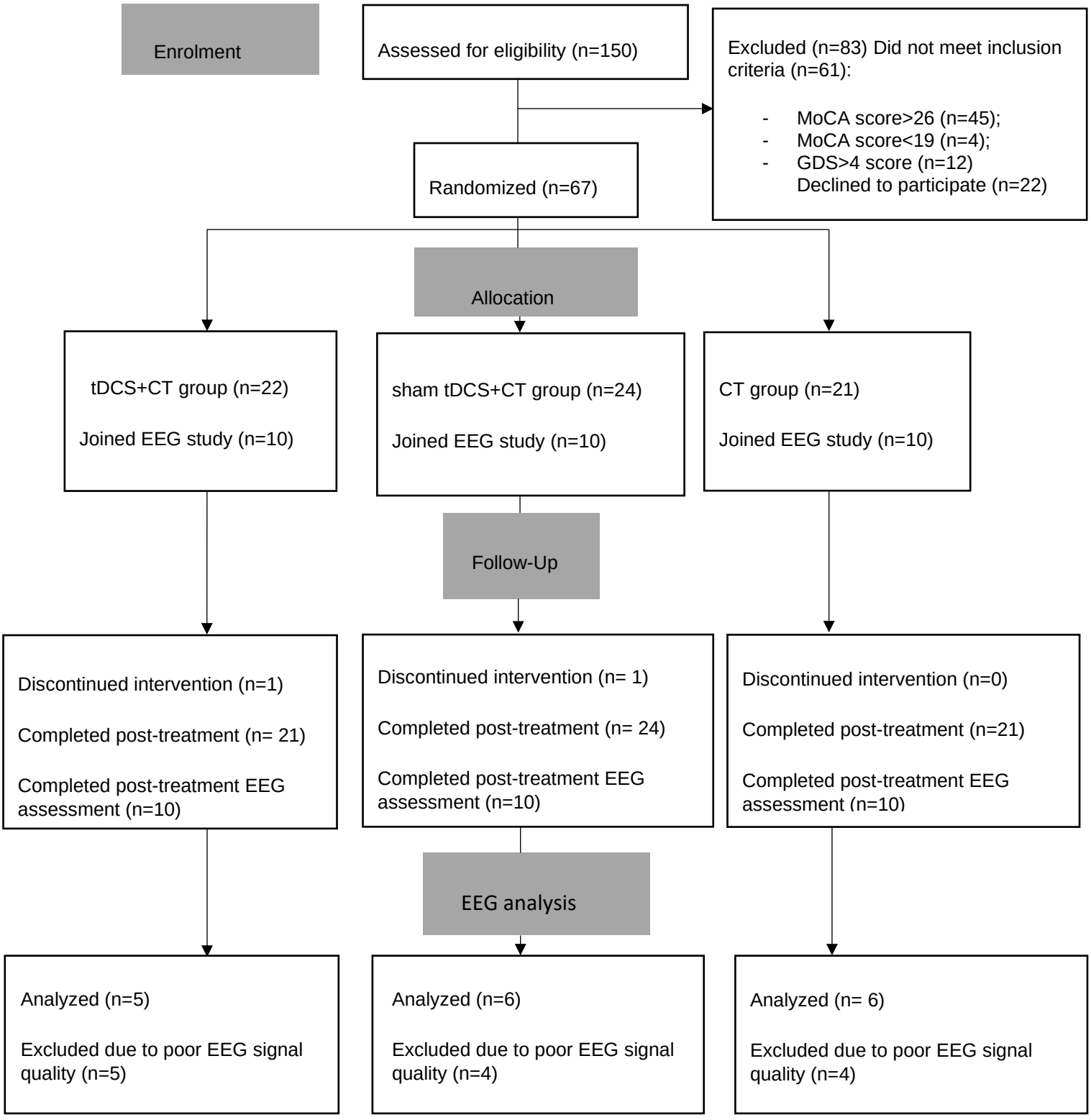

Figure 8.1. CONSORT flow diagram.

8.2.3 Intervention and study settings

The common factor regarding the intervention is that all groups received three-weeks of computerized CT with the same content. The groups differed in whether CT was performed alone or combined concurrently with either tDCS or sham tDCS. The therapists who performed the evaluation of participants were blind to the allocation process and were not aware of the type of intervention the participants were assigned to. However, the therapist who administered the interventions was not blind to the type of intervention participants received.

