MONASH University

Investigating the Cognitive and Electrophysiological Effects of Non-Invasive Transcranial Electrical Stimulation in Healthy Individuals and Individuals with Major Depressive Disorder

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BSc, BA (Psych) (Hons)

This thesis is submitted in partial fulfilment of the requirements for the degree of Doctor of Psychology (Clinical Neuropsychology) at Monash University in 2019

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List of Abbreviations

DC-offset	Direct-Current offset
DMN	Default Mode Network
DLPFC	Dorsolateral Prefrontal Cortex
DSM-IV	Diagnostic and Statistical Manual, 4th Edition
DSM-5	Diagnostic and Statistical Manual, 5th Edition
EEG	Electroencephalography
EMG	Electromyography
ERD	Event-related Desynchronisation
ERS	Event-related Synchronisation
fMRI	Functional Magnetic Resonance Imaging
FMT	Frontal-Midline Theta
GABA	Gamma-aminobutyric Acid
HAM-D	Hamilton Depression Rating Scale
ICA	Independent Components Analysis
LTD	Long-Term Depression
LTP	Long-Term Potentiation
MEG	Magnetencephalography
MEP	Motor Evoked Potential
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
NMDA	N-methyl-D-Aspartate
PASAT	Paced Auditory Serial Addition Task
PET	Positron Emission Tomography
QIDS	Quick Inventory of Depressive Symptomology

RMT	Resting Motor Threshold
rTMS	Repetitive Transcranial Magnetic Stimulation
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
STAI	State-Trait Anxiety Inventory
tACS	Transcranial Alternating Current
tDCS	Transcranial Direct Current Stimulation
tES	Transcranial Electrical Stimulation
TMS	Transcranial Magnetic Stimulation
TMS-EEG	Transcranial Magnetic Stimulation - Electroencephalography
TRD	Treatment Resistant Depression
tRNS	Transcranial Random Noise Stimulation
WAIS-IV	Wechsler Adult Intelligence Scale, 4th edition
WM	Working Memory

List of Published Manuscripts

This thesis includes the following papers which were published in peer reviewed journals during candidature:

Murphy, O. W., Hoy, K. E., Wong, D., Bailey, N. W., Fitzgerald, P. B., & Segrave, R. A. (2019). Individuals with depression display abnormal modulation of neural oscillatory activity during working memory encoding and maintenance. *Biological psychology*, *148*, 107766.

List of Prepared Manuscripts

This thesis includes the following manuscripts submitted for peer-review during candidature:

Murphy, O. W., Hoy, K. E., Wong, D., Bailey, N. W., Fitzgerald, P. B., & Segrave, R. A. (submitted in *Brain Stimulation*, invited for revision). Transcranial Random Noise Stimulation is More Effective than Transcranial Direct Current Stimulation for Enhancing Working Memory in Healthy Individuals: Behavioural and Electrophysiological Evidence.

Murphy, O. W., Hoy, K. E., Wong, D., Bailey, N. W., Fitzgerald, P. B., & Segrave, R. A. (submitted in *Brain Stimulation*, currently under consideration). Effects of Transcranial Direct Current Stimulation and Transcranial Random Noise Stimulation on Working Memory in Major Depressive Disorder: Behavioural and Electrophysiological Outcomes.

List of Presentations

The following conference presentation was made during the thesis candidature:

Murphy, O. W. (presenter), Hoy, K. E., Fitzgerald, P. B., Wong, D., & Segrave, R. A. (2017). *Behavioural and neurophysiological effects of transcranial electrical stimulation (tES) in healthy and depressed individuals: A TMS-EEG study.* Poster presented at 2nd International Brain Stimulation Conference, Barcelona, Spain. Abstract published in *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, 2018, *10*(2), 393.

Declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes zero original papers published in peer reviewed journals and three papers which have been submitted for publication. The core theme of the thesis is the neurophysiological and cognitive effects of transcranial electrical stimulation in healthy and depressed individuals. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, Oscar Murphy, working within the School of Psychological Science under the supervision of Dr Rebecca Segrave, A/Prof. Kate Hoy, and Dr Dana Wong. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters Five through Seven, my contribution to the work involved the following:

Thesis Chapter	**Publication Title**	**Status *(published, in press, accepted or returned for revision)***	**Nature and % of student contribution**	**Co-author name(s) Nature and % of Co-author's contribution***	**Co-author(s), Monash student Y/N***
Chapter Five	Individuals with depression display abnormal modulation of neural oscillatory activity during working memory encoding and maintenance	Published in *Biological Psychology*.	80%. Project design, recruitment, data collection, data analysis and interpretation, writing manuscript	1. Assoc. Prof Kate Hoy: Provided advice interpretation of findings and feedback on manuscript (5%) 2. Dr Dana Wong: Review of manuscript, supervisory input (3%) 3. Dr Neil Bailey. Technical advice, review of manuscript (3%) 4. Prof. Paul Fitzgerald: Provided feedback on manuscript (1%) 5. Dr Rebecca Segrave: Provided advice on study design, recruitment, and interpretation of findings. Provided feedback on manuscript (8%)	1. No 2. No 3. No 4. No 5. No

Chapter Six	Transcranial random noise stimulation is more effective than transcranial direct current stimulation for enhancing working memory in healthy individuals: behavioural and electrophysiological evidence	Submitted in *Brain Stimulation*, invited for revision and resubmission	80%. Project design, recruitment, data collection, data analysis and interpretation, writing manuscript	1. Assoc. Prof Kate Hoy: Provided advice on study design and interpretation of findings. Provided feedback on manuscript (5%) 2. Dr Dana Wong: Review of manuscript (3%) 3. Dr Neil Bailey. Assistance with analysis, review of manuscript (3%) 4. Prof. Paul Fitzgerald: Provided feedback on manuscript (1%) 5. Dr Rebecca Segrave: Provided advice on study design, recruitment, and interpretation of findings. Provided feedback on manuscript (8%)	1. No 2. No 3. No 4. No 5. No
Chapter Seven	Effects of transcranial direct current stimulation and transcranial random noise stimulation on working memory in Major Depressive Disorder: behavioural and electrophysiological outcomes	Submitted in *Brain Stimulation*, currently under consideration	80%. Project design, recruitment, data collection, data analysis and interpretation, writing manuscript	1. Assoc. Prof Kate Hoy: Provided advice on study design and interpretation of findings. Provided feedback on manuscript (5%) 2. Dr Dana Wong: Review of manuscript (3%) 3. Dr Neil Bailey. Assistance with analysis, review of manuscript (3%)	1. No 2. No 3. No

				4. Prof. Paul Fitzgerald: Provided feedback on manuscript (1%) 5. Dr Rebecca Segrave: Provided advice on study design, recruitment, and interpretation of findings. Provided feedback on manuscript (8%)	4. No 5. No

I have renumbered sections of submitted in order to generate a consistent presentation within the thesis.

Student signature: **Date:** 25/07/2019

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authours' contributions to this work. In instances where I am not the responsible authour I have consulted with the responsible authour to agree on the respective contributions of the authours.

Main Supervisor signature: **Date:** 30/07/2019

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Abstract

Major Depressive Disorder (MDD) is a highly prevalent and frequently debilitating mental illness. Working memory (WM) impairment is a core neuropsychological feature of MDD which contributes to functional limitations. Current first-line treatment are relatively ineffective for treating cognitive deficits in MDD and are associated with a range of practical limitations which drive the need for development of alternative antidepressant treatment modalities. Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulatory technique which has been shown to enhance a range of cognitive functions in healthy and depressed individuals, however, effects are variable between studies and individuals. Transcranial random noise stimulation (tRNS) has been shown to induce equal or even greater neurophysiological and cognitive effects than tDCS but has yet to be systematically investigated in MDD. A greater understanding of how stimulation influences underlying neurobiological activity and how these effects facilitate cognitive processing could help improve the reliability of cognitive outcomes. One method to investigate the neurobiological effects of these techniques is through recording of electroencephalography (EEG) to examine changes in the neural oscillatory activity which supports WM processing.

The current thesis aimed to compare the cognitive and electrophysiological effects of tDCS and tRNS in healthy individuals and in MDD. A secondary aim was to investigate the pattern of neural oscillatory activity associated with WM processing in MDD. A series of three studies were undertaken to achieve these aims. Firstly, Study One used task-related EEG to examine whether individuals with MDD displayed altered patterns of oscillatory activity during WM encoding and maintenance when compared to healthy individuals. Next, Study Two compared the effects of a single session of tDCS, tRNS or sham stimulation on cognitive and electrophysiological measures of WM in healthy individuals, using task-related EEG recording to examine effects of stimulation on oscillatory activity during WM encoding

and maintenance. Finally, Study Three compared the effects of tDCS, tRNS, and sham stimulation on cognitive and neurophysiological measures of WM in individuals with MDD, using the same experimental protocol as Study Two.

Study One revealed that individuals with MDD display widespread alterations in theta, upper alpha, and gamma activity during WM processing even when achieving the same level of WM performance as healthy controls, indicating that WM processing in MDD relies upon different neurophysiological mechanisms to healthy individuals. Study Two provided the first evidence that delivering tRNS in healthy individuals can induce more pronounced and reliable enhancements in WM performance when compared to tDCS. tRNS-induced enhancements in WM performance were accompanied by increases in theta and gamma power during WM encoding, thereby providing the first evidence for effects of tRNS on WM-related oscillatory activity. Finally, Study Three found that neither tDCS nor tRNS were more effective than sham stimulation for improving WM performance in MDD. Despite this, tDCS increased upper alpha power during WM maintenance, thereby supporting the potential of tDCS to alter neurophysiological activity supporting WM processing. The findings of this thesis significantly contribute to the characterisation of altered oscillatory activity during WM processing in MDD, as well as providing valuable information regarding the cognitive and neurophysiological effects of tDCS and tRNS in healthy individuals and in MDD.

CHAPTER ONE

Introduction and Thesis Overview

Major Depressive Disorder (MDD) is a highly prevalent psychiatric illness associated with significant rates of morbidity and mortality (Kessler et al., 2009, 2005). Cognitive deficits in MDD are amongst the strongest predictors of functional limitations and often persist following remission of affective symptoms (Conradi, Ormel, & De Jonge, 2011; Cotrena, Branco, Kochhann, Shansis, & Fonseca, 2016; Lam, Kennedy, McIntyre, & Khullar, 2014; Snyder, 2013). Impairments in working memory (WM) are amongst the most common cognitive symptoms observed in individuals with MDD and are associated with increased rumination and poorer treatment outcomes (Dunkin et al., 2000; Joormann & Gotlib, 2010; Snyder, 2013). Although current first-line psychopharmaceutical and counselling treatments have demonstrated effectiveness in reducing the affective symptoms of MDD, these treatment modalities are less effective for treating cognitive impairments (Herrera-Guzmán et al., 2010; Raskin et al., 2007). Further research is needed to better understand the neurobiological changes which lead to WM impairments in MDD, and to develop alternative interventions which are effective for improving WM functioning in this population.

Non-invasive transcranial electrical stimulation (tES) refers to a range of neuromodulatory techniques which involve the application of a weak electrical current to the brain via electrodes placed on the scalp (Woods et al., 2016). Transcranial direct current stimulation (tDCS) is the most widely-used form of tDCS and involves delivery of a weak direct current with a fixed polarity which flows from a positively charged anode to a negatively charged cathode (Nitsche & Paulus, 2000). Anodal tDCS is believed to facilitate cortical excitability via subthreshold modulation of neuronal membrane potentials, whilst cathodal stimulation induces more variable, but typically opposing effects (Fertonani & Miniussi, 2017; Nitsche & Paulus, 2000). tDCS has been shown to modulate cognitive functioning in healthy and clinical populations (Boggio et al., 2006; Fregni, Boggio, Nitsche, Rigonatti, & Pascual-Leone, 2006; Hoy et al., 2013), however, effects are typically modest in

size and highly variable between individuals (Hill, Fitzgerald, & Hoy, 2016; Martin et al., 2018; Nikolin, Martin, Loo, & Boonstra, 2018). A further limitation in the use of tDCS is that the neurobiological effects of stimulation delivered to cognitive and behaviourally relevant brain regions (i.e. prefrontal cortex) are poorly understood. Thus, there is a need to improve our understanding of how tDCS influences the neurophysiological mechanisms of cognitive functioning, and to investigate whether other forms of tES may induce larger or more consistent modulation of cognitive performance.

Transcranial random noise stimulation (tRNS) is another form of tES which delivers an alternating current with a randomly fluctuating frequency and intensity (Fertonani, Pirulli, & Miniussi, 2011; Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). The neuromodulatory effects of tRNS are believed to rely upon different underlying neurobiological mechanisms to tDCS, raising the possibility that tRNS may overcome some of the factors contributing to high variability in tDCS outcomes (Ho, Taylor, & Loo, 2015; Moliadze, Fritzsche, & Antal, 2014; Prichard, Weiller, Fritsch, & Reis, 2014; Terney, Chaieb, Moliadze, Antal, & Paulus, 2008). One factor thought to limit the effectiveness of tDCS is the activation of homeostatic neural mechanisms which counter-regulate the persistent changes in neuronal membrane potentials induced by stimulation with a constant direct current (Fertonani & Miniussi, 2017; Fertonani et al., 2011). In contrast to tDCS, it has been proposed that tRNS may induce more pronounced and reliable neuromodulatory effects by delivering a randomly fluctuating electrical field which prevents activation of homeostatic mechanisms (Fertonani et al., 2011). tRNS has been shown to induce more pronounced neurophysiological effects than anodal tDCS (Fertonani et al., 2011; Inukai et al., 2016), however, there is very little research investigating the cognitive effects of tRNS in healthy individuals and only a single case study has applied this technique in MDD (Chan et al., 2012). tRNS can also be delivered with a direct current offset (DC-offset) to produce a unidirectional current flow analogous to tDCS,

thereby combining the characteristics of tDCS (i.e. net polarisation of neuronal membrane potentials) and tRNS (i.e. randomly fluctuating electrical field) (Ho, Taylor, & Loo, 2015). Recent evidence suggests that tRNS + DC-offset can induce more pronounced enhancements in cortical excitability than tRNS without an offset (Ho et al., 2015). This raises the possibility that tRNS + DC-offset may prove more effective than anodal tDCS as a means to enhance cognitive performance in healthy and clinical populations. However, we are not aware of any research examining the effects of tRNS + DC-offset on WM performance in healthy individuals or individuals with MDD.

If the effectiveness and reliability of tDCS as a neuromodulatory tool is to be improved, and the potential of tRNS to be established, it will require greater understanding of how these techniques alter the neurobiological processes which support WM processing, and how changes in neurophysiology relate to changes in cognitive performance. Electroencephalography (EEG) is an excellent tool by which to achieve this. EEG research in healthy individuals has demonstrated that WM processing is supported by reliable and robust modulation of oscillatory activity within the theta (4 – 8 Hz), upper alpha (10 – 12.5 Hz), and gamma (30 – 100 Hz) frequency ranges (Jensen, Gelfand, Kounios, & Lisman, 2002; Jensen & Tesche, 2002; Roux, Wibral, Mohr, Singer, & Uhlhaas, 2012). Increasing WM load has been shown to elicit greater modulation of theta, upper alpha, and gamma power during the maintenance phase of WM processing (Axmacher et al., 2007; Howard, 2003; Jensen et al., 2002; Jensen & Tesche, 2002; van Vugt, Schulze-Bonhage, Litt, Brandt, & Kahana, 2010), indicating a crucial role for neural oscillations in supporting efficient WM processing. Research in healthy individuals has found that tDCS-induced enhancements in WM performance are accompanied by modulation of oscillatory activity on EEG recorded during WM processing (Choe, Coffman, Bergstedt, Ziegler, & Phillips, 2016; Hoy et al., 2013; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011). These findings suggest that

modulation of WM-related oscillatory activity may reflect a neurophysiological process underlying the cognitive-enhancing effects of tDCS. However, we are not aware of any research utilising EEG to examine the neurophysiological changes which underlie the cognitive effects of tRNS in either healthy individuals or individuals with MDD.

In light of the above, the current thesis has two overarching aims:

- To compare the effects of tDCS and tRNS on cognitive and neurophysiological measures of WM in healthy individuals and MDD. This was achieved by delivering anodal tDCS, tRNS + DC-offset, or sham stimulation to the left dorsolateral prefrontal cortex and recording cognitive and neurophysiological measures before and after stimulation.
- To investigate the neural oscillatory dynamics which underlie altered WM processing in MDD. This was achieved by comparing task-related EEG recorded from a large cohort of individuals with MDD to that recorded from a sample of healthy individuals closely balanced on demographic variables and WM ability.