8.2.3.1 tDCS

A Soterix Medical 1 X 1 low-intensity tDCS device (1300A, Soterix Medical, USA) was used to deliver direct current to the scalp. The anode electrode was placed over the LDPFC (F3 region based on the \/20 EEG international system) and the cathode electrode was positioned on the contralateral brachioradialis muscle. These electrodes were inserted into 5x3 cm (15 cm2) sponges soaked in saline solution and attached to the targeted areas with elastic bands. Stimulation was applied for 30 minutes at a current intensity of 1.5 mA for the tDCS+CT group. Stimulation was preceded, and ended, with a 30 second ramp-up and ramp-down of current intensity, respectively. In the sham tDCS+CT group, all procedures and parameters were replicated excluding the delivery of constant current at 1.5 mA for 30 mins but including the ramp-up and ramp-down sequences to reproduce the physical sensations produced by tDCS. The CT was delivered concurrently with the onset of tDCS and sham tDCS in every session. The

participants from the CT group only performed the CT tasks and did not receive any additional treatment.

8.2.3.2 Computerized CT

The computerized CT selected for the intervention was ‘Neuron Up’ (Fdz de Piérola & Sastre, 2015), a web platform (https://www.neuronup.com/) which provides customizable training materials to enable CR. This CT was selected because it has been shown to improve various cognitive outcomes in persons with MCI (Mendoza Laiz, Del Valle Diaz, Rioja Collado, Gomez-Pilar, & Hornero, 2018) and has been previously used for pairing with tDCS, showing mild cognitive gains (Cruz Gonzalez, Fong, & Brown, 2018).

The CT included seven tasks associated with components of executive functions such as working memory and attention (Diamond, 2013). The participants realized the CT with a touchscreen laptop-tablet hybrid (13.30 inches) in individual sessions for 30 minutes under the supervision of a therapist.

8.2.3 Outcome measures

The outcome measure was the spectral analysis of absolute power by means of EEG.

8.2.3.1 EEG data acquisition

EEG was captured by 64 multipin-shaped dry-contact electrodes inserted into an equidistant layout elastic cap using a mobile digital amplifier (waveguardTM touch, ANT Neuro b.v., Hengelo, Netherlands). Two extra snap electrodes were attached to the

mastoids as ground and reference electrodes after cleaning the areas with alcohol pads.

> “The equidistant electrode layout is required to ensure homogeneous flexibility of the cap fabric and homogeneous electrode adduction, which is an important requirement for optimal dry electrode functioning” (di Fronso et al., 2019, p.3)

This dry EEG device has been previously validated (Fiedler et al., 2015; Patrique Fiedler et al., 2016). When putting the cap on, a manual inspection was completed to ensure the dry electrodes were well attached to the scalp. A visual inspection of data quality was then performed by checking signal quality indicators provided by the EEG data acquisition software (eego software ANT Neuro b.v., Hengelo, Netherlands). The signal was sampled at 1024 Hz. The participants were asked to remain seated, still, and relaxed with their eyes fixated on a cross located on a sheet of A4 paper in front of them. Resting EEG was recorded for five minutes on two occasions, once before the commencement of the interventions and once immediately after the end of the intervention within the time window of the offline effects of tDCS.

8.2.3.2 EEG pre-processing

EEG data was processed offline using EEGLAB (Delorme & Makeig, 2004) and custom-made Matlab scripts. Raw EEG data was down-sampled to 128 Hz and band-pass filtered between 1 and 30 Hz. Data was then visually inspected to identify noisy signals and defective channels and rejected accordingly. Data was re-referenced to a common average and independent component analysis (Delorme & Makeig, 2004) was run to

remove signals from significant eye movements such as blink artifacts. Defective channels were interpolated using spherical spline interpolation (Ferree, 2006).

8.2.3.3 EEG frequency band and absolute power

Spectral analysis of absolute power on the area of interest was conducted. The area of interest was the left prefrontal cortex which corresponds with channel 1LB and 2L in the equidistant 64 layout which is also the target area of the anode electrode during the tDCS intervention. The following four frequency bands were analyzed: delta (1-4Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-25 Hz). If significant changes were found, averaged powers at the fixed frequency band were created to illustrate the EEG topographies by the topoplot function of EELAB (Delorme & Makeig, 2004).

8.2.4 Sample size

The sample size of this study was extracted from a parallel study that focused on the effectiveness of the interventions on behavioral outcomes (see Chapter 6 and 7 for sample size estimation). The total sample size of that study was 67 participants: 22 participants in the tDCS+CT group, 24 participants in the sham tDCS+CT group, and 21 participants in the CT group. Since there is no reference in the literature which conducted an EEG study with similar characteristics to ours, the sample size targeted for this pilot was set using rule of thumb for an EEG study at 30 participants (10 participants in each group). Therefore, participants who met the inclusion criteria and were invited to join the intervention were invited to participate in an EEG recording before and after the intervention.

8.2.5 Statistical analysis

Differences at baseline among groups in demographics and EEG measures were tested using Chi-square tests and One-way ANOVAs for categorical and continuous variables, respectively. A two-way repeated-measures ANOVA (time x intervention) was used to examine changes in the spectral analysis of absolute power between interventions of the delta, theta, alpha and beta frequency bands in 1LB and 2L channels. If there was a significant interaction effect, *post-hoc* paired comparisons were conducted to investigate the within-group differences for each group. Statistical analysis was conducted using SPSS version 22 with statistical significance set at $p = 0.05$.

8.3 Results

Thirty participants agreed to join the EEG assessment, ten from each intervention group. Due to poor EEG signal quality, 14 cases were discarded, and the remaining 16 cases carried forward for data analysis (tDCS+CT, n = 6; sham tDCS+CT, n = 5; CT, n = 5; see Table 8.1). There were no differences in demographic variables or baseline power values of each frequency band across groups (see Table 8.1).

Variable	tDCS+CT group (n = 6) Mean (SD)	Sham tDCS+CT group (n = 5) Mean (SD)	CT group (n = 5) Mean (SD)	F/x^2	*p*
Gender (Male/Female)	1/5	1/4	0/5	1.067 x^2	0.587
Age	68.20 (5.07)	70.40 (6.69)	69.67 (6.59)	0.164	0.850
Years of education	10.20 (2.95)	9.00 (3)	11.00 (4.51)	0.412	0.671
MoCA	23.20 (2.38)	23.40 (3.43)	22.83 (2.31)	0.062	0.941
Delta (1LB)	3.09 (1.29)	2.87 (1.85)	2.77 (2.06)	0.044	0.957
Theta (1LB)	0.81 (0.31)	0.79 (0.52)	1.01 (0.85)	0.203	0.819
Alpha (1LB)	0.91 (0.59)	0.59 (0.47)	1.02 (1.26)	0.329	0.725
Beta (1LB)	0.63 (0.50)	0.32 (0.12)	0.47 (0.32)	0.972	0.404
Delta (2L)	4.48 (1.51)	3.99 (1.28)	2.47 (1.63)	2.728	0.102
Theta (2L)	1.31 (0.44)	1.15 (0.60)	0.69 (0.49)	2.157	0.155
Alpha (2L)	1.05 (0.45)	0.79 (0.69)	0.62 (0.64)	0.674	0.527
Beta (2L)	0.66 (0.45)	0.39 (0.24)	0.45 (0.48)	0.582	0.573

Table 8.1. Demographic and absolute power data at baseline. *p*-value was between groups.

Two-way repeated measures ANOVA showed a significant interaction effect (time x intervention) in channel 1LB (see Table 8.2) for absolute power of the theta band (p = 0.047)

	tDCS+CT (n = 5)		Sham tDCS+CT (n = 5)		CT alone (n = 6)		Within group		Time x Intervention	
	Baseline	**Post**	**Baseline**	**Post**	**Baseline**	**Post**	**F**	***p***	**F**	***p***
Delta (1LB)	3.09(1.29)	5.71(2.78)	2.87(1.85)	4.76(2.64)	2.77(2.06)	2.80(1.03)	5.79	0.032*****	1.63	0.233
Theta (1LB)	0.81 (0.31)	1.34(0.37)	0.79 (0.52)	0.96(0.26)	1.01 (0.85)	0.67(0.37)	0.88	0.363	3.89	0.047*****
Alpha (1LB)	0.91 (0.59)	1.19(0.33)	0.59 (0.47)	0.64(0.29)	1.02 (1.26)	0.53(0.27)	0.08	0.777	1.40	0.281
Beta (1LB)	0.63 (0.50)	0.64(0.33)	0.32 (0.12)	0.27(0.12)	0.47 (0.32)	0.48(0.30)	0.01	0.920	0.44	0.958
Delta (2L)	4.48 (1.51)	5.05(1.81)	3.99 (1.28)	6.01(2.53)	2.47 (1.63)	1.62(1.09)	1.54	0.236	3.30	0.069
Theta (2L)	1.31 (0.44)	1.58(0.54)	1.15 (0.60)	1.36(0.70)	0.69 (0.49)	0.54(0.49)	0.69	0.421	1.00	0.393
Alpha (2L)	1.05 (0.45)	1.08(0.47)	0.79 (0.69)	0.87(0.72)	0.62 (0.64)	0.41(0.39)	0.04	0.830	0.46	0.637
Beta (2L)	0.66 (0.45)	0.57(0.26)	0.39 (0.24)	0.29(0.14)	0.45 (0.48)	0.28(0.18)	1.64	0.223	0.07	0.925

Table 8.2. Comparison of absolute power data across and withing groups (Raw means, SD). Note: * Significant at the level of $p < 0.05$.