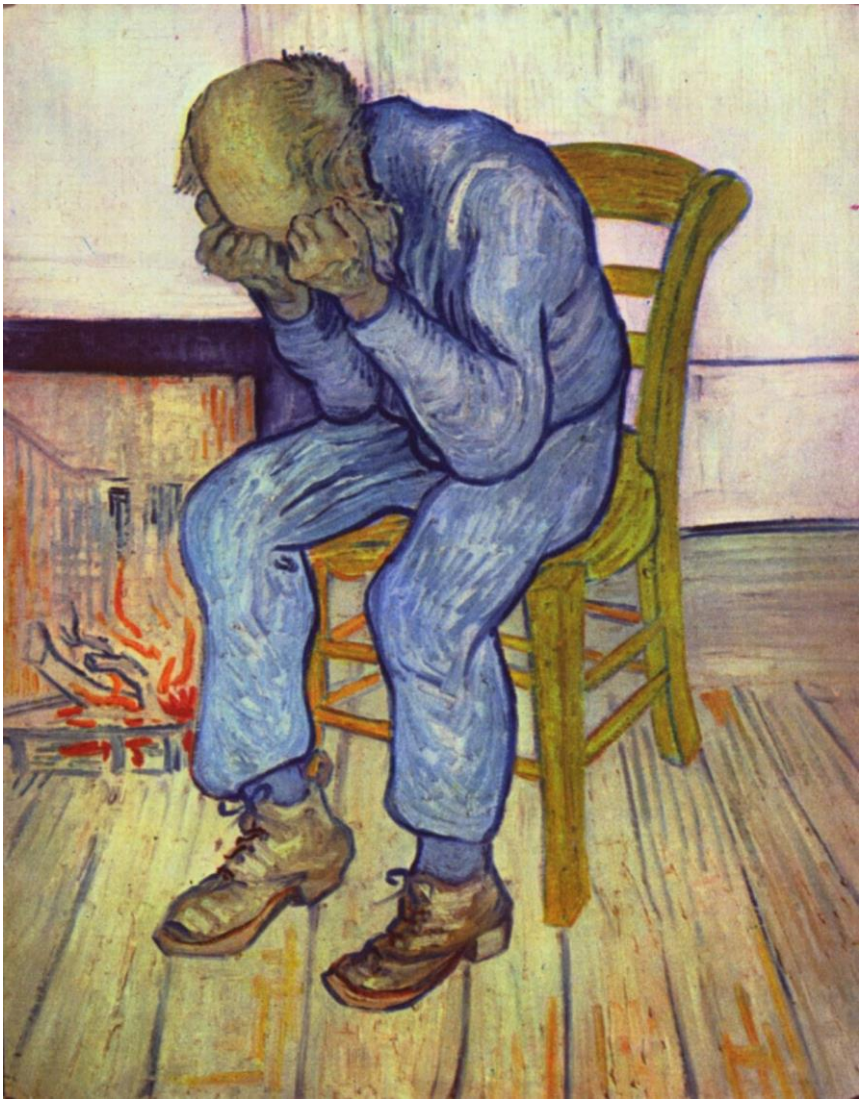
This thesis consists of eight chapters, including three manuscripts (all under consideration for publication). Chapter One provides a brief introduction and overview of the thesis. Chapters Two through Four presents a review of literature relevant to the thesis aims. Specifically, Chapter Two provides an overview of MDD with a focus on cognitive dysfunction. An overview of tDCS and tRNS as neuromodulatory tools is presented in Chapter Three, including a discussion of their stimulation parameters, underlying neurobiological mechanisms, and cognitive effects in healthy individuals. Chapter Four specifically addresses the application of non-invasive brain stimulation techniques in MDD and provides a summary of the literature reviews and a statement of the thesis aims.

The experimental papers are presented in Chapters Five through Seven. Chapter Five presents results from research using task-related EEG to examine whether individuals with MDD displayed altered patterns of oscillatory activity during WM encoding and maintenance when compared to a sample of healthy individuals closely balanced on potentially confounding demographic and cognitive variables. Chapter Six presents results from the first study to directly compare cognitive and neurophysiological effects of tDCS and tRNS + DC-offset in a sample of healthy individuals. In this paper, effects of stimulation are assessed for WM performance while task-related EEG recording is used to examine effects of tES on oscillatory activity during WM encoding and maintenance. Chapter Seven presents results from the first sham-controlled study to deliver tRNS in MDD. In this paper, the cognitive and neurophysiological effects of tRNS and tDCS are examined in a sham-controlled study using the same experimental protocol as Study Two. Due to the thesis-by-publication format, some repetition of material is unavoidable in the literature review chapters and introduction sections of each paper. Explanatory notes are included prior to each manuscript and provide any necessary clarification regarding the rationale or methodology.

Finally, Chapter Eight presents a summary of the experimental chapters of this thesis and integrated discussion. This includes a discussion of the overall implications of the thesis findings, methodological considerations, and directions for future research which stem from this work.

CHAPTER TWO

Major Depressive Disorder



Sorrowing Old Man (At Eternity's Gate), 1890

"The heart of man is very much like the sea, it has its storms, it has its tides and in its depths it has its pearls too"

Artwork and quote by Vincent Van Gogh (1853 - 1890)

2.1. Impact, symptoms, and course

Major Depressive Disorder (MDD) is among the most common psychiatric conditions with a global lifetime prevalence rate of approximately 15% (Bromet et al., 2011; Kessler et al., 2005b; Kessler & Bromet, 2013; Üstün, Ayuso-Mateos, Chatterji, Mathers, & Murray,

2004). A recent study by the World Health Organisation ranked depression as the second-greatest cause of disability due to illness worldwide (Ferrari et al., 2013). At the individual level, MDD represents a chronic and debilitating disorder which is associated with significant functional impairment and lowered quality of life (Papakostas et al., 2004; Saarni et al., 2010). MDD is associated with increased risk of developing additional medical conditions (Moussavi et al., 2007; Patten et al., 2009), is a risk factor for medical morbidity and mortality (Carney, Freedland, Miller, & Jaffe, 2002; Rovner et al., 1991), and is among the leading risk-factors for suicide (Beautrais, 1996; Goldston et al., 2009; Hawton, Comabella, Haw, & Saunders, 2013). In addition to the individual psychological and medical consequences, MDD exerts a substantial societal cost due to increased use of healthcare services, effects on occupational performance, and increased absenteeism (Greenberg, Fournier, Sisitsky, Pike, & Kessler, 2015; McIntire, McKinley, Goodyear, & Nelson, 2014; Wittchen et al., 2011).

MDD is an extremely heterogenous disorder which can present with a broad constellation of affective, behavioural, and cognitive symptoms. According to DSM-5 criteria, the two core diagnostic features of major depression are a pervasive lowered mood and a markedly reduced interest in previously desirable activities or diminished ability to experience pleasure (American Psychiatric Association, 2013). These cardinal symptoms are often accompanied by a range of affective symptoms which include feelings of pessimism, worthlessness, excessive guilt, and recurrent thoughts of death or suicidal ideation. The negative emotional states experienced as part of MDD are distinct from the feelings of sadness that exist as part of normal human experience and are typically more pervasive, severe, and resistant to change from external sources. Cognitive symptoms include a diminished ability to think clearly or concentrate, and indecisiveness. Core symptoms also include behavioural and physiological changes, such as altered sleeping patterns (these can

include either insomnia or hypersomnia), reduced appetite and weight loss (although weight gain may also be observed), psychomotor agitation or retardation, increases in fatigue and lethargy, and reduced libido. These behavioural and somatic symptoms often impact on social and occupational functioning, which may contribute to increased feelings of guilt and worthlessness (Lam et al., 2014; Simon, VonKorff, Piccinelli, Fullerton, & Ormel, 1999). The presentation and severity of these symptoms varies notably between individuals, as well as between depressive episodes within the same individual (Chen, Eaton, Gallo, & Nestadt, 2000). While numerous attempts have been made to classify depression into distinct sub-types, such as melancholic, atypical, treatment-resistant, and psychotic (for a review see Harald & Gordon, 2012), significant heterogeneity exists even within these subtypes.

MDD frequently presents as a chronic relapsing condition with individuals experiencing multiple major depressive episodes throughout their lifetime. Although the DSM-5 criteria for a major depressive episode requires a persistent cluster of depressive symptoms for a period of at least two weeks, depressive episodes can last for much longer and typically persist for several months or years (Lewinsohn, Clarke, Seeley, & Rohde, 1994; Nolen-Hoeksema, 1991; Spijker et al., 2002). Many individuals with MDD continue to display depressive symptoms of a reduced severity following the end of a depressive episode (Judd et al., 1998). Individuals who have experienced one depressive episode have an 80% chance of experiencing a further episode (Kessler, McGonagle, Swartz, Blazer, & Nelson, 1993; Üstün et al., 2004) and the risk of suffering a subsequent depressive episode increases with each successive episode (Burcusa & Iacono, 2007; Kessing, Hansen, Andersen, & Angst, 2004).

Several genetic, physiological and social factors have been identified which confer an increased risk of developing MDD. The risk of experiencing a depressive episode is two to three times higher for individuals who have a first-degree relative with MDD (Beekman et

al., 1995; Lewinsohn, Rohde, & Seeley, 1998; Sullivan, Neale, & Kendler, 2000), indicating that heritable genetic factors can increase the likelihood of developing MDD. Indeed, MDD has an estimated heritability of 31-42% (McGuffin, Katz, Watkins, & Rutherford, 1996; Sullivan et al., 2000), and a concordance rate of 40-50% in twins (Kendler, Gardner, & Prescott, 1999; Kendler, Gatz, Gardner, & Pedersen, 2006). Numerous environmental factors also increase the risk of developing MDD, such as history of trauma, substance use, and chronic stress (Kendler, Neale, Kessler, Heath, & Eaves, 1993; Penza, Heim, & Nemeroff, 2003; Peterson & Seligman, 1984). Further, gender plays a role with females twice as likely as males to be diagnosed with MDD (Cyranowski, Frank, Young, & Shear, 2000; Piccinelli & Wilkinson, 2000). Given these findings, the current predominant view is that genetic and environmental factors interact to influence the risk of developing MDD (Caspi & Moffitt, 2006; Kendler, Gatz, Gardner, & Pedersen, 2006; Uher, 2008).

2.2. Cognitive dysfunction in MDD

While decades ago it was believed that MDD was associated with only minor cognitive deficits (e.g. Friedman, 1964), DSM-5 criteria now acknowledge cognitive dysfunction as a core feature of this condition, with cognitive symptoms including indecisiveness and a diminished ability to think or concentrate (American Psychiatric Association, 2013). Studies of subjective cognitive complaints indicate that approximately 40-60% of individuals with MDD report moderate to severe cognitive dysfunction during acute depressive episodes (Lahr, Beblo, & Hartje, 2007; Mowla et al., 2008; Potvin, Charbonneau, Juster, Purdon, & Tourjman, 2016), and approximately 30-40% of individuals report ongoing cognitive complaints following remission (Conradi et al., 2011; Lahr et al., 2007). Consistent with these subjective reports, neuropsychological evaluation of MDD has revealed dysfunction across a broad range of domains, including deficits in attention, speed

of information processing, and learning and memory (Beblo, Baumann, Bogerts, Wallesch, & Herrmann, 1999; Bora, Harrison, Yücel, & Pantelis, 2013; Jaeger, Berns, Uzelac, & Davis-Conway, 2006; Lee, Hermens, Porter, & Redoblado-Hodge, 2012; Rock, Roiser, Riedel, & Blackwell, 2014). Impairments in executive function are typically the most prominent and severe feature of cognitive dysfunction in MDD and include difficulties with selective attention, cognitive inhibition, planning, problem solving, cognitive flexibility, and working memory (WM) (Fossati, Ergis, & Allilaire, 2002; Moritz et al., 2002; Snyder, 2013; Tuulio-Henriksson et al., 2011; Veiel, 1997). These cognitive impairments have been observed on relatively simple tasks but are most prominent on tasks which require sustained and effortful cognitive processing (Austin, Mitchell, & Goodwin, 2001; Zakzanis, Leach, & Kaplan, 1998).

While cognitive impairments are often conceptualised as secondary to the affective symptoms of MDD, impairments in cognitive function are amongst the strongest predictors of functional limitations (Baune et al., 2010; Cotrena et al., 2016; Jaeger et al., 2006; Lam et al., 2014), and are linked to reduced quality of life (Cotrena et al., 2016; McCall & Dunn, 2003; Naismith, Longley, Scott, & Hickie, 2007; Papakostas et al., 2004; Shimizu et al., 2013). For example, it has been found that approximately 25% of the impact of MDD on occupational performance is directly attributable to cognitive impairments, including poor memory, difficulty concentrating, and a reduced ability to think clearly (Buist-Bouwman et al., 2008). Cognitive impairments can persist following remission of affective symptoms and are among the most common complaints in individuals who have recovered from a depressive episode (Conradi et al., 2011; Fava et al., 2006; Herrera-Guzmán et al., 2010). For example, it has been shown that approximately 30-50% of individuals who achieved full remission from depression continued to experience cognitive impairments that interfere with their functional abilities (Fava et al., 2006).

2.2.1. Working memory

Impairments in WM are amongst the most common cognitive symptoms of MDD and are directly associated with increased rumination, poorer treatment outcomes, and reduced quality of life (Buist-Bouwman et al., 2008; Dunkin et al., 2000; Joormann & Gotlib, 2010; Snyder, 2013). WM is a higher-order cognitive system encompassing the encoding, short-term maintenance, and manipulation of information related to goal-oriented behaviour (Baddeley, 2002). Given that WM has a limited-capacity, accurate and efficient processing of information relies upon the inhibition of unrelated stimuli which compete for limited neural resources (Joormann & Gotlib, 2010; Lustig, May, & Hasher, 2001; May, Hasher, & Kane, 1999; Miyake & Friedman, 2012). The ability to maintain and manipulate relevant information in WM is essential to many aspects of executive function and supports a wide range of cognitive processes (Baddeley, 2003; de Fockert, Rees, Frith, & Lavie, 2001; Kane et al., 2004). Consistent with this, impairments in WM function are amongst the strongest predictors of reduced psychosocial and occupational functioning in MDD (Daniel et al., 2013; Lam et al., 2014; Lee et al., 2013).

Individuals with MDD display impairments across multiple aspects of WM processing, including the initial encoding of information, short-term maintenance of memory representations, and cognitive inhibition of task-unrelated stimuli. Acutely depressed individuals have been shown to display inefficiencies in the initial encoding of information, which are not fully explained by reduced effort or attentional difficulties (Behnken et al., 2010; Mowla et al., 2008). MDD also includes impairments in the active maintenance of WM stimuli, reflected as reduced WM capacity and increased retroactive interference from previously encoded information (Christopher & MacDonald, 2005; Weiland-Fiedler et al., 2004). MDD involves prominent impairments in cognitive inhibition, defined as the ability to selectively inhibit task-irrelevant stimuli or information (Joormann & Gotlib, 2010). For

instance, individuals with MDD frequently display disproportionate impairments on WM tasks which feature distractor stimuli during the WM maintenance phase, indicating reduced inhibition of task-irrelevant stimuli (Gohier et al., 2009; Joormann & Gotlib, 2010). These impairments are most pronounced for WM tasks featuring emotionally-salient distractors (Goeleven, De Raedt, Baert, & Koster, 2006; Joormann & Gotlib, 2008, 2010; Lau, Christensen, Hawley, Gemar, & Segal, 2007; Segrave et al., 2012; Surguladze et al., 2004), but are also present when including non-emotive distractors (Gohier et al., 2009; Markela-Lerenc, Kaiser, Fiedler, Weisbrod, & Mundt, 2006; Moritz et al., 2002).

Taken together, a wealth of research has demonstrated that individuals with MDD commonly present with WM impairments which contribute to functional limitations and reduced quality of life. Current psychopharmaceutical and counselling treatments are relatively ineffective for treating the cognitive symptoms of MDD (Herrera-Guzmán et al., 2010; Raskin et al., 2007) (see Chapter Four of this thesis), and impairments in cognitive function often persist following remission of affective symptoms (Conradi et al., 2011; Snyder, 2013). These limitations highlight the need to develop alternative interventions that are more effective for improving WM functioning in MDD. To do so will require a greater understanding of how the neurobiological processes underlying WM processing are altered in MDD, and how these neurobiological changes contribute to the development of cognitive impairment.

2.3. EEG to examine working memory processing in MDD

A range of functional neuroimaging techniques are available which can provide information regarding the neurobiological processes underlying impaired WM functioning in MDD. Neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and

positron emission tomography (PET) possess a high anatomical resolution which can provide useful information regarding structural and functional changes associated with WM processing in MDD (Cabeza & Kingstone, 2006). However, their temporal resolution is poor which precludes fine grained examination of rapid neural activity during specific phases of WM processing (Huettel, Song, & McCarthy, 2004; Levin & Hoffman, 1999). In contrast, electroencephalography (EEG) allows examination of rapid changes in cortical activity within a millisecond timeframe and can therefore be used to differentially investigate neural processes associated with the initial encoding, short-term maintenance, and retrieval aspects of WM processing (Laufs et al., 2003; Michel, 2009). Moreover, EEG has been widely used to characterise the neural correlates of WM processing in healthy individuals (e.g. Klimesch, Sauseng, & Hanslmayr, 2007; Roux & Uhlhaas, 2014; Sauseng et al., 2005), thereby providing an existing framework for research investigating the neural underpinnings of altered WM processing in MDD.