Post-hoc paired comparisons revealed that this change in absolute power was statistically significant only in the tDCS+CT group (p = 0.047) (see Figure 8.2). There were no other significant changes in absolute power in the remaining frequency bands between groups, although there were statistically significant changes within groups in channel 1LB in the delta band (p = 0.032).

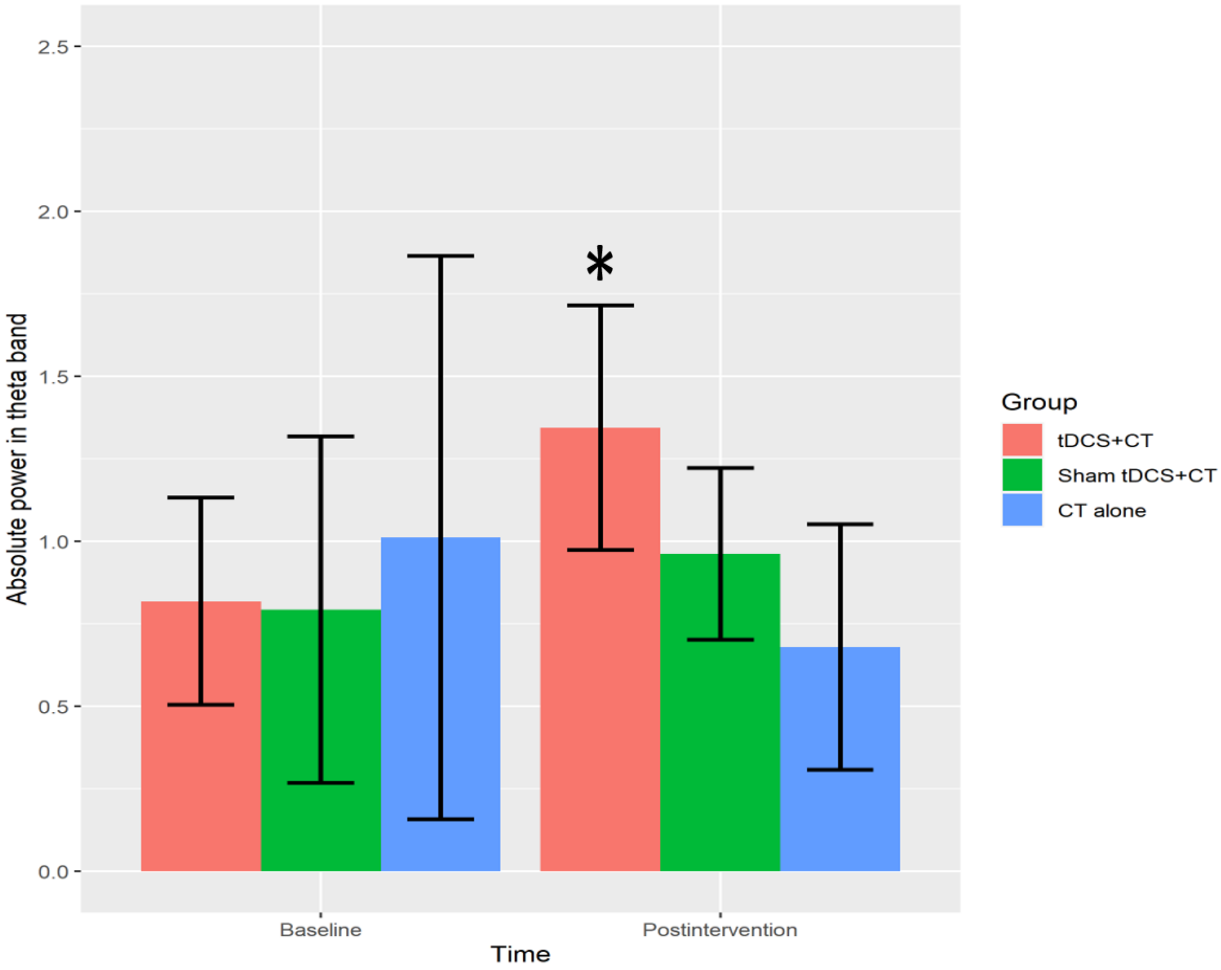

Figure 8.2. Comparison of absolute power in theta band frequency in channel 1LB.

Note: Absolute power values are expressed in μV^2. * Significant difference from baseline (p = 0.047).

The topography of absolute theta power for all channels before the intervention and at post-intervention in the three groups is shown in Figure 8.3.

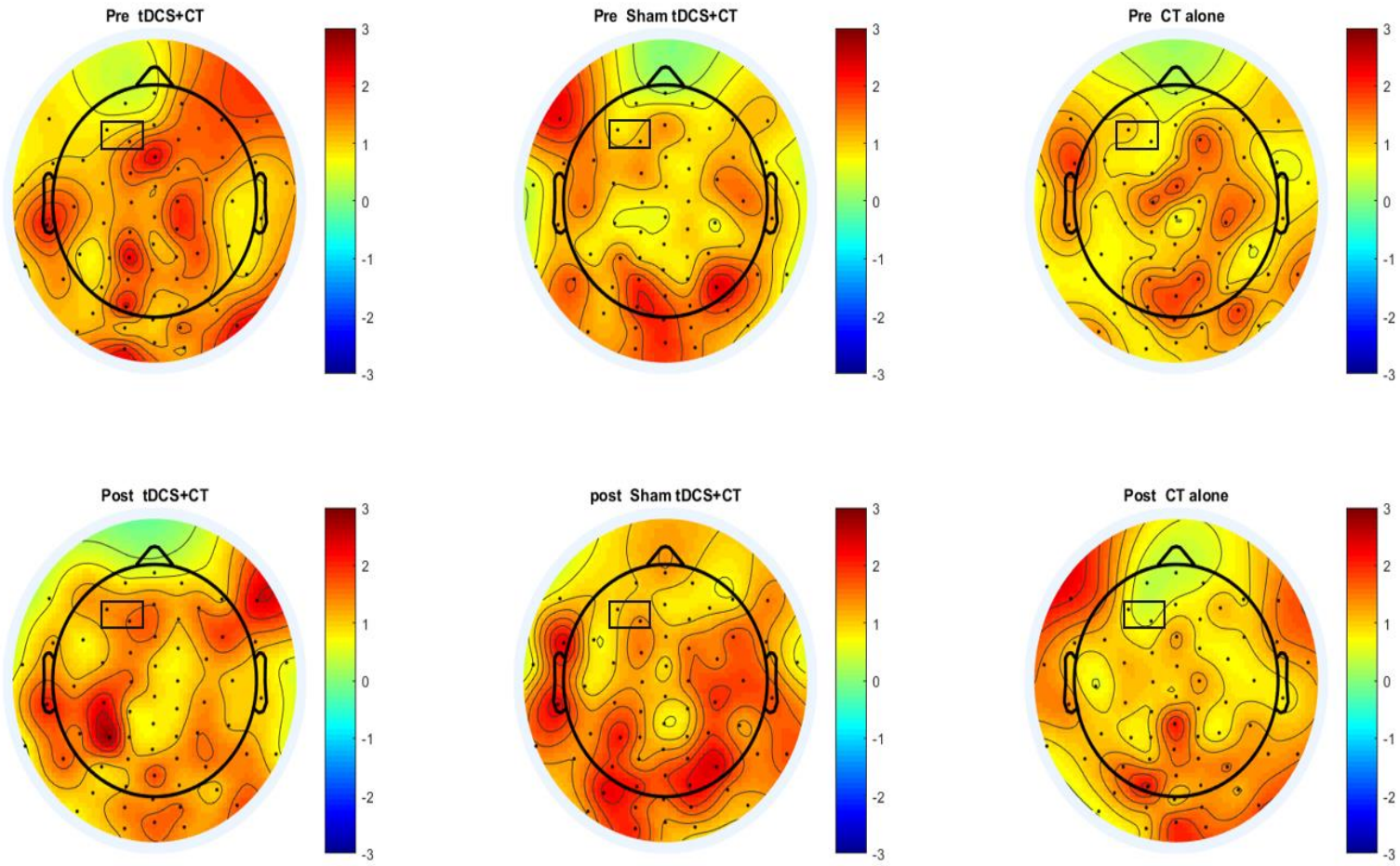

Figure 8.3. Absolute theta band (4-8 Hz) power from 64 channel EEG recorded before and after intervention whilst at rest with eyes fixated.

8.4 Discussion

A recent systematic review involving persons with MCI who received tDCS showed that there were no studies using EEG to assess the effects of tDCS (Cruz Gonzalez, Fong, Chung, et al., 2018). The purpose of this study was to explore whether multiple sessions of anodal tDCS applied to the left DLPFC paired with CT would alter the spectral analysis of absolute power relative to sham tDCS paired with CT and CT alone in older adults with MCI. We investigated the neurophysiological effects of the three interventions, by means of resting EEG (eyes open), on the change of absolute power in delta, theta, alpha and beta frequency bands in the left prefrontal cortex targeted by tDCS. We sought to yield more knowledge about the underlying mechanism of tDCS.