Neural oscillations are a ubiquitous feature of EEG recorded from the healthy human brain. Oscillations reflect temporally synchronised post-synaptic dendritic potentials of cortical pyramidal neurons underlying the region of the active recording site (Niedermeyer & da Silva, 2005; Ward, 2003). Oscillatory activity is typically subdivided into pre-defined frequency-bands that include delta (1 – 4 Hz), theta (4 – 8 Hz), alpha (8 – 13 Hz), beta (13 – 30 Hz), and gamma (30 – 100 Hz) (Figure 2.1). The power and frequency of neural oscillations within cortical regions are modulated by external events, such as exposure to sensory stimuli, or internal events, such as engaging in mental processing (Pfurtscheller & Da Silva, 1999; Ward, 2003). Changes in oscillatory power during a task or event are typically evaluated through comparison to a reference period, whereby relative increases and decreases in power are termed event-related synchronisation (ERS) and event-related desynchronisation (ERD), respectively (Pfurtscheller, 2001; Pfurtscheller & Da Silva, 1999). Modulations in

oscillatory activity are associated with a broad range of sensory, motor, and cognitive processes, with each frequency band serving multiple functions depending on the demands of the task being undertaken and the brain structures that participate in the oscillation (for a review see Ward, 2003).

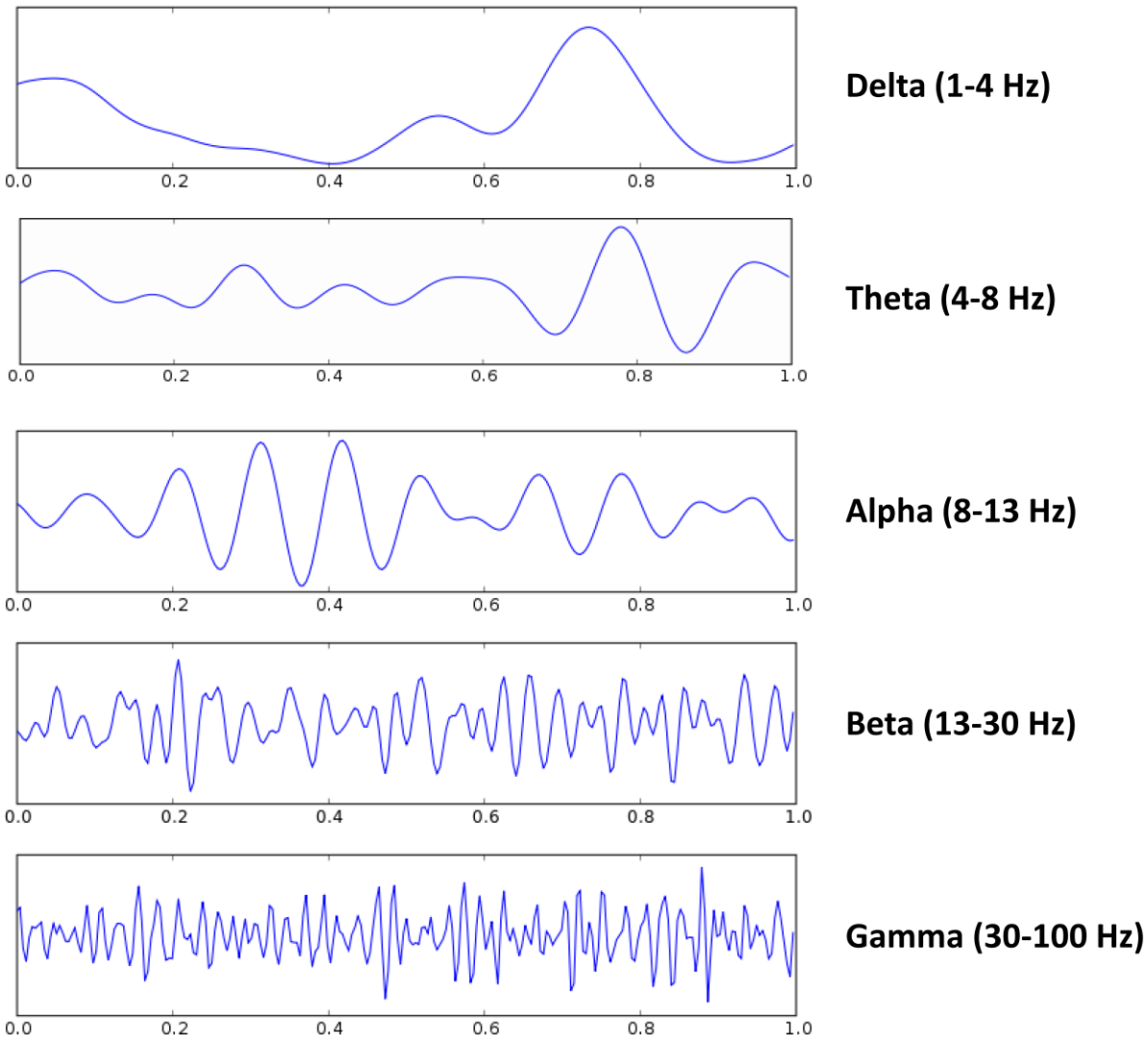


Figure 2.1. A sample of EEG (1 second duration) acquired over electrode Oz, filtered to present only delta, theta, alpha, beta, or gamma activity. *Adapted from content available under creative commons.*

A large body of EEG research has investigated the electrophysiological correlates of WM processing in healthy individuals, which includes reliable and robust modulation in oscillatory activity within the theta, alpha, and gamma frequency ranges (Jensen et al., 2002; Jensen & Tesche, 2002; Roux et al., 2012). Increasing WM load has been shown to elicit greater modulation of theta, upper alpha, and gamma power during the maintenance phase of WM processing (Axmacher et al., 2007; Howard, 2003; Jensen et al., 2002; Jensen & Tesche, 2002; van Vugt et al., 2010), and a greater magnitude of theta and gamma power during encoding has been shown to predict higher accuracy of subsequent recall (Sederberg, Kahana, Howard, Donner, & Madsen, 2003; White et al., 2013). These findings indicate a crucial role for theta, alpha, and gamma oscillations in supporting efficient WM processing. Indeed, some have proposed oscillatory activity as a neural substrate responsible or the short-term maintenance of information within WM (Jensen, Kaiser, & Lachaux, 2007). Examination of potential pathophysiological alterations in oscillatory activity may therefore elucidate the neurobiological processes underlying WM dysfunction in MDD. The following section will provide a brief overview of evidence concerning the functional significance of theta, alpha, and gamma oscillations during WM processing, followed by a discussion of research investigating altered WM-related oscillatory activity in MDD.

2.3.1. Alpha

Oscillations within the alpha range (8 -13 Hz) are the dominant oscillation observed in EEG recorded from the relaxed and alert brain (Berger, 1929; Shaw, 2003). These oscillations were traditionally viewed as a marker of cortical inactivity due to the observation that alpha power in parietal and occipital regions was greatest when the eyes were closed and reduced when the eyes were opened or engaging in effortful cognitive processing (Adrian & Matthews, 1934; Pfurtscheller, Stancak, & Neuper, 1996). However, rather than simply reflecting cortical inactivity, subsequent research has demonstrated that alpha oscillations

play an important functional role in cognitive processing by modulating the level of inhibition in cortical regions (Klimesch et al., 2007; S. Palva & Palva, 2007). Alpha oscillations can be further divided into sub-bands which display distinct patterns of synchronous activity during cognitive processing. Oscillations within the lower alpha range (8 – 10 Hz) typically display topographically widespread ERD over cortical regions during active cognitive processing and are believed to reflect general, non-specific attentional demands including alertness and anticipation of external stimuli (Klimesch, 1999). In contrast, oscillations within the upper alpha range (10 – 12.5 Hz) are more restricted in topography and function and can simultaneously increase in power within task-relevant regions and decrease in power within task-irrelevant regions (Klimesch, Doppelmayr, Roehm, Pöllhuber, & Stadler, 2000; Neuper & Pfurtscheller, 2001). While lower alpha oscillations respond primarily to task-extrinsic demands (i.e. alertness, distraction), upper alpha oscillations are believed to reflect more task-specific components of brain processes, such as task-dependent changes in top-down cognitive inhibition (Klimesch, 1999; Sauseng et al., 2005).

Oscillations within the upper alpha range display prominent modulation in power during WM processing. As WM is a limited-capacity system that is vulnerable to interference, efficient and accurate processing of task-related information relies upon the functional inhibition of neural processes which are irrelevant to task demands (Klimesch, 2012; Klimesch et al., 2007). The Sternberg WM task is particularly well-suited for assessing the role of alpha oscillations during WM processing as it temporally separates the information encoding, maintenance, and retrieval components of WM and thereby allows investigation of electrophysiological activity during distinct phases of processing (e.g. Jensen et al., 2002; Klimesch et al., 2000; Sternberg, 1966). Modulation of upper alpha oscillations is particularly prominent over parieto-occipital regions during the encoding and maintenance

phases of the Sternberg WM task and is thought to reflect the expression of top-down functional inhibition over neural regions in response to changing task-demands (Klimesch et al., 2007). Specifically, reductions in upper alpha activity over parieto-occipital regions during WM encoding are thought to facilitate accurate encoding of information via reduced functional inhibition of posterior regions associated with sensory and perceptual processing (Hanslmayr, Staudigl, & Fellner, 2012; Mölle, Marshall, Fehm, & Born, 2002). In contrast, parieto-occipital regions display prominent increases in upper alpha power during WM maintenance, which are believed to reflect greater functional inhibition of competing sensory and perceptual processes which may interfere with WM maintenance (Jensen et al., 2002; Klimesch et al., 2007). Consistent with this view, the magnitude of posterior alpha ERS increases alongside WM load (Jensen et al., 2002; Leiberg, Lutzenberger, & Kaiser, 2006), indicating that greater inhibition of potentially interfering processes is required to maintain cognitive performance in the context of limited neural resources and increased cognitive load. The functional importance of upper alpha activity is further supported by evidence that greater parieto-occipital upper alpha power during WM maintenance predicts higher WM task performance and decreased chance of interference from distractor stimuli (Bonnefond & Jensen, 2012, 2013; Palva, Monto, Kulashekhar, & Palva, 2010).

2.3.2. Theta

Theta oscillations (4 – 8 Hz) are the dominant neural rhythm recorded from the brain during childhood and are gradually replaced by alpha oscillations as the brain develops throughout adolescence and adulthood (Klimesch, 1999; Schäfer, Morgan, Ye, Taylor, & Doesburg, 2014). Modulations of theta power are particularly prominent in EEG recorded over the frontal midline (known as frontal-midline theta; FMT) (Ishii et al., 1999; Onton, Delorme, & Makeig, 2005). FMT oscillations are believed to be generated bilaterally in the anterior cingulate cortex and medial prefrontal cortex (Asada, Fukuda, Tsunoda, Yamaguchi,

& Tonoike, 1999; Ishii et al., 1999; Sasaki, Tsujimoto, Nishikawa, Nishitani, & Ishihara, 1996), neural regions which possess robust neuroanatomical connections nodes of the central executive network, including the DLPFC and parietal cortex (Pizzagalli, 2011). FMT activity is among the most prominent neural markers of sustained and focussed attention. Increased FMT power is elicited by tasks with high attentional requirements, such as meditation (Aftanas & Golocheikine, 2001; Kubota et al., 2001), completing novel driving or flight simulations (Laukka, Järvilehto, Alexandrov, & Lindqvist, 1995; Smith, Gevins, Brown, Karnik, & Du, 2001), and engaging in effortful cognitive processing (Jacobs, Hwang, Curran, & Kahana, 2006; Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999; Klimesch, 1999).

Prominent modulations of FMT power are observed during WM processing (Jensen & Tesche, 2002; Onton et al., 2005; Roberts, Hsieh, & Ranganath, 2013; Scheeringa et al., 2009). During the Sternberg WM task, FMT power typically increases during the information encoding and maintenance before diminishing once a response has been provided (Jensen & Tesche, 2002; Onton et al., 2005). FMT power during the maintenance phase increases parametrically alongside WM load and task difficulty (Gevins, Smith, McEvoy, & Yu, 1997; Jensen & Tesche, 2002), and greater FMT power during the information encoding and maintenance phases of WM is predictive of improved accuracy of information retrieval (Itthipuripat, Wessel, & Aron, 2013; Maurer et al., 2015; Sederberg et al., 2003). Drawing from this research, FMT activity has been proposed to reflect executive components of WM processing which are subsumed by prefrontal regions, such as coordinating the maintenance of memory representations (Hsieh & Ranganath, 2014), maintaining sustained and focussed attention (Clayton, Yeung, & Kadosh, 2015; Sauseng, Hoppe, Klimesch, Gerloff, & Hummel, 2007), and exerting top-down cognitive control over task-irrelevant regions (Cavanagh & Frank, 2014; Sauseng, Griesmayr, Freunberger, & Klimesch, 2010). Although the precise

functional significance of FMT activity remains a subject of some debate, these oscillations are believed to support WM processing through both executive and integrative functions.

2.3.3. Gamma

Gamma activity (30 - 200 Hz) reflects low amplitude oscillations which are elicited during a wide range of sensory, perceptual, and cognitive processes (Başar, Başar-Eroglu, Karakaş, & Schürmann, 2001; Herrmann, Munk, & Engel, 2004). Oscillations within the gamma range are believed to be generated by fast-spiking γ-aminobutyric acid (GABA)-ergic inhibitory interneurons (Bartos, Vida, & Jonas, 2007; Hájos et al., 2004; Mann & Mody, 2010). The higher frequency of gamma oscillations are thought to enable more rapid and robust synchronisation of distal neuronal populations when compared to lower frequencies, and have been proposed as major neural candidate underlying the integration of activity across neural regions (Bressler, 1995; Rodriguez et al., 1999; Salinas & Sejnowski, 2001). Gamma oscillations have been functionally linked to a broad range of sensory, perceptual, and cognitive processes in humans, including sensory integration and stimulus binding, temporal encoding of information, and the representation of complex information within consciousness (Fries, Reynolds, Rorie, & Desimone, 2001; Herrmann et al., 2004; Hopfield, 1995). Gamma activity has also been proposed as a neural mechanism underlying the active maintenance of WM representations in the absence of external stimuli (Fries et al., 2001; Jensen et al., 2007; Roux & Uhlhaas, 2014). Consistent with this functional role, frontal and parieto-occipital display reliable and sustained increases in gamma power during the short-term maintenance of information (Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998), which increases in magnitude alongside WM load (Howard, 2003; Palva, Monto, Kulashekhar, & Palva, 2010; Roux et al., 2012). Moreover, synchronisation of gamma activity has been shown to predict individual WM capacity (Palva, Monto, Kulashekhar, &

Palva, 2010; Palva, Kulashekhar, Hamalainen, & Palva, 2011), thereby indicating an important role for gamma activity in supporting the maintenance of WM representations.

2.3.4. Working memory-related oscillatory activity in MDD

Despite the presence of considerable evidence highlighting the importance of oscillatory activity in supporting WM processing, the pattern of oscillatory activity associated with WM processing in MDD remains poorly characterised. Overall performance on WM tasks reflects the combined functioning of various cognitive processes which support WM processing, including attentional allocation, initial encoding of information, online information maintenance, and top-down inhibition of task-irrelevant information and competing neural processes (Ecker, Lewandowsky, Oberauer, & Chee, 2010; Morris & Jones, 1990; Oberauer, 2002). For this reason, cognitive measures of WM performance are relatively limited in their ability to examine which aspects of cognitive processing are impaired in MDD (i.e. encoding, maintenance, inhibition, or retrieval), and how these impairments contribute to overall WM impairment. In contrast, neural oscillations can act as markers for individual cognitive processes (e.g. inhibition in the case of upper alpha activity) and may therefore inform which aspects of WM processing are altered in MDD.

There is some evidence that individuals with MDD display altered modulation of upper alpha power during WM maintenance, however, the presence and direction of these alterations are variable between studies. Firstly, Segrave et al. (2010) recorded EEG from 15 females with MDD and 15 healthy controls while they completed a verbal Sternberg WM task, reporting that MDD was associated with significantly greater upper alpha power over parieto-occipital regions during WM maintenance. The authours suggested that this may reflect a compensatory increase in the inhibition of task-irrelevant material in depressed individuals, whereby increased neural resources were required to achieve the same level of accuracy as the control group. In contrast, a similar study by Bailey et al. (2014) examined

upper alpha modulation during the Sternberg task (17 with MDD; 31 healthy matched controls), but observed that individuals with MDD displayed significantly less parieto-occipital upper alpha power than healthy controls during the maintenance period. Here the authours proposed that abnormal upper alpha activity may reflect a potential mechanism for WM impairments in MDD, whereby reduced upper alpha activity may result in difficulty inhibiting depressive ruminations which interfere with WM processing. Finally, a recent study by Bailey et al., (2018) failed to find any evidence for differences in parieto-occipital upper alpha power between MDD and healthy individuals during WM maintenance.

Conflicting evidence regarding the pattern of WM-related oscillatory activity in MDD is likely contributed to by small sample sizes as well as heterogeneity of WM task characteristics, participant demographics, and depression severity between studies. One important confound in previous research relates to the influence that differences in WM capacity and performance may exert on oscillatory activity (Palva et al., 2010). Namely, previous WM-EEG studies have typically compared the oscillatory activity associated with WM impairment in MDD to that recorded from healthy controls who display intact WM performance (Bailey et al., 2014; Segrave et al., 2010). As WM-related oscillatory activity varies between individuals with high and low WM capacity (Palva et al., 2010), previous evidence of aberrant WM-related oscillatory activity in MDD may have been a product of differences in WM performance between the MDD and control groups, rather than reflecting altered neural processing specifically related to the pathophysiology of MDD. Although conflicting results have been described, the results of these studies highlight abnormal alpha modulation and dysfunctional inhibition as potential mechanisms underlying depression-related cognitive dysfunction. However, the presence of notable variability in outcomes highlights the need for further research to resolve discordant findings. As these studies relied upon relatively small sample sizes, this would be best achieved by using substantially larger

sample sizes and matching groups on key demographic variables which influence WM-related oscillatory activity, such as WM capacity, age, gender, and education (Clark et al., 2004; Missonnier et al., 2011; Palva et al., 2010; Stam, van Walsum, & Micheloyannis, 2002).

Previous WM-EEG research in MDD has largely focussed on oscillatory upper alpha activity power during WM maintenance, and whether depression is associated with aberrant oscillatory activity in other frequency bands and during other phases of WM processing is less understood. Abnormalities in theta and gamma power have been linked to WM impairment in other psychiatric conditions, including anxiety (Cavanagh & Frank, 2014) and schizophrenia (Griesmayr et al., 2014), hence it is plausible that similar task-related abnormalities in theta and gamma activity may be contribute to altered WM processing in MDD. Indeed, FMT activity is associated with aspects of cognitive processing which are known to be dysfunctional in MDD, including WM processing, sustained attention, and the execution of top-down cognitive control (Clayton et al., 2015; Sauseng et al., 2010, 2007). Similarly, gamma oscillations are closely linked to WM capacity and accurate maintenance of WM representations (Herrmann et al., 2004; Palva et al., 2010; Roux et al., 2012), both of which are commonly impaired in MDD (Hubbard et al., 2016; Snyder, 2013). Despite this, we are not aware of any previous research investigating whether WM processing in MDD involves alterations within these frequency bands. Moreover, despite behavioural evidence that MDD is associated with inefficient encoding of information (Bearden et al., 2006; Rock et al., 2014), and EEG evidence that individuals with MDD display altered neural responses in occipital regions during the initial encoding of information into WM (Coullaut-Valera, Arbaiza, Coullaut-Valera, & Ortiz, 2007), past research has yet to investigate the pattern of oscillatory activity associated with WM encoding in MDD. These gaps in understanding

warrant further research investigating the presence and functional significance of altered oscillatory activity during WM encoding and maintenance in MDD.

2.4. Summary of Major Depressive Disorder

MDD is a highly prevalent mental illness associated with a broad constellation of affective, behavioural, and cognitive symptoms. Individuals with MDD often display cognitive impairments which are particularly prominent and pervasive for WM functioning. In addition to exerting considerable limitations in daily functioning, WM impairments are implicated in the maintenance of affective symptoms and predict increased rumination and decreased treatment response. Understanding which components of WM processing are altered in MDD, and the neurobiological processes underpinning these alterations, is an important initial step in developing novel treatments which demonstrate efficacy in treating both the cognitive and affective symptoms of MDD. EEG-derived measures of oscillatory activity are well-suited to achieve this goal. EEG studies have provided preliminary evidence that MDD is associated with abnormalities in upper alpha activity during WM maintenance, however, existing evidence is inconsistent regarding the presence and direction of these abnormalities. Less is known about whether MDD involves altered oscillatory activity in other frequency bands or phases of WM processing (e.g. initial encoding of information). Given the considerable body of evidence highlighting the importance of neural oscillations in supporting WM processing, further research is warranted to investigate the potential role of altered neural oscillatory activity during WM processing in MDD. Such research will in turn inform the development of more effective and targeted treatment approaches for MDD, such as non-invasive brain stimulation techniques.

CHAPTER THREE

Transcranial Electrical Stimulation

3.1. Non-Invasive Transcranial Electrical Stimulation

Non-invasive transcranial electrical stimulation (tES) refers to a group of neuromodulatory techniques which involve the delivery of a weak electrical current to the brain via two or more electrodes placed on the scalp (Fertonani & Miniussi, 2017; Woods et al., 2016). Although the electrical current delivered by tES is insufficient to directly induce neuronal firing, stimulation interacts with ongoing neural activity to modulate neuronal membrane potentials and thereby alter the likelihood of action potentials (Fertonani & Miniussi, 2017). These modifications causally influence the widespread neuromodulatory effects of stimulation across multiple levels of brain function, including alterations in cortical excitability, oscillatory activity, and functional connectivity (Yavari, Jamil, Samani, Vidor, & Nitsche, 2017). By modulating neurophysiological activity, tES offers the potential to influence the cognitive and behavioural functions which arise from these neurophysiological processes and have increasingly being investigated as potential therapeutic tools for a wide variety of neurological and psychiatric conditions.

Several forms of tES have been developed which differ in the properties of the electrical current delivered. The most widely used form of tES is transcranial direct current stimulation (tDCS), which delivers a weak direct current with a fixed polarity that flows from a positively charged anode to a negatively charged cathode (Nitsche & Paulus, 2000). Transcranial alternating current stimulation (tACS) is another form of tES which delivers an alternating current with a set frequency (Figure 3.1) (Antal & Paulus, 2013). Finally, transcranial random noise stimulation (tRNS) is a promising yet under-researched form of tES which involves the application of an alternating current with a randomly fluctuating frequency and intensity (Figure 3.1) (Terney et al., 2008). While tDCS, tACS, and tRNS induce subthreshold modulation of neural activity, differences in the properties of the

electrical current delivered result in varied neurophysiological and cognitive outcomes (Fertonani & Miniussi, 2017; Paulus, 2011).

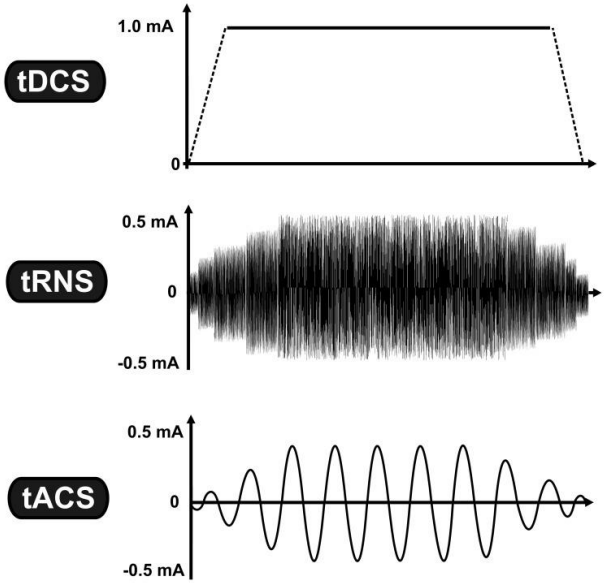


Figure 3.1. Visual representation of electrical waveform for tDCS, tACS, and tRNS. *Reprinted from Saiote, Polanía, Rosenberger, Paulus, & Antal (2013) with permission granted under open-access guidelines by Frontiers Media.*

Research investigating the potential applications of tES has increased significantly in the last two decades, with the number of academic papers including "transcranial direct current stimulation" in the title increasing from two publications in 2002 to over 700 in 2018 (Figure 3.2). Interest in the application of tES to enhance cognition in healthy and clinical populations has been bolstered by these techniques relatively high safety profile, portability, and low cost, making them particularly attractive candidates for widespread application. Despite significant academic interest, the efficacy of these techniques as a form of cognitive enhancement or therapeutic tool is currently limited by an incomplete understanding of their underlying neurophysiological mechanisms of action as well as the myriad of factors influencing the outcome of stimulation. Although there is considerable evidence supporting

the potential of tDCS to influence neural regions and the behaviour which they control, several meta-analyses have noted that the effects of tDCS on cognitive and neurophysiological outcomes are typically modest in size and highly variable between studies (e.g. Hill, Fitzgerald, & Hoy, 2016; Jacobson, Koslowsky, & Lavidor, 2012). These findings highlight the need to improve understanding of the underlying neurophysiological effects of tDCS and how these translate into modulation of cognitive function. Moreover, the presence of modest and variable tDCS outcomes warrants further research examining whether other forms of tES may induce more pronounced or consistent effects on cognitive performance.

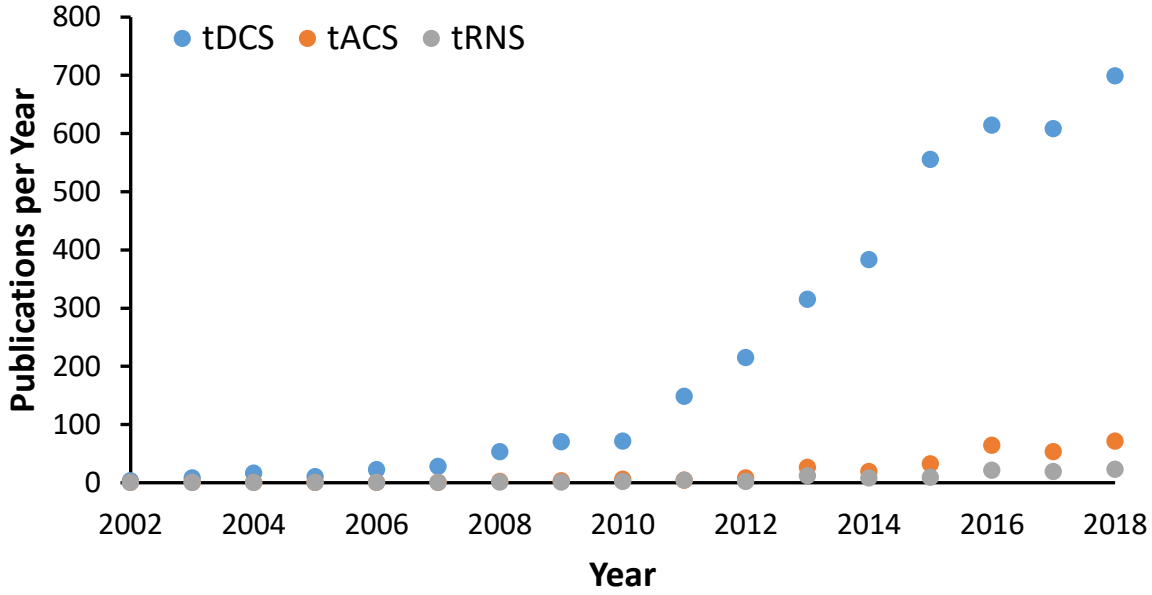


Figure 3.2. The number of academic articles published each year with "transcranial direct current stimulation", "transcranial random noise stimulation", or "transcranial alternating current stimulation" in the title, from the period 2002 - 2018. Information gathered from PubMed on 27/08/19.

Although substantially less researched than tDCS, preliminary evidence supports the potential of tRNS to enhance cognitive function in healthy individuals and various brain-

based conditions (Alm & Dreimanis, 2013; Fertonani, Pirulli, & Miniussi, 2011; Herpich et al., 2015). The cognitive effects of tRNS are believed to rely upon different underlying neurophysiological mechanisms to tDCS (Fertonani & Miniussi, 2017; Ho et al., 2015; Moliadze et al., 2014a; Prichard et al., 2014; Terney et al., 2008), raising the possibility that tRNS may overcome some of the factors contributing to high variability in tDCS outcomes. While there is a small amount of evidence that tRNS can induce more pronounced enhancements in cortical excitability when compared to tDCS (Ho et al., 2015; Inukai et al., 2016; Moliadze et al., 2014), very few studies have directly compared the efficacy of tDCS and tRNS as a form of cognitive enhancement, in either healthy or clinical populations. Moreover, while the neurophysiological mechanisms underlying the cognitive enhancing effects of tDCS remain poorly understood, in the case of tRNS this information is almost entirely absent. Improving understanding of the neurophysiological effects of tDCS and tRNS is an important first step in determining the true potential of these techniques as neuromodulatory tools for enhancing cognitive function in healthy or clinical populations.

The following sections will provide an overview and discussion of tDCS and tRNS, as these two tES techniques serve as the focus of this thesis. For the sake or parsimony, tACS will not be discussed. Discussion of tDCS and tRNS will include an introduction to technical parameters, an overview of research concerning their neurobiological mechanisms of action, as well as a review of the efficacy of these techniques as a form of cognitive enhancement. A discussion of prominent theoretical gaps in our understanding will be provided, as well as an overview of research tools that are particularly suited for illuminating these gaps in our current understanding of tES. Discussion will focus primarily on research investigating the effects of tDCS and tRNS in healthy individuals, with the therapeutic effects of these techniques in MDD being discussed in Chapter Four of this thesis.

3.2. Transcranial Direct Current Stimulation

The potential of using weak electrical stimulation to alter neurophysiological activity was first demonstrated in animal research during the 1960s, which showed that applying weak electrical currents directly to the exposed cortex could induce subthreshold and polarity-dependent modulations in neural activity which persisted for several hours after stimulation (Figure 3.3) (Bindman, Lippold, & Redfearn, 1964; Purpura & McMurtry, 1965). While these findings generated interest in the potential of applying weak electrical stimulation transcranially in humans using electrodes placed on the scalp (Ramsay & Schlagenhauf, 1966; Redfearn, Lippold, & Costain, 1964), this line of research was largely abandoned for several decades due to the lack of evidence regarding a direct physiological effect in humans (for a historical review see Priori, 2003). However, the subsequent development of transcranial magnetic stimulation (TMS) provided researchers with a means to non-invasively probe the neuromodulatory effects of tDCS on cortical excitability. Namely, delivering a single pulse of TMS to the motor cortex can produce a motor-evoked potential (MEP) which can be recorded from peripheral muscles using electromyography (EMG), with the amplitude of this MEP providing a relatively direct measure of corticospinal excitability (Pascual-Leone et al., 2011, 1998). Using combined TMS-EMG, seminal research by Priori et al. (1998) and Nitsche and Paulus (2000) demonstrated that delivering tDCS to the motor cortex for relatively short durations could induce polarity-dependent shifts in cortical excitability which persisted up to 90-minutes following the end of stimulation. Specifically, anodal stimulation was found to increase, and cathodal stimulation decrease the amplitude of MEPs. This pioneering research triggered renewed interest in the use of tDCS as a neuromodulatory technique in humans, leading researchers to investigate the potential to improve cognitive performance or treat various clinical conditions by modulating neurophysiological activity within functionally related cortical regions.

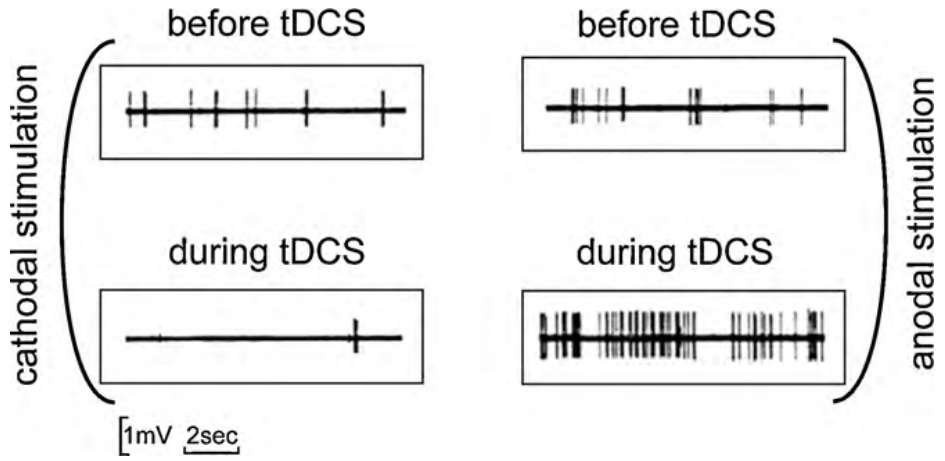


Figure 3.3. Changes in neuronal firing rates following delivery of anodal and cathodal direct current stimulation to the rat cortex. Stimulation delivered at 1mV for two seconds. *Reprinted from Utz, Dimova, Oppenländer, & Kerkhoff (2010) with permission from Elsevier.*

3.2.1. Technical overview of tDCS

tDCS is driven by a small battery-powered device that delivers a weak constant current (typically 1 – 2 mA) to the head via two or more scalp electrodes. During stimulation, an electrical current is injected via the positively-charged anodal electrode and while much of the current is shunted across the scalp, some passes through underlying neural tissue before exiting via the negatively-charged cathodal electrode (Bikson et al., 2004; Miranda, Lomarev, & Hallett, 2006; Stagg & Nitsche, 2011). Computational modelling of current flow has demonstrated that the spatial distribution of the electrical current during tDCS is determined through an interaction between the stimulation parameters used (e.g. stimulation intensity, electrode size, and the distance between the electrodes) and the anatomical characteristics of the individual receiving stimulation (e.g. shape of the head, thickness of the skull, and the distance between the skull and brain) (Bikson, Rahman, & Datta, 2012; Miranda et al., 2006).