Our statistical analysis confirmed that tDCS concurrently paired with CT modulated neuronal activity as shown by significant differences in the absolute power of the theta band relative to the other two conditions, sham tDCS+CT and CT alone. These findings are in line with previous studies which used the anode electrode of tDCS to target the medial prefrontal cortex and recorded EEG at rest in healthy young adults. Interestingly, there was an increase in theta power in the frontal-midline and right DLFPC recorded after stimulation (Miller, Berger, & Sauseng, 2015) which could be due to the diffuse effect that tDCS has on neighboring and distal areas, since even small brain regions far from each other can be functionally connected (Jaberzadeh et al., 2019). Increased theta power was also reported in another study using resting EEG (eyes close) during ongoing tDCS followed by an increase in alpha and beta power, yet, the anode was placed over

the right posterior parietal cortex (Anna L. Mangia, Marco Pirini, & Angelo Cappello, 2014).

Theta EEG waves are the dominant EEG frequency over the prefrontal cortex (Miller et al., 2015; Sauseng, Griesmayr, Freunberger, & Klimesch, 2010). Theta oscillations have been associated with attention (Green & McDonald, 2008; Sauseng et al., 2010; Sauseng, Hoppe, Klimesch, Gerloff, & Hummel, 2007) and working memory domains, especially when performing working memory tasks that involve processes such as encoding and retrieving information or suppressing task distractors (Jensen & Tesche, 2002; Miller et al., 2015; Raghavachari et al., 2001; Sammer et al., 2007). Enhanced frontal-midline theta power has been linked to multitask video game training that enhanced cognitive control abilities (working memory and attention) in healthy older adults. These results could be taken as an indicator of robust plasticity of the prefrontal cognitive control system in the ageing brain (Anguera et al., 2013). Conversely, the enhanced prefrontal theta power resulting from tDCS+CT in our study occurred in the left prefrontal area, our area of interest determined by the position of the anodal tDCS electrode. The few studies which have evaluated CT with measures of EEG showed increased frontal theta activity (Falkenstein & D. Gajewski, 2016). However, we did not observe any changes in theta activity in our comparison groups, sham tDCS+CT and CT alone, despite both of them receiving three weeks of the same content CT as the tDCS+CT. A possible explanation for this phenomenon is the addition of tDCS which could have changed brain excitability and increased theta activity in the left prefrontal cortex (Miller et al., 2015). Thus, only synapses already undergoing plasticity due to CT

would be modulated by tDCS (Kronberg et al., 2017; Morya et al., 2019). This concept is known as exquisite selectivity which states that only the brain areas activated by a task (CT) would be predisposed to modulation by tDCS (Morya et al., 2019). This is line with our findings in relation to task-specific outcomes (see chapter 6) in which we explained that enhanced processing speed of CT tasks related to working memory and attention occurred because of the advantages of tDCS modulation. These advantages might only be evidenced through task-specific training and expressed physiologically by increased theta power in the stimulated area. The associations aforementioned about theta power, working memory and attention are also noteworthy since the CT delivered in our experiment was centered upon executive function, particularly working memory and attention. This level of specificity in the intervention and evaluation might have influenced the excitability of the brain in the tDCS+CT group.

This study was not free of limitations. Originally, thirty participants joined the EEG assessment but eventually fourteen participants were discarded due to the poor quality of the signal and the elevated number of channels that had to be interpolated. These two factors have affected the interpretation of our findings, first because the sample size in each group was small, and second, some neural patterns could have been masked because of the quality of the signal in some samples. Another important point is that this study lacked a fourth group - tDCS alone, which would have enabled us to draw more solid interpretations regarding the modulatory effects of tDCS on brain activity. Despite these complications, this preliminary study has yielded some valuable insights in CR and neuromodulation.

8.5 Conclusion

Multisession anodal tDCS applied to the LDPFC combined with CT increased absolute theta power in the left prefrontal cortex in persons with MCI as compared to sham tDCS with CT and CT alone. The application of tDCS acted as a modulator of neuronal activity which may have been boosted by the task-specific effects of CT. Further study with larger sample sizes and additional conditions is warranted.

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CHAPTER 9: CONCLUSIONS

This chapter closes this thesis, and the reader is provided with a “key message” in point form for the findings generated from the 3-phase study mentioned in the thesis.