The interaction between these factors typically results in a non-focal, widespread distribution of electrical current which influences neural activity under the electrodes and can also induce distal effects in other cortical and even subcortical regions (Baudewig, Nitsche, Paulus, & Frahm, 2001; Datta, Elwassif, Battaglia, & Bikson, 2008; Keeser et al., 2011). Therefore, achieving optimal outcomes for tDCS requires careful consideration of how stimulation parameters and individual characteristics interact to influence current flow through the brain.

3.2.2. Neurobiological mechanisms underlying tDCS

tDCS induces acute polarity-dependent alterations in cortical excitability that can persist for more than an hour after the end of stimulation and are dependent on the stimulation intensity and duration. Applying anodal tDCS to the motor cortex for several seconds induces acute increases in cortical excitability but is insufficient to produce effects which persist beyond the end of stimulation (1 mA, 35 cm^2 electrodes) (Nitsche & Paulus, 2000). Delivering motor cortex tDCS for longer durations can induce prolonged modulations in cortical excitability - after-effects lasting for several minutes may be observed following 5-minutes of stimulation (Figure 3.4), whereas after-effects lasting up to an hour may be achieved by delivering stimulation for 9-13 minutes (Nitsche et al., 2003; Nitsche & Paulus, 2000, 2001). The induction of after-effects is dependent on stimulation being delivered with a sufficient current intensity, with persistent after-effects being observed following 5-minutes of stimulation with higher current intensities (0.8-1.0 mA) but not for lower (0.2-0.6 mA) (Nitsche & Paulus, 2000). However, while the induction of long-term after-effects requires tDCS to be delivered using a sufficient duration and stimulation intensity (Nitsche et al., 2000), further increases in these stimulation parameters does not necessarily induce a linear increase in the magnitude or duration of after-effects but may result in a diminution or reversal of the desired effect (e.g. Batsikadze, Moliadze, Paulus, Kuo, & Nitsche, 2013; Jamil et al., 2017). The following sections will provide an overview of neurobiological mechanisms

which are believed to underlie the acute and longer-term effects of tDCS, as well as those contributing to non-linear effects of tDCS at higher dosages.

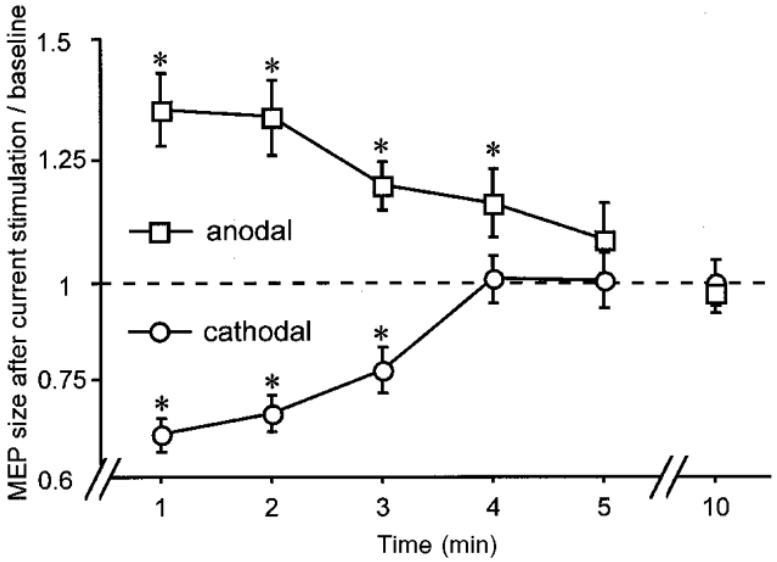


Figure 3.4. The time-course of MEP amplitude following the delivery of anodal and cathodal tDCS with a current intensity of 1 mA for 5-minutes. *Reprinted from Nitsche & Paulus (2000) with permission from John Wiley and Sons.*

3.2.2.1. Acute intrastimulation effects

tDCS alters spontaneous neuronal activity and cortical excitability during stimulation by inducing subthreshold modulations of neuronal membrane potentials (Nitsche & Paulus, 2000). Neuromodulatory effects of tDCS on cortical excitability are dependent on the orientation of neurons relative to the direction of current flow, with inward current flow at the anode typically inducing hypopolarisation of neuronal membrane potentials and an increase in neuronal excitability, whereas cathodal stimulation typically induces opposing effects (Bikson et al., 2004; Rahman et al., 2013). Pharmacological studies have demonstrated that the acute effects of anodal tDCS are dependent on polarity-specific alterations in the

conductance of ion channels, whereby the facilitatory effects of anodal stimulation on motor cortex excitability are diminished by blocking calcium channels and eliminated following the blockage of sodium channels (Nitsche et al., 2003). In contrast, the acute effects of cathodal tDCS are unaffected by ion channel blockade, presumably because cathodal stimulation-induced hyperpolarisation of membrane potentials results in inactivation of ion channels and therefore negates any effects of pharmacological blocking (Nitsche et al., 2003). The acute intrastimulation effects of tDCS are primarily dependent on these polarity-dependent shifts in neuronal membrane potentials and are not affected by pharmacological modulation of excitatory or inhibitory neurotransmitter systems such as gamma-aminobutyric acid (GABA)-ergic or glutaminergic receptors (Nitsche et al., 2003; Nitsche, Liebetanz, et al., 2004).

3.2.2.2. Induction of after-effects

The ability of tDCS to induce persistent after-effects which are sustained beyond the end of stimulation is believed to be dependent on the induction of long-term potentiation (LTP)-like and long-term depression (LTD)-like plasticity. LTP/LTD are neuroplastic mechanisms for inducing long-lasting and activity-dependent increases (LTP) or decreases (LTD) in synaptic strength (Malenka & Bear, 2004). The induction of LTP/LTD-like plasticity in the neocortex is primarily a glutaminergic process involving modulations in the efficacy of N-methyl-D-aspartate (NMDA) receptors, which occurs in response to persistent changes in post-synaptic calcium levels (Madison, Malenka, & Nicoll, 1991; Malenka & Bear, 2004). The importance of NMDA receptor function in the after-effects of tDCS has been demonstrated by pharmacological studies which observed that pharmacological blocking of NMDA receptors abolished the after-effects of both anodal and cathodal stimulation, whereas the duration of excitability enhancement induced by anodal tDCS was prolonged following administration of a partial NMDA-receptor agonist (Nitsche et al., 2003; Nitsche, Jaussi, et al., 2004). Importantly, pharmacological modulation of NMDA receptor

function does not influence the acute modulation of resting neuronal membrane potentials (Nitsche et al., 2003), indicating that NMDA receptors are specifically involved in the process of translating the acute effects of stimulation into persistent changes in cortical excitability. While the effects of tDCS are believed to be dependent on these neurobiological processes, stimulation is also associated with a cascade of neurobiological changes which include alterations in gene expression and protein synthesis, as well secondary influences on glutaminergic and GABAergic neurotransmission (for a review of neurobiological mechanisms see Stagg & Nitsche, 2011).

3.2.2.3. Evidence of non-linear effects

Delivery of tDCS with higher dosages (i.e. higher current density or longer durations) can induce antagonistic, non-linear outcomes. Batsikadze et al. (2013) observed that increasing the current intensity of cathodal stimulation from 1 to 2 mA (20 minutes, 35 cm^2 electrodes) reversed the direction of motor cortex excitability modulation from inhibition to facilitation (Figure 3.5). Similar findings are observed when extending stimulation duration, with Monte-Silva et al. (2013) reporting that while the delivery of anodal stimulation for 13-minutes facilitated motor cortex excitability, extending the duration to 26-minutes resulted in inhibitory after-effects (1 mA, 35 cm^2 electrodes). These non-linear effects are believed to be driven by homeostatic neural mechanisms which counter-regulate large and prolonged changes in neuronal membrane potentials (Fertonani & Miniussi, 2017). Research using animal models and *in vitro* neuronal slices have observed that ion channels undergo a progressive down-regulation in excitability following constant depolarisation via external stimulation (Kurachi & Ishii, 2004; Levitan & Kaczmarek, 2015). In the case of tDCS, increasing the duration or intensity of stimulation has been proposed to activate these homeostatic processes and result in antagonistic regulatory after-effects on cortical excitability (Fertonani & Miniussi, 2017; Fertonani, Pirulli, & Miniussi, 2011). While

antagonistic effects of homeostatic mechanisms are most pronounced when delivering tDCS with higher dosages, homeostatic mechanisms are also believed to counter-regulate the neuromodulatory effects of tDCS at lower dosages and have been proposed as a major factor limiting effectiveness and driving variability in tDCS outcomes (Fertonani & Miniussi, 2017; Fertonani et al., 2011).

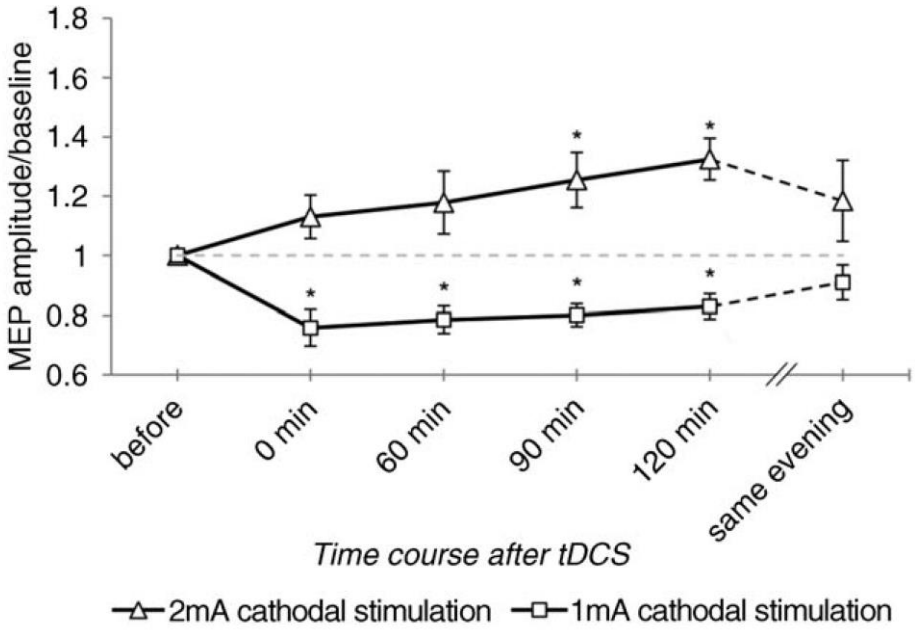


Figure 3.5. The time-course of MEP amplitude following the delivery of cathodal tDCS to the motor cortex with a current intensity of 1 mA or 2 mA for 20-minutes. Note that 1 mA cathodal tDCS inhibits MEP amplitude whereas 2 mA cathodal tDCS facilitates MEP amplitude. *Adapted from Batsikadze et al. (2013) with permission from John Wiley and Sons.*

In summary, the primary mechanism of action for the acute neuromodulatory effects of tDCS is believed to be the modulation of resting neuronal membrane potentials. If delivered using appropriate stimulation parameters, tDCS can induce persistent modulations in cortical excitability which are dependent on the induction of NMDA receptor-mediated

LTP/LTD-like plasticity. The direction, magnitude, and duration of these effects are critically dependent on the stimulation parameters applied, and higher stimulation dosages can result in antagonistic, non-linear effects which are likely driven by homeostatic neural mechanisms.

3.2.3. Factors Influencing the neuromodulatory effects of tDCS

While studies of the motor cortex have highlighted the importance of stimulation parameters in determining the outcome of tDCS, the precise effects of stimulation depend on a complex and dynamic interaction between these parameters and the neural state of the cortex being stimulated. As previously discussed, tDCS does not directly generate action potentials but rather alters spontaneous neuronal activity via subthreshold modulation of resting membrane potentials. The neuromodulatory effects of tDCS are therefore crucially dependent on the state of neuronal activation during stimulation, a phenomenon known as state-dependence. This has been demonstrated in animal models, whereby the delivery of a weak direct current of a similar intensity to that used in tDCS is insufficient to induce LTP unless it is also paired with ongoing intrinsic neural activity (Fritsch et al., 2010). Many factors influence the state of the brain and can thereby alter the outcome of tDCS, including endogenous characteristics such as age, sex, genetics, and neurochemistry, as well as exogenous factors such as the context in which tDCS is delivered (i.e. either at rest or while completing a behavioural or cognitive task) (for a review see Li, Uehara, & Hanakawa, 2015). While studies typically control for the influence of exogenous factors by using a standardised methodology for all participants, variation in endogenous characteristics can result in tDCS exerting different effects between individuals even when delivering identical stimulation parameters. Achieving the desired outcome therefore requires consideration how these factors influence the effects of stimulation. To this end, the following section will provide a review of prominent factors which have been shown to influence the outcome of tDCS. Discussion will focus on the influence of age, sex, and baseline cognitive ability, as

these factors have some of the most available evidence and may also be effectively controlled by researchers during participant selection.

3.2.3.1. Sex

Animal studies have demonstrated that males display higher baseline levels of cortical excitability than females, with this difference believed to be driven by excitability-enhancing effects of testosterone in males and an interaction between excitatory and inhibitory effects of estrogen and progesterone, respectively, in females (Smith et al., 2002). Due to the state-dependency of tDCS effects, gonadal hormones which influence resting cortical excitability are likely to alter the neurophysiological response to tDCS (Smith, Jones, & Wilson, 2002; Smith et al., 1999). Consistent with this, Kuo, Paulus, and Nitsche (2006) observed a polarity-dependent dissociation in the effects of tDCS on motor cortex excitability between males and females, whereby the inhibitory after-effects of cathodal tDCS were significantly larger and persisted for longer in females, whereas the facilitatory after-effects of anodal tDCS persisted for significantly longer in males. Interestingly, opposing effects were observed in a study by Chaieb, Antal, and Paulus (2008) who applied anodal tDCS to the visual cortex and used TMS-evoked phosphene thresholds to index changes in excitability, whereby the facilitatory effects of stimulation were significantly greater for females than for males. Although the precise pattern of influence resulting from sex differences in gonadal hormones is yet to be fully understood, these studies provide compelling evidence that the neuromodulatory effects of tDCS are at least partially influenced by sex.

3.2.3.2. Age

The physiological process of ageing is associated with changes in brain structure and function which can significantly alter the neuromodulatory effects of tDCS. Studies using TMS-based measures of cortical activity have repeatedly observed that older individuals

display a diminished potential for synaptic plasticity (Müller-Dahlhaus, Orekhov, Liu, & Ziemann, 2008; Pascual-Leone et al., 2011; Tecchio et al., 2008). Computational modelling of tDCS current flow has indicated that age-related atrophy of the cerebral cortex influences the proportion of electrical current which passes through neural tissue during tDCS (Li et al., 2015; Mahdavi, Towhidkhah, & Initiative, 2018; Thomas, Datta, & Woods, 2018). Further, neuroimaging studies have observed that older individuals tend to display reduced neural activation during cognitive processing (Burke & Barnes, 2006; Kameyama, Fukuda, Uehara, & Mikuni, 2004). Due to the state-dependency of tDCS, reductions in synaptic plasticity and task-related neural activation are likely to influence the after-effects of tDCS in older adults. Consistent with this notion, Fujiyama et al. (2014) observed that while anodal tDCS induced a comparable magnitude of facilitatory effects on motor cortex excitability in younger and older adults, these effects were initially strongest for younger individuals but persisted for longer in older individuals. A similar age-dependent dissociation in the timing of tDCS after-effects was reported by Heise et al. (2014), who found that the induction of excitatory effects of anodal tDCS on the motor cortex developed significantly later in older as compared to younger individuals. Taken together, these studies suggest that age-related changes in brain structure and function will result in variation in neuroplastic after-effects of tDCS, highlighting the need for future research to control for potentially confounding effects of group variation in age.

3.2.3.3. Baseline ability

There is compelling evidence that an individual's baseline level of cognitive performance or expertise on a task can influence the capacity of tDCS to modulate task performance, with most studies observing greater behavioural improvement in individuals with lower baseline task performance. Studies applying cathodal tDCS to the motor cortex observed that individuals with low baseline performance on motor coordination tasks

displayed clear improvements in motor coordination following stimulation, whereas improvements were significantly lower for individuals with high baseline motor coordination (McCambridge, Bradnam, Stinear, & Byblow, 2011; Uehara, Coxon, & Byblow, 2015). The observation of greater stimulation-induced cognitive gains in individuals with low baseline performance has been replicated across numerous cognitive domains, including visuospatial attention (Benwell, Learmonth, Miniussi, Harvey, & Thut, 2015), short-term memory (Hsu, Tseng, Liang, Cheng, & Juan, 2014), visual learning and memory (Bullard et al., 2011), and working memory (WM) (Arciniega, Gözenman, Jones, Stephens, & Berryhill, 2018; Heinen et al., 2016). Divergent effects of tDCS in high verses low performers are likely influenced by ceiling effects on cognitive tasks. Another potential explanation for this disparity in outcome relates to the potentially confounding effects of regression to the mean, whereby a variable that is extreme upon initial measurement tends to shift towards the mean upon subsequent measurement (Barnett, 2005; Newman et al., 2014; Stigler, 1997). Participants who perform poorly in the baseline testing session of tDCS studies are likely to display large improvements over time regardless of the effects of tDCS, thereby giving the impression that the benefits of stimulation are specific to those with low baseline performance (Berryhill et al., 2014). Although this may partially contribute to the observed disparity in tDCS outcome between low and high performers, other tDCS studies have shown that low baseline performers continue to display more pronounced effects of tDCS even after statistically correcting for regression to the mean (Shen et al., 2016). Moreover, studies using electroencephalography (EEG) have observed that high and low performing individuals also differ in their electrophysiological response to tDCS (Hsu et al., 2014; Tseng et al., 2012). These findings raise the intriguing possibility that the observed dissociation in performance is not simply due to ceiling effects on behavioural measures or regression to the mean, but rather reflects divergent neurophysiological effects of stimulation.

Overall, research has highlighted several inter-individual characteristics which can influence the neuromodulatory effects of tDCS, including age, sex, and baseline cognitive ability. Although the precise mechanisms and influences of these factors requires further systematic investigation, there is convincing evidence indicating that inter-individual variation in these factors introduce variability in the outcome of tDCS, even when delivering identical stimulation protocols. In addition to the aforementioned effects of age, sex, and baseline ability, there is evidence that the effects of tDCS are influenced by endogenous characteristics such as genetics (e.g. Plewnia et al., 2013), handedness (e.g. Schade, Moliadze, Paulus, & Antal, 2012), and the presence of psychiatric illness (e.g. Moreno et al., 2015). Further, various psychoactive substances alter cortical excitability and influence the neurophysiological response to tDCS, including prescription medications such as antidepressants, benzodiazepines and antiepileptics (Ziemann et al., 2015), as well as recreational drugs such as caffeine, nicotine and alcohol (Grundey et al., 2012; Lücke et al., 2014; Specterman et al., 2005). Given the presence of a broad range of factors which can influence the outcome of tDCS, strict methodological control of participant sampling and exclusion criteria is required to reduce the potentially confounding effects of these factors.

3.2.4. tDCS to enhance working memory

As cognitive processes arise from neurophysiological activity and excitability within the cerebral cortex, it is presumed that modulation of cerebral activity with tDCS can alter aspects of cognitive function. Following initial evidence of the neuromodulatory effects of tDCS on motor cortex excitability, the capacity of tDCS to enhance performance across a broad range of brain functions, including sensory perception, learning and memory, problem solving, emotional regulation, and social cognition was investigated (for a review see Kuo & Nitsche, 2012). However, the most frequently targeted cognitive domain in tDCS research is WM (Santarnecchi et al., 2015), which encompasses the encoding, short-term maintenance,

manipulation, and retrieval of information relevant to a particular goal- or task-directed behaviour (Baddeley, 2003; D'Esposito, 2007). WM is a fundamental component of many higher-order cognitive functions and activities of daily living, and WM capacity predicts learning and memory (O'Reilly & Frank, 2006), reading and comprehension (Cain, Oakhill, & Bryant, 2004), educational achievement (Alloway & Alloway, 2010), mental arithmetic (Ashcraft & Kirk, 2001), and general intellectual ability (Colom, Abad, Quiroga, Shih, & Flores-Mendoza, 2008; Oberauer, Süβ, Wilhelm, & Wittmann, 2008). In addition, WM impairments WM are a feature of many neuropsychiatric disorders, such as depression, severe anxiety, and schizophrenia, and contribute to symptom severity (Barch, Sheline, Csernansky, & Snyder, 2003; Gohier et al., 2009). Due to its importance for both healthy individuals and those living with brain-based illnesses, the enhancement of WM has been a popular goal in cognitive neuroscience and clinical tDCS research.

Research aiming to enhance WM performance in healthy individuals have typically delivered anodal tDCS to the dorsolateral prefrontal cortex (DLPFC) as it represents a central node in fronto-parietal WM network (Barbey, Koenigs, & Grafman, 2013; Santarnecchi et al., 2015). The DLPFC possesses strong neuroanatomical connections with many subcortical and cortical regions and is believed to support efficient WM through its roles in the monitoring and top-down control of information processing within posterior cortical regions (Edin et al., 2009; Gazzaley, Cooney, McEvoy, Knight, & D'esposito, 2005; MacDonald, Cohen, Stenger, & Carter, 2000). As verbal and visuospatial skills are typically lateralised to the left and right hemispheres, respectively, studies using verbal WM paradigms have typically applied anodal tDCS to the left DLPFC while placing the cathodal electrode over the contralateral supraorbital region (Fregni et al., 2005; Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011; Teo, Hoy, Daskalakis, & Fitzgerald, 2011). While delivery of anodal tDCS to the left DLPFC has been shown to enhance WM performance (Andrews, Hoy, Enticott,

Daskalakis, & Fitzgerald, 2011; Fregni et al., 2005; Jeon & Han, 2012; Meiron & Lavidor, 2013; Ohn et al., 2008; Teo et al., 2011; Zaehle, Sandmann, Thorne, Jäncke, & Herrmann, 2011), there is a high degree of variability in the outcomes reported between studies. For instance, studies vary in the aspects of WM performance which are improved (e.g. accuracy or response time), the relative timing at which improvements in performance were observed (e.g. either during or after stimulation), and the ideal stimulation protocols required to improve WM (i.e. higher or lower current densities, stimulation duration, location of cathodal electrode) (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016; Tremblay et al., 2014). Other studies have not observed evidence of improvements in WM performance following tDCS on the DLPFC (Mylius et al., 2012; Nikolin et al., 2018). Interpreting the potential causes of variability in tDCS outcomes is complicated by broad methodological heterogeneity between studies, including variability in participant demographics, stimulation parameters, as well as whether WM was assessed during ('online') or shortly after ('offline') the delivery of tDCS. Variation in cognitive outcomes measure is also influence divergent findings between studies, as WM tasks vary in their difficulty, cognitive load, and the cognitive processes relied upon for effective completion (i.e. selective attention, short-term maintenance, inhibition, etc.).

The following section will provide a discussion of relevant research concerning the effects of tDCS on WM performance in healthy individuals, focussing on the influence of the aforementioned stimulation parameters and methodological variables. These sections will focus on evidence regarding effects of tDCS on the *n*-back task and Sternberg WM task, as these represent two of the most widely used measures to of WM performance in tDCS research.

3.2.4.1. N-back task

The *n*-back task has been widely used to examine the effects of tDCS. During the task, individuals are presented with a series of individual stimuli (letters, numbers, or images) and must respond when a stimulus is identical to the one presented *n* positions earlier (i.e. 2-back: two positions back; 3-back: three positions back) (Jaeggi, Buschkuehl, Perrig, & Meier, 2010; Kane, Conway, Miura, & Colflesh, 2007). Effective performance on this task requires simultaneous active monitoring of stimuli, maintaining activation of recently viewed items, discarding of items that are no-longer relevant, and identification of target items (Barbey et al., 2013; Kane et al., 2007). Neuroimaging during the *n*-back shows broad activation of the frontoparietal WM network, with the DLPFC believed to be involved in the processing of stimulus information and the parietal lobe encompassing the storage of perceptual attributes of stimuli (Callicott et al., 1999; Owen, McMillan, Laird, & Bullmore, 2005; Owen et al., 1998). Fregni et al. (2005) was the first to demonstrate improvements in WM performance using tDCS, with 10-minutes of anodal tDCS to the left DLPFC significantly enhancing accuracy on the 3-back as compared to sham, with no significant changes in reaction time. Subsequent studies have replicated these increases in *n*-back accuracy following the delivery of anodal tDCS to the left DLPFC (Carvalho et al., 2015; Keeser et al., 2011; Meiron & Lavidor, 2013; Ohn et al., 2008), however, other studies have reported improvements in reaction time on the *n*-back task but not accuracy (Hoy et al., 2013; Mulquiney et al., 2011; Teo, Hoy, Daskalakis, & Fitzgerald, 2011; Zaehle et al., 2011). Interpretation of these conflicting findings has provided valuable information regarding the factors which influence the efficacy of tDCS in improving WM.

The timing of tDCS relative to the completion of the *n*-back task has been shown to influence the behavioural effects of stimulation. A recent meta-analysis of studies using tDCS to modulate WM performance revealed that tDCS of the left DLPFC improved reaction time

only when stimulation was delivered prior to completion of the *n*-back (offline stimulation), whereas no significant effects on either accuracy or reaction time were observed when stimulation was delivered during completion of the task (online stimulation) (Hill et al., 2016). Interestingly, there is some evidence that the optimal stimulation parameters required to induce behavioural change in healthy individuals differs between online and offline stimulation. Namely, Teo et al. (2011) observed that a higher current density (0.057 mA/cm^2) was more effective than a lower current density (0.029 mA/cm^2) for enhancing online *n*-back performance, whereas Hoy et al. (2013) observed the opposite pattern of results for offline performance. These findings highlight the state-dependence of tDCS effects, whereby cognitive outcomes are determined through a complex interaction between stimulation parameters and the state of the brain at the time of stimulation.

Converging evidence suggests that completing a WM task during the delivery of tDCS maximises the after-effects of stimulation (Andrews et al., 2011; Martin, Liu, Alonzo, Green, & Loo, 2014). Importantly, some work has shown that the beneficial effects of pairing tDCS with a concurrent WM task are only observed when the intrastimulation task is of sufficient difficulty to induce endogenous activation of the DLPFC. For instance, Gill, Shah-Basak, and Hamilton (2015) observed that pairing anodal tDCS of the left DLPFC with a concurrent 3-back task resulted in subsequent improvements in offline WM performance, whereas no benefits were observed when stimulation was paired with a relatively simple 1-back task. These findings are consistent with the view that the effects of delivering anodal tDCS to the DLPFC are maximised when stimulation is paired with a task which induces endogenous activation of the stimulated region. Although research using the *n*-back has demonstrated the potential to modulate WM performance by the delivery of anodal tDCS to the left DLPFC, the optimal stimulation parameters and methodological design required to induce these improvements require further elucidation.

3.2.4.2. Sternberg WM task

The Sternberg WM task is a commonly used paradigm in tDCS research. In contrast to the *n*-back task, which requires simultaneous encoding, maintenance, and manipulation with each new stimulus presented, the Sternberg WM task temporally separates encoding, online maintenance, and retrieval aspects of WM processing. In this task, individuals are presented with a set of stimuli to remember (typically letters or objects), which are then removed for a retention period of several seconds during which time the stimuli must be maintained in WM. Individuals are then presented with a probe stimulus and are required to indicate whether the probe was present in the initial stimuli set (Sternberg, 1966). The Sternberg task is a prototypical task of WM maintenance and primarily assesses the ability to hold information in short-term memory whilst ignoring interference from previously learnt stimuli (Altamura et al., 2007; Veltman, Rombouts, & Dolan, 2003). The maintenance period of this task is associated with robust activation of the DLPFC which increases in magnitude alongside WM load (Kirschen, Chen, Schraedley-Desmond, & Desmond, 2005; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999).

Several studies have evaluated the effects of tDCS on WM using the Sternberg task, with variable results. Mulquiney et al. (2011) reported no benefit of anodal tDCS for online Sternberg task accuracy or reaction time, however, improvements in response time were observed for offline 2-back performance. Although these findings could be interpreted as evidence for selective benefit for anodal tDCS on offline WM performance, Teo et al. (2011) did not observe benefits of anodal tDCS on offline Sternberg task performance when delivering stimulation with either a high (0.057 mA/cm^2) or low current density (0.029 mA/cm^2). Interestingly, Teo et al. observed that the higher current density was associated with online improvements in reaction time for a 3-back task. These findings indicate that anodal tDCS of the left DLPFC does not induce robust or reliable enhancements in aspects of

WM processing evaluated by the Sternberg WM task, however, several methodological factors may have contributed to these conflicting findings. These studies included relatively few trials of the Sternberg WM task in comparison to the *n*-back tasks (e.g. Mulquiney et al. included 20 Sternberg trials and 100 *n*-back trials), thereby reducing the sensitivity of the Sternberg WM task to detect subtle changes in performance following tDCS. Ceiling effects on the Sternberg WM task were likely to have further limited the sensitivity of this measure, as participants displayed higher baseline accuracy on the Sternberg WM task as compared to the more difficult *n*-back tasks. These limitations highlight the importance of future tDCS research including cognitive measures of sufficient difficulty and number of trials to effectively identify potentially subtle cognitive effects of stimulation.

Taken together, there is some evidence for beneficial effects of prefrontal tDCS on WM performance, however, these improvements are typically modest in size, unreliable between studies, and variation exists in terms of which aspects of performance are improved (i.e. task accuracy or reaction time). Determining whether the reliability and efficacy of tDCS can be improved will require a deeper understanding of the neurophysiological mechanisms through which stimulation modulates WM processes, including which neural regions are influenced by stimulation and how this is reflected during distinct phases of WM processing (i.e. encoding, maintenance, manipulation, retrieval). However, most studies completed to-date have not included measures of the neurophysiological effects of tDCS during WM processing and have instead inferred neurophysiological changes based on observed cognitive effects.

Several lines of reasoning highlight the importance of assessing the neurophysiological activity associated with WM enhancement. Much of our current knowledge regarding the neurophysiological effects of tDCS is derived from studies of the motor cortex, due to the availability of MEPs as an observable and sensitive index of changes

in motor cortex excitability. For this reason, many studies applying tDCS to the DLPFC cite motor cortex-based research as the mechanistic foundation when choosing stimulation parameters (e.g. Fregni et al., 2005; Gladwin et al., 2012). However, differences in cytoarchitecture, neuronal organisation, and receptor type and density between cortical regions makes it inaccurate to extrapolate tDCS motor cortex effects to other cortical regions, such as the prefrontal cortex (Laakso et al., 2016; Rahman et al., 2013; Russell, Goodman, Wang, Groshong, & Lyeth, 2014; Stagg et al., 2013). Similarly, while there is evidence that tDCS can induce non-linear effects on motor cortex excitability when delivered using higher current densities or longer durations (e.g. Batsikadze et al., 2013; Monte-Silva et al., 2013), it is not clear whether the same non-linear relationship would be observed in non-motor regions. The absence of neurophysiological data in regions outside of the motor cortex therefore limits the ability to evaluate potential reasons why a given tDCS protocol may fail to exert the desired cognitive outcome. To overcome these challenges, it is important that studies examining cognitive changes also include measures capable of assessing the neurophysiological effects of tDCS.

3.2.5. EEG to examine the neurophysiological effects of tDCS

EEG possess several properties which make it particularly well-suited for assessing the neurophysiological changes which underpin the cognitive effects of tDCS in regions outside of the motor cortex. Firstly, in contrast to the limited temporal resolution of most neuroimaging techniques, EEG allows recording of brain activity with a sub-millisecond temporal resolution and can therefore provide information regarding rapid changes in neural activity that occur during specific phases of WM processing (Laufs et al., 2003; Michel, 2009). Secondly, while neuroimaging techniques can only provide indirect measures of neural activity (e.g. cerebral blood flow, glucose metabolism, etc.), EEG records electrophysiological activity produced by ionic current flow in neurons and therefore

provides a relatively direct means of assessing elements of neural activity that are influenced by tDCS (Medeiros et al., 2012; Stagg & Nitsche, 2011). Finally, an large body of research has characterised the electrophysiological correlates of cognition in both healthy and clinical populations, thereby providing an existing framework for studies investigating how tDCS influences the aspects of neural activity which support cognition (see Chapter Two) (Kahana, 2006; Klimesch, 1999; Ward, 2003). Taken together, these properties make EEG particularly well suited for investigating the neural mechanisms underlying the cognitive effects of tDCS, particularly in regions outside of the motor cortex.

EEG recording can provide a sensitive measure for the effects of tDCS on resting and task-related neurophysiological activity. Evidence suggests that a single session of anodal tDCS to the prefrontal cortex can induce oscillatory changes on resting EEG, which persist beyond the end of stimulation (Jacobson, Ezra, Berger, & Lavidor, 2012; Miller, Berger, & Sauseng, 2015). Moreover, Miller et al. (2015) reported that anodal tDCS increased resting frontal theta power but did not modulate performance on a sustained attention task, thereby indicating that neurophysiological measures derived from EEG can be more sensitive than behavioural or cognitive measures for assessing the effects of tDCS. Similar findings have been observed for WM, whereby the delivery of anodal tDCS to the left DLPFC was found to modulate the amplitude of event-related potentials over frontal regions in the absence of observable changes in WM performance (Nikolin et al., 2018). These findings highlight the potential of EEG to investigate the underlying neurophysiological effects of tDCS both at rest and during cognitive processing.