In this thesis, we proposed the concurrent combination of tDCS and CT as a novel therapy in CR for persons with MCI. The aim of this thesis was to advance our understanding of its effects in cognitive functioning in three dimensions; domain- and task-specific outcomes of CT tasks, and everyday function outcomes in older adults with MCI. We hypothesized that the proposed intervention would be superior to the administration of CT alone. We were also interested to explore the physiological response of the brain towards the different interventions applied on our experiment, seeking to elucidate the mechanism of action that underpins the combination of tDCS and CT. To validate our hypothesis, we implemented a three-phase research project, the conclusions of which are drawn below according to the research studies conducted.

9.1 Phase 1: Systematic review and meta-analysis

We conducted a systematic review and meta-analysis regarding the effects of tDCS on persons with MCI and dementia to answer the following question: can tDCS serve as a clinical intervention to improve cognitive functions of persons with MCI and dementia? To answer this question in greater depth, we reformulated the question into three specific questions below:

(1) Does tDCS alone improve cognitive functioning in persons with MCI and dementia?

tDCS alone appeared to have a positive effect on cognition, especially for memory and language in PwD with mild to moderate cognitive decline, and MCI.

(2) Does tDCS coupled with CT, or applied as a primer to other cognitive interventions, yield greater benefits in cognitive functioning than the administration of tDCS alone?

There was no conclusive advantage of coupling tDCS with CT as it seems that the benefits might be identical to the administration of tDCS alone. However, most of the studies applied tDCS alone, further studies are warranted in order to add more evidence to answer this question.

(3) Do the effects of tDCS on cognitive functions persist over time?

We explored the short- and long-term effects of tDCS targeting the DLPFC in PwD on the memory domain. Our findings show that tDCS has a significant immediate effect, but this effect could not be maintained over time.

tDCS is regarded as a diffuse NIBS technique due to the way the current passes through the skull and enters the brain, thus, the neuromodulatory effects may extend to other regions beyond the targeted area (Rahman, Lafon, Parra, & Bikson, 2017). Subsequently, this would make it difficult to limit the effects of tDCS on the cognitive functioning of a specific brain region. One solution would be to reduce the size of the electrodes that deliver the current, this would increase the focality of stimulation to the targeted brain regions and may provide a more controlled modulation of the associated cognitive domains (Nitsche et al., 2008). Another precise approach to consider, regarding the location of delivery of tDCS and the domains of cognition targeted, would be the use of neuroimaging techniques such as EEG online or fMRI offline prior to the commencement of the treatment. These techniques would allow us to understand the neural basis of how people learn and interact while performing cognitive tasks, hence researchers would have valuable information to design experiments or interventions to boost patients' cognitive performance and develop better training interventions in clinical settings. These would lead to development in neuroscience-based techniques that would improve the quality of the training and increase the effectiveness of the interventions (Clark et al., 2012).

Regarding the risk of bias of the selected manuscripts, it would help to improve the quality of the studies if the randomization and allocation processes were conducted properly and reported with greater transparency. For this reason, it is always recommended when planning a research study to follow the Non-pharmacological

Consolidated Standards for Reporting Trials (CONSORT) (Boutron, Altman, Moher, Schulz, & Ravaud, 2017).

9.2 Phase 2: Pilot study

Due to limited available evidence on the application of tDCS in older adults with MCI, we piloted a single-subject design with four phases (A-B-C-A) and multiple non-concurrent treatments in five participants with MCI; anodal tDCS + CS, sham tDCS + CS, and CS alone. After the baseline with the administration of CS (phase A), sham tDCS with CS was applied (phase B). Then, tDCS treatment was delivered in combination with CS (phase C). Phase A was then repeated at the end. We aimed to compare the impact of tDCS versus sham tDCS applied to the left DLPFC on cognitive performance during CS. Although our hypothesis was that there would be a significant improvement in cognitive task performance after the use of tDCS in various cognitive domains associated with the CS tasks, We found only mild beneficial effects on CS tasks associated with processing speed, selective attention, planning ability, and working memory during the application of tDCS as compared to CS alone or by sham tDCS. None of the benefits translated into gains in standardized cognitive outcomes and the frequency for using tDCS for an optimal benefit remains unclear.

9.3 Phase 3: RCT

We conducted a double-blinded sham-controlled randomized trial to determine whether receiving multisession tDCS (targeting the left DLPFC) combined with computerized CT based on executive functions would be superior to receiving multisession sham tDCS+CT or CT alone on domain- and task-specific cognition, and everyday functioning in older adults with MCI. Age-related degeneration of the prefrontal cortex is more exacerbated than neurodegeneration of other areas. The prefrontal cortex is responsible for higher cognitive functions and volume loss of this region results in executive control deficits (Salat et al., 2001; Cabeza et al., 2012). In addition, we investigated the offline effects of the three interventions on the change of power in delta, theta, alpha, and beta frequency bands by means of resting EEG in the left DLPFC targeted by tDCS.