Preliminary evidence has shown that tDCS-induced enhancements in WM performance are accompanied by modulation of WM-related oscillatory activity. A single session of anodal tDCS to the DLPFC was found to enhance WM performance on the *n*-back task and significantly increase task-related theta power over the frontal midline and posterior

parieto-occipital regions (Hoy et al., 2013; Zaehle et al., 2011). Given that FMT power is strongly linked to attentional control and is positively correlated with the accuracy of subsequent recall (Khader, Jost, Ranganath, & Rösler, 2010; Klimesch, Schack, & Sauseng, 2005; Missonnier et al., 2006), these increases in theta power following tDCS are consistent with more efficient WM processing and may reflect a potential neural mechanism underlying the cognitive enhancing effects of tDCS. These studies also reported effects of tDCS on task-related alpha activity, including decreased alpha power over frontal regions and increased alpha power over parieto-occipital regions (Hoy et al., 2013; Zaehle et al., 2011). Given that alpha oscillations are thought to reflect top-down inhibitory processes (Klimesch et al., 2007, 2005), these alterations in task-related alpha power following tDCS would indicate decreased inhibition of prefrontal regions which play an important role in supporting WM processing (Altamura et al., 2007; Barbey et al., 2013), as well as greater functional inhibition of posterior sensory and perceptual processes which may interfere with WM maintenance (Jensen et al., 2002; Klimesch et al., 2007). Taken together, these findings demonstrate the utility of using task-related EEG recording to examine the neurophysiological effects of tDCS and highlight the modulation of WM-related oscillatory activity as a potential mechanism underlying the cognitive effects of stimulation. Importantly, however, these studies are limited in their ability to determine whether tDCS improved WM performance via enhancements in specific aspects of WM processing (i.e. initial encoding, online maintenance, or manipulation of information), as EEG was recorded during the *n*-back task which requires simultaneous encoding, maintenance, and manipulation of information. Further research using the Sternberg WM task, which temporally separates the phases of WM processing, would be beneficial to investigate the neural correlates of tDCS-induced WM enhancements, and inform the mechanisms through which stimulation enhances WM task performance.

3.2.6. Summary of tDCS

While early research provided promising evidence of improved WM performance following a single session of tDCS in healthy individuals (Fregni et al., 2005), more recent studies and meta-analyses have demonstrated that effects of tDCS on WM performance are often modest in size and highly variable between individuals (Hill et al., 2016; Martin et al., 2018; Nikolin et al., 2018). Determining whether there are conditions under which tDCS can reliably and effectively improve WM performance, and thus it's utility as a neuromodulatory tool, requires a greater understanding of how stimulation alters the neurobiological processes which support WM processing, and how these changes translate to improved cognitive performance. EEG is a particularly useful tool for examining the neurophysiological effects of tDCS and has been used to characterise the neurophysiological changes which underlie improvements in WM performance. Prior research has found that tDCS-induced enhancements in WM performance are accompanied by modulation in task-related frontal and parieto-occipital oscillatory activity, highlighting the modulation of WM-related oscillatory activity as a potential mechanism underlying the cognitive enhancing effects of tDCS. Greater knowledge of how stimulation influences neural oscillatory activity is also likely to inform the therapeutic use of tDCS in neuropsychiatric conditions which feature WM dysfunction and abnormalities in oscillatory activity, such as depression. The presence of broad variability in tDCS outcomes also warrants investigation of whether other forms of tES may induce more reliable cognitive effects.

3.3. Transcranial Random Noise Stimulation

tRNS is a promising form of tES which involves the application of an alternating current with a randomly fluctuating frequency and intensity. tRNS has received relatively less

research attention than tDCS, with only 20 journal articles published in 2018 featuring "transcranial random noise stimulation" in the title, as compared to 699 featuring "transcranial direct current stimulation" (PubMed, accessed on 20/01/2019). The neuromodulatory effects of tRNS are believed to rely upon different underlying neurophysiological mechanisms of action than tDCS. tRNS may therefore overcome some of the factors limiting the effectiveness of tDCS, in particular, the induction of neuroplastic homeostatic mechanisms (see section 3.2.2.3 - Evidence of non-linear effects). Indeed, preliminary studies have observed that tRNS has the potential to induce larger facilitatory effects on cortical excitability than does tDCS, raising the possibility that tRNS may also prove more effective and / or reliable as a form of cognitive enhancement (e.g. Inukai et al., 2016; Moliadze, Fritzsche, & Antal, 2014). However, there is very limited research directly comparing the cognitive effects of tDCS and tRNS, and initial findings have utilised divergent stimulation parameters and produced conflicting results. Furthermore, while the neurophysiological mechanisms underlying the cognitive enhancing effects of tDCS remain poorly understood, this information is almost entirely absent in tRNS due to a paucity of studies utilising concurrent cognitive and neurophysiological measures. The following sections will provide a discussion of available evidence regarding the neuromodulatory effects of tRNS, including purported neurobiological mechanisms of action and potential efficacy as a method for cognitive enhancement.

3.3.1. Technical overview of tRNS

tRNS is a form of tES which involves the delivery of a weak alternating current with a randomly fluctuating frequency and amplitude via electrodes placed on the scalp. Unlike tDCS where the anodal and cathodal electrode maintain a consistent polarity throughout stimulation, tRNS delivers an alternating current in which electrodes are polarity-independent, functionally equivalent, and deliver identical stimulation output over the course

of the session (Fertonani et al., 2011; Pirulli, Fertonani, & Miniussi, 2013). While the related technique of tACS delivers an alternating current with a fixed frequency (e.g. 40 Hz), tRNS delivers an alternating current which randomly fluctuates within a broad frequency range (0.1-640 Hz) (Fertonani & Miniussi, 2017; Fertonani et al., 2011; Terney et al., 2008). tRNS can be delivered using a broad frequency spectrum (i.e. 0.1 – 640 Hz) or using narrower frequency ranges, including low (0.1 – 100 Hz) or high frequency (101 – 640 Hz). The alternating current produced during tRNS varies in frequency and amplitude according to a randomly generated 'white noise' structure, meaning that all frequencies contained within the pre-defined spectrum occur with approximately equal probability and amplitude (Figure 3.6) (Fertonani et al., 2011; Terney et al., 2008).

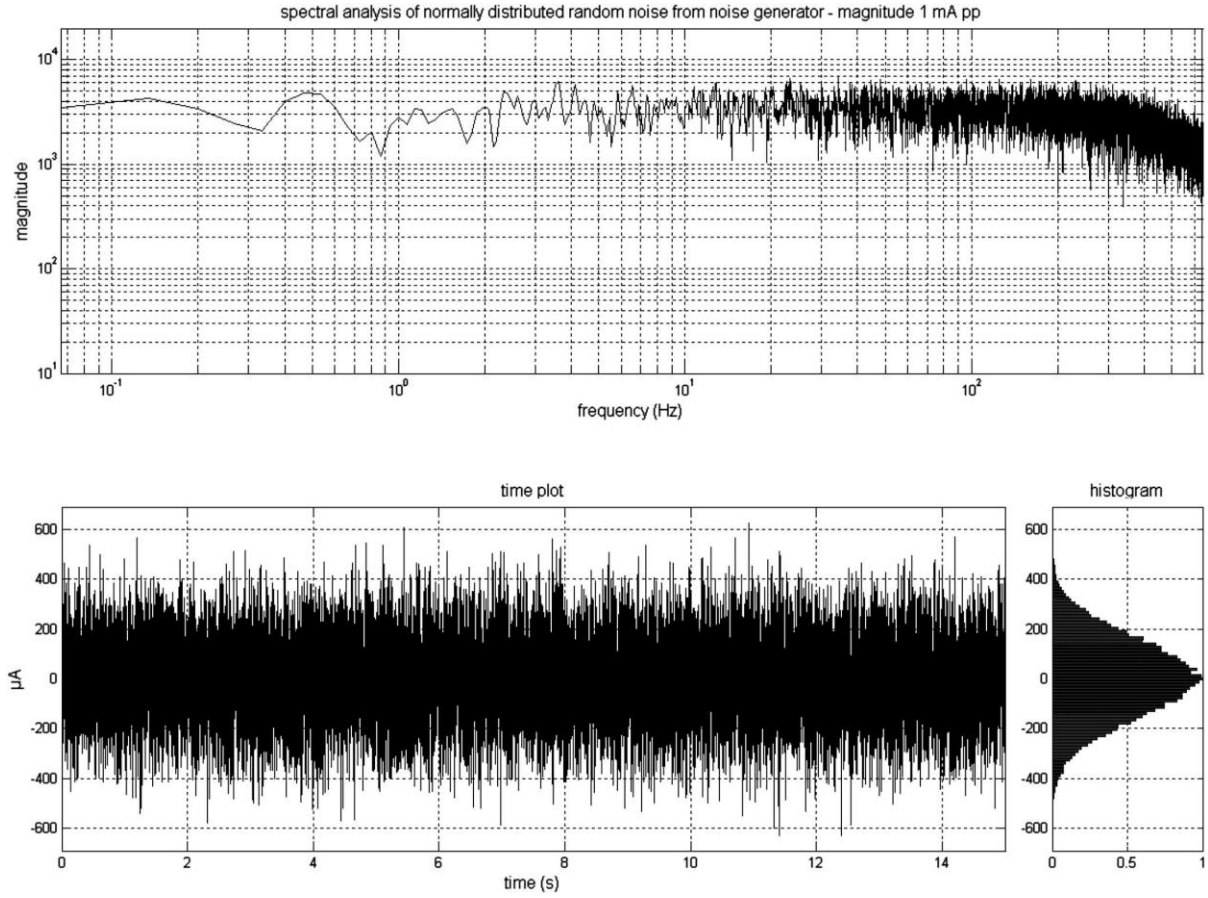


Figure 3.6. Electrical characteristics of the tRNS waveform. Frequencies contained within the pre-defined spectrum all occur with equal probability (top panel). Stimulation amplitude

fluctuates according to a random noise distribution (bottom-left panel), with an amplitude of 1 mA resulting in 99% of all amplitude values falling within 0.5 and 1.5 mA (bottom-right panel). *Reprinted from Terney, Chaieb, Moliadze, Antal, and Paulus (2008), copyright 2008 Society of Neuroscience.*

3.3.2. Neurobiological mechanisms underlying tRNS

Like tDCS, tRNS can induce acute and long-lasting changes in cortical excitability which are dependent on stimulation intensity and the frequency range applied. Terney et al. (2008) provided the first evidence for the facilitatory effects of tRNS, whereby applying a broad spectrum of tRNS (0.1-640 Hz) to the motor cortex for 10-minutes increased motor cortex excitability by 20-50%, with these effects persisting for up to an hour following the end of stimulation. A second experiment within this study revealed that the facilitatory effects of tRNS are primarily driven by higher frequencies (101-640 Hz), a finding which has since been replicated in many studies (Chaieb, Antal, & Paulus, 2015; Chaieb et al., 2009; Chaieb, Paulus, & Antal, 2011; Ho et al., 2015; Laczó, Antal, Rothkegel, & Paulus, 2014; Moliadze et al., 2014). The neuromodulatory effects of tRNS are also crucially dependent on current intensity. Specifically, research by Moliadze, Atalay, Antal, & Paulus (2012) investigated the neuromodulatory effects of tRNS on motor cortex excitability using a range of different current intensities, observing that 1 mA tRNS facilitated excitability, tRNS with moderate intensities (0.6-0.8 mA) had no effects, and tRNS with low intensities (0.4 mA) induced inhibitory effects of a comparable magnitude to cathodal tDCS (Moliadze, Atalay, Antal, & Paulus, 2012). Taken together, these results demonstrate the potential of high frequency tRNS to induce facilitatory effects on cortical excitability which persist beyond the end of stimulation and are dependent on stimulation intensity and frequency range.

3.3.2.1. Acute intrastimulation effects

Several lines of evidence indicate that the intrastimulation effects of tRNS are achieved via the repeated potentiation of voltage-gated sodium channels. Animal studies have demonstrated that the application of a high-frequency alternating current to rat hippocampal slices can induce an influx of sodium ions which result in weak depolarisation of neuronal membrane potentials (Schoen & Fromherz, 2008). Pharmacological studies in humans suggest that the effects of tRNS are at least partially dependent on sodium-channel activity, with Chaieb et al. (2015) observing that pharmacological blocking of sodium channels reduced the facilitatory effects of tRNS on motor cortex excitability. Drawing from these findings, researchers have proposed that tRNS induces the repeated opening of sodium channels, with each successive reopening increasing depolarisation and the likelihood of inducing an action potential (Chaieb et al., 2015; Fertonani & Miniussi, 2017). This purported mechanism is consistent with findings that the excitatory effects of tRNS are primarily generated by higher frequencies, whereby rapid oscillations in polarity induce more frequent opening of sodium channels and thus greater depolarisation.

3.3.2.2. Induction of after-effects

The precise neurobiological mechanisms responsible for the after-effects of tRNS are yet to be fully elucidated, however, pharmacological studies indicate that persistent effects of tRNS rely upon different neurophysiological mechanisms than those involved for tDCS. By repeatedly inducing the opening of sodium channels, tRNS is believed to facilitate the synchronous firing of neurons and thereby induce LTP-like plasticity (Chaeib et al., 2015). Interestingly, while the after-effects of tDCS are believed to be dependent on NMDA receptor activity (Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2003), pharmacological studies suggest that the after-effects of tRNS are NMDA receptor independent, as these were not altered by administration of a partial NMDA receptor agonist

or NMDA receptor antagonist (Chaieb et al., 2015). Further, Chaieb, Antal, and Paulus (2015) observed that the facilitatory effects of tRNS were reduced following the administration of a $GABA_A$ agonist, while previous studies have observed that administration of a $GABA_A$ agonist induce both enhanced and prolonged the facilitatory after-effects of anodal tDCS (Nitsche, Liebetanz, et al., 2004). Taken together, these results indicate that the after-effects of tRNS are NMDA-receptor independent and are at least partially dependent on sodium-channel and GABAergic activity. Hence while both tDCS and tRNS modulate ion-channel activity and neuronal membrane potentials, evidence suggests these techniques differ in the mechanisms through which they induce persistent after-effects on cortical excitability.

3.3.2.3. Neuromodulatory effects of tDCS and tRNS

It has been proposed that the ability of tRNS to induce repetitive depolarisation of sodium channels may allow for the induction of greater neuromodulatory effects than tDCS (Fertonani & Miniussi, 2017; Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010). Anodal tDCS provides a positive charge which can induce an initial facilitation but is thought to be followed by homeostatic adaptations that down-regulate neuronal membrane potentials (Fertonani & Miniussi, 2017). Several studies have observed that ion channels undergo a progressive down-regulation in excitability following constant stimulation with a direct current (Kurachi & Ishii, 2004; Levitan & Kaczmarek, 2015). This process of homeostatic regulation is primarily observed in sodium channels (Levitan & Kaczmarek, 2015), and has been proposed to limit the magnitude and reliability of neuromodulatory effects of tDCS on cortical excitability (Fertonani & Miniussi, 2017; Fertonani et al., 2011; Pirulli, Fertonani, & Miniussi, 2013). In contrast, the randomly fluctuating alternating current delivered by tRNS allows repeated depolarisation and repolarisation of sodium channels and may therefore bypass the induction of the homeostatic mechanisms observed following stimulation with a direct current (Terney et al., 2008; Fertonani et al., 2011). By preventing the induction of

homeostatic regulation, it has been suggested that tRNS may be able to induce more pronounced and / or reliable neuromodulatory effects than tDCS (Fertonani & Miniussi, 2017; Fertonani et al., 2011).

Despite this, there is limited research directly comparing the facilitatory after-effects induced by these techniques, and the few available studies have produced conflicting findings. For instance, Moliadze, Antal, and Paulus (2010) found no significant differences in the facilitatory effects of tRNS or anodal tDCS on motor cortex excitability, Moliadze et al. (2014) reported that the facilitatory after-effects of stimulation were largest for tDCS but lasted longer for tRNS, and Inukai et al. (2016) found that tRNS resulted in the largest facilitation of excitability. While the ability of tRNS to avoid the induction of homeostatic mechanisms speaks to a potential superiority over tDCS, further research is required to replicate comparisons of the facilitatory effects of tDCS and tRNS on cortical excitability.

tRNS can also be delivered with a direct-current offset (DC-offset) to produce an electrical waveform which combines the electrical characteristics of tDCS and tRNS. The alternating current delivered by tRNS typically has no DC-offset, meaning that the current fluctuates from positive to negative polarity with a mean amplitude of zero (Terney et al., 2008) (Figure 3.7). In contrast, delivering tRNS with a DC-offset results in electrodes delivering a consistent polarity with a randomly fluctuating current intensity and produces a unidirectional current flow analogous to tDCS (Ho et al., 2015). For example, as illustrated in Figure 3.7, delivering tRNS with an amplitude of 1 mA and without a DC-offset results in the current at both electrodes rapidly fluctuating in intensity between -0.5 and 0.5 mA. Applying tRNS without a DC-offset results in both electrodes delivering identical stimulation over the course of the stimulation session (Fertonani et al., 2011; Pirulli, Fertonani, & Miniussi, 2013). In contrast, applying tRNS with an amplitude of 1 mA and a DC-offset of 1 mA results in one electrode delivering a positive charge (i.e. anodal electrode) which fluctuates

between 0.5 and 1.5 mA and the other delivering a negative charge (i.e. cathodal electrode) which fluctuates between -0.5 and -1.5 mA (Figure 3.7). tRNS + DC-offset produces a unidirectional current flow from the anodal to the cathodal electrode, and thereby combines the electrical characteristics of tDCS (i.e. net polarisation of neuronal membrane potentials) and tRNS (i.e. introducing noise into the neural system) (Ho et al., 2015) (Figure 3.7).