Our results revealed that tDCS+CT was not superior to sham tDCS+CT and CT alone. Although, standardized cognitive outcomes (domain-specific) did not show any statistically significant differences between groups at the end of treatment or at FU, all groups significantly improved in general cognitive functioning. Interestingly, this improvement was greater in the tDCS+CT group as shown by the larger effect sizes relative to the other two conditions.

Although standardized cognitive outcomes (domain-specific) did not show any statistically significant differences between groups at the end of treatment or at FU, all groups significantly improved in general cognitive functioning. Therefore, we concluded

that tDCS appears to boost the execution of CT tasks (task-specific cognitive outcomes) by enhancing the processing speed of brain activity related to working memory and attention.

We also investigated whether multisession tDCS with concurrent CT may produce transfer effects noticeable in everyday functioning outcomes measured by the RBMT-3. No tDCS specific effect was found between groups, although significant within-group differences were evidenced in verbal, visual, prospective memory, and new learning areas. In addition, a larger effect size was noted in the tDCS+CT group after the intervention and a FU. We concluded that CT of executive function appeared to produce transfer effects of enhanced everyday memory, yet concurrent tDCS+CT provided no superior transfer effect than using CT alone.

Regarding the study of the electrophysiological dynamics that resulted from the interventions, multisession anodal tDCS applied over the LDPFC combined with CT increased absolute theta power in the left prefrontal cortex in older adults with MCI as compared to sham tDCS with CT or CT alone. The modulation of neuronal activity by tDCS was consistent with the improvement in processing speed for the task-specific effects of CT.

9.4 Future directions

Based on our findings, we would like to suggest the following for future studies:

- Despite our robust experimental design, in terms of having control and sham groups in the randomized controlled trial, more evident conclusions could have been drawn if two comparison groups were included. The first group is receiving tDCS alone ("tDCS alone"), which would help to elucidate if any neurophysiological differences arise from the administration of tDCS and CT, or tDCS alone. This group would yield more information to test our theory of using NIBS and allow us to delineate whether brain areas activated by CT would be modulated by tDCS alone, and if such modulation induces plasticity and improved functional performance without the need for CT. However, given the fact that using this group would not be able to provide data regarding task-specific outcomes of CT, the second option would be a waitlist group. This group would receive no intervention and would help to add understanding to the testing effects between groups and delineate gains attributable to the interventions and testing.

- An interesting topic in this context could also be to evaluate the montage and tDCS intervention regime. Given the time-dependent effects and the variant outcome of tDCS in patients with different cognitive difficulties, even when using similar montages, the intervention could evert a patient-dependent rather than a group or disease-oriented effect. Taking this factor into consideration, an option would be to study the individual differences in behavioral and physiological responses, and allow the researchers to customize individualized treatment based on these perspectives. However, such an approach would incur a lengthy intervention, and conducting longer period of interventions involving tDCS and CT can be cumbersome and would require additional

financial resources and manpower. Apart from this caveat, this approach deserves further investigation in order to clarify the characteristics of different treatment combinations that could produce maximum therapeutic benefits.

-We would like to suggest a longer period for follow-up assessments. Based on the literature and our results, it would be reasonable to think that CT can be an effective intervention. However, once the tDCS is removed, the effects of CT tend to fade. Since the long-term mechanism of tDCS is based on LTP, we could hypothesize that the group that received tDCS could maintain the gains produced by CT. LTP is a mechanism that can induce functional changes that last years and is associated with learning and memory. Therefore, adding more follow-up measures at different time points, at 3, 6, and 12 months, would help to elucidate if the effectiveness of the interventions (CT) could be maintained or declined less than those in the absence of tDCS.

- Further investigations are necessary to expand knowledge of tDCS in older adults with MCI and PwD and the underlying mechanisms by linking EEG data with behavioral outcome variables. One of the suggestions is to extend the scope of investigation of the neural response to other cortical areas of interests other than the tested area of stimulation by tDCS. As we have mentioned, tDCS provides diffuse stimulation to the cortex, meaning that not only the targeted area of stimulation is activated, but also neighboring or even distal areas are affected. Therefore, apart from studying spectral power analysis relative to the interventions received, we recommend investigating the functional interactions between different neural networking via EEG coherence.

Moreover, another aspect that deserves to be explored is the EEG online responses while the participants are receiving the interventions in real time.

- Finally, further studies should seek to verify the population dependent effects using the interventions mentioned in this thesis. It could be useful in the future to conduct a comparative study between using the intervention for PwD and their healthy counterparts, and in a larger sample.

9.5 References

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