To date there has been only one study to systematically investigate the neuromodulatory effects of tRNS with a DC-offset. Ho, Taylor, and Loo (2015) found that delivery of tRNS with a 1 mA DC-offset significantly increased motor cortex excitability, whereas no significant effects were observed when applying tRNS without a DC-offset. This study provides extremely preliminary evidence that delivering tRNS with a DC-offset induces more pronounced neuromodulatory effects than tRNS without an offset. As modulation of cortical excitability is thought to be a key component of tES-induced cognitive enhancement, this raises a speculative but intriguing possibility that tRNS + DC-offset could be a more effective as a means of cognitive enhancement. However, the effects of tRNS + DC-offset on WM performance has yet to be systematically investigated, and no studies have compared this form of tES to tDCS.

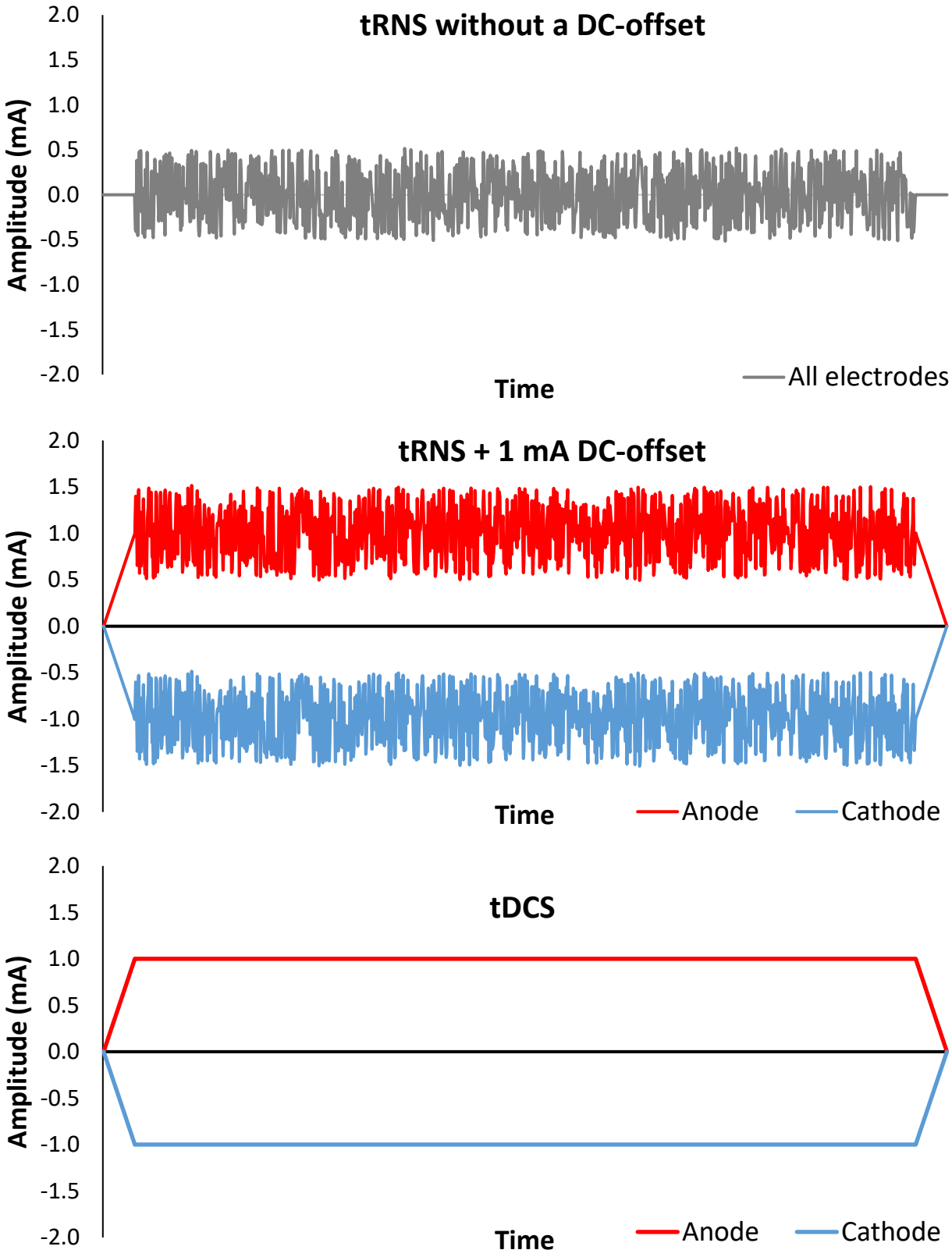


Figure 3.7. Visual representation of the electrical waveform for 1 mA tRNS without a DC-offset (top), 1 mA tRNS with a 1 mA DC-offset (middle), and 1 mA tDCS (bottom). Note that all electrodes deliver equivalent electrical charge for tRNS without a DC-offset.

3.3.3. Factors influencing the neuromodulatory effects of tRNS

All forms of tES are presumed to be both state-dependent and influenced by individual characteristics, however there is extremely limited research directly investigating which variables are most influential for tRNS outcomes. tDCS delivers a uniform electrical field which can exert both facilitatory and inhibitory effects within a cortical region dependent on the orientation of neurons relative to current flow (Bikson et al., 2004; Rahman et al., 2013). tRNS largely overcomes this limitation by delivering a rapid oscillating current which induces excitatory effects regardless of neuronal orientation (Pirulli et al., 2016; Fertonani et al., 2011; Terney et al., 2008). Although speculative, these features may allow tRNS to exert more consistent effects than tDCS at the level of neurophysiological modulation, which may thereby limit the potentially confounding effects of variation in individual characteristics (Pirulli et al., 2016; Fertonani et al., 2011; Terney et al., 2008). Such research investigating the consistency of tRNS outcomes has yet to be conducted.

3.3.4. tRNS to enhance cognition

Research using tRNS is in its infancy and as such there have only been a limited number of studies investigating its potential to enhance aspects of cognition, however early results have been promising. Studies evaluating the effects of a single session of tRNS have reported evidence of benefits in a range of cognitive processes, including motor learning (Prichard et al., 2014; Saiote et al., 2013), perception of faces (Romanska, Rezlescu, Susilo, Duchaine, & Banissy, 2015), and visual perceptual learning (Fertonani et al., 2011; Herpich et al., 2015; Tyler, Contò, & Battelli, 2015). Further, several studies have provided evidence that delivery of tRNS during cognitive training programs can enhance cognitive outcomes for both trained and untrained material, as compared to cognitive training alone (Cappelletti et al., 2013; Popescu et al., 2016; Snowball et al., 2013; although see Holmes, Byrne, Gathercole, & Ewbank, 2016).

Although both anodal tDCS and tRNS have been shown to enhance cortical excitability (e.g. Nitsche & Paulus, 2001; Terney et al., 2008), the neuromodulatory effects of these techniques rely upon different underlying neurobiological mechanisms (Fertonani & Miniussi, 2017), hence it is unlikely that they will induce comparable effects on cognitive performance. Despite the strong interest in tES and cognitive augmentations, there have been very few studies directly comparing the effects of tRNS and tDCS on cognitive performance using the same methodological design. For instance, Fertonani, Pirulli, and Miniussi (2011) observed that high-frequency tRNS was more effective than anodal tDCS in improving visual perceptual learning, whereas Pirulli et al. (2013) observed that anodal tDCS was superior to tRNS at enhancing perceptual learning when delivered prior to task execution. While superficially these studies seem to suggest that tDCS and tRNS differ in regard to the optimal timing of stimulation to improve learning, others have observed that anodal tDCS and high frequency tRNS induce comparable enhancements in motor learning regardless of stimulation timing (Prichard et al., 2014; Saiote et al., 2013). These studies provide preliminary evidence that tDCS and tRNS exert differing effects on cognitive function, however, there is much research needed to understand which factor influence outcome.

3.3.4.1. Working memory

To-date, only one study has directly compared the impact of anodal tDCS and tRNS on WM performance. Mulquiney et al. (2011) compared the effects of anodal tDCS, broad frequency (1-640 Hz) tRNS without a DC-offset, or sham stimulation to the left DLPFC during the completion of a Sternberg verbal WM task and assessed offline effects on WM performance using the *n*-back task (1- and 2-back versions). Interestingly, tRNS did not significantly improve Sternberg WM task or *n*-back performance, whereas anodal tDCS improved reaction time on the 2-back task but no other performance indices. Several methodological factors may have contributed to these null findings. Firstly, as higher

frequencies (i.e. 101-640 Hz) are primarily responsible for the facilitatory effects of tRNS on cortical excitability (Terney et al., 2008), it is likely that the use of a broad frequency spectrum (i.e. 0.1-640 Hz) in this study limited the neuromodulatory effects of tRNS. Secondly, the stimulation duration of 10-minutes may have been insufficient to induce improvements in the tRNS condition. Although delivery of tRNS for a duration of 10-minutes has been shown to induce enhancements in motor cortex excitability for up to an hour after stimulation (Terney et al., 2008), it is possible that longer stimulation durations are required to modulate excitability and cognitive performance in the prefrontal cortex due to variation in cytoarchitecture, neuronal organisation, and receptor type and density (Laakso et al., 2016; Rahman et al., 2013; Russell et al., 2014; Stagg et al., 2013). Moreover, given the rationale presented above illustrating that delivering tRNS with a DC-offset may induce maximal neurophysiological effects (Ho et al., 2015) and absence of research investigating the impact of tRNS + DC-offset on cognitive modulation, it would be of interest to investigate whether tRNS + DC-offset may also prove more effective as a means to enhance WM performance. Given these factors, research is warranted to directly compare the effects of tRNS + DC-offset and tDCS on WM performance.

3.4. Summary of Transcranial Electrical Stimulation

tDCS and tRNS are promising tools for enhancing aspects of human behaviour and cognitive function via modulation of underlying neurophysiological activity. Evidence has demonstrated the potential of these techniques to induce immediate and long-lasting effects on cortical excitability and cognitive function. tDCS is the most researched for of tES and has been shown to modulate cognitive functions, particularly WM, however null findings are also abundant, and observed enhancements performance are typically limited in magnitude and highly variable between studies. Early research has provided promising evidence for the

capacity of tRNS to modulate cortical excitability and cognitive performance. tDCS and tRNS rely upon different underlying neurobiological mechanisms of action, with the randomly fluctuating tRNS waveform being proposed to bypass activation of homeostatic mechanisms which interfere with the neuromodulatory effects of tDCS. This raises the possibility that tRNS may overcome some of the factors currently limiting the efficacy of tDCS. Recent evidence indicates that delivering tRNS with a DC-offset facilitates cortical excitability to a greater degree than tRNS without an offset, potentially because it combines the characteristics of tRNS (i.e. introducing noise into the neural system) with those of tDCS (i.e. consistent polarisation of neuronal membrane potentials). However, the potential of tRNS + DC-offset to enhance WM performance has yet to be investigated. Further research should aim to include neurophysiological measurement techniques, such as EEG, which allow examination of the neurophysiological effects of stimulation in regions outside of the motor cortex and offer the potential of informing the neural correlates of tES-induced cognitive enhancement. Obtaining a greater understanding of the underlying neurophysiological effects of tDCS and tRNS is a vital step in determining whether it is possible to improve the reliability and effectiveness of these techniques as a form of cognitive enhancement in healthy individuals or as therapeutic tools in psychiatric conditions such as MDD.

CHAPTER FOUR

Non-Invasive Brain Stimulation in Major Depressive Disorder

4.1. Treatment modalities for MDD

A range of pharmacological, psychological and brain stimulation treatments have demonstrated efficacy in alleviating the affective and cognitive symptoms of Major Depressive Disorder (MDD). Results from double-blind randomised controlled trials (RCTs) have highlighted several treatments which are effective in treating depression and reducing the risk of relapse, including pharmacological medication (Cipriani et al., 2009; Fournier et al., 2010; Geddes et al., 2003), psychotherapy (Dobson et al., 2008; Parikh et al., 2009; Vittengl, Clark, & Jarrett, 2009), and electroconvulsive therapy (ECT) (Janicak et al., 2002; Sackeim et al., 2007). The first-line treatment choice for MDD differs as a function of depression severity, with mild depression typically being managed with lifestyle changes and / or psychotherapy, moderate depression typically being treated with antidepressant medication, psychotherapy, or a combination of both, and severe depression typically being treated with a combination of antidepressants and psychotherapy (Davidson, 2010; Malhi et al., 2015). Severe cases of MDD which fail to respond to standard first-line treatments may require the use of alternate strategies such as ECT or repetitive transcranial magnetic stimulation (rTMS) (Kennedy et al., 2009; Lam et al., 2009).

Although the above-mentioned treatments for MDD have repeatedly demonstrated efficacy in reducing depression severity, these methods present with a number of limitations which highlight a need for the development of novel treatment modalities. Firstly, while pharmacological treatment may be effective for some individuals, approximately 30-40% of individuals do not respond to the first antidepressant administered and approximately 10% will remain treatment resistant to multiple trials of antidepressant medications (Fava, 2003; Fava & Davidson, 1996; McClintock et al., 2011; Rush et al., 2006). These individuals are described as experiencing treatment resistant depression (TRD) and often experience debilitating symptoms which are not effectively managed with current treatments modalities

(Fava, 2003). Secondly, current treatments for MDD have practical limitations which contribute to high drop-out rates and thereby reduce their overall efficacy. Psychotherapy is time-intensive and can be associated with social stigma (Livingston & Boyd, 2010; Rosen et al., 2011; Rüsch et al., 2009; Thompson, Bazile, & Akbar, 2004). Adverse medical, psychological, or cognitive side-effects have been linked to reduced compliance for pharmacological treatments (Hodgkin, Volpe-Vartanian, & Alegría, 2007; Keller, Hirschfeld, Demyttenaere, & Baldwin, 2002; Olfson, Marcus, Tedeschi, & Wan, 2006) and ECT (Prudic, Peyser, & Sackeim, 2000; Rose, Fleischmann, Wykes, Leese, & Bindman, 2003; Sackeim et al., 2007). Finally, psychotherapy and many pharmacological treatments are relatively ineffective at treating the cognitive deficits associated with MDD (e.g. Keefe et al., 2014; Rosenblat, Kakar, & McIntyre, 2016). Further, some treatments such as ECT or certain pharmacological medications may actively cause cognitive difficulties (e.g. Lisanby, Luber, Schlaepfer, & Sackeim, 2003; Sackeim et al., 2000). Taken together, these issues highlight the critical need for the development of alternate methods for treatment MDD which may overcome these practical limitations and prove more efficacious in the treatment of depression.

There has been significant interest in recent years regarding the potential application of non-invasive transcranial stimulation techniques to improve mood and cognitive function in MDD. The most prominent and well-researched form of non-invasive transcranial stimulation is rTMS. While rTMS has demonstrated promising treatment efficacy for MDD, it possesses a number of practical limitations which restrict it's widespread clinical application. Namely, rTMS treatment is time-intensive and currently requires individuals to regularly attend a clinic or hospital for stimulation sessions, and the high cost of the TMS machine currently limits the availability of this treatment for many individuals. rTMS additionally carries a risk of inducing seizures and therefore requiring careful screening of

individuals prior to treatment (Boes et al., 2016; Machii, Cohen, Ramos-Estebanez, & Pascual-Leone, 2006; Maizey et al., 2013). In contrast to rTMS, transcranial electrical stimulation (tES) techniques possess a relatively high safety profile and low cost, thereby making them attractive candidates for widespread clinical application. Moreover, tES devices are easily portable, increasing their potential for at-home application as an adjunct to standard first-line antidepressant psychopharmacological and counselling treatments. Ongoing at-home treatment with tES may additionally prove useful for reducing risk of replace following successful treatment with first-line treatment modalities. These practical advantages make tES methods promising tool for the treatment of affective and cognitive symptoms in MDD, either as a monotherapy or adjunct to standard first-line treatment.

The current chapter will provide an overview of research concerning the effects of non-invasive transcranial stimulation on the affective and cognitive symptoms of MDD, in addition to a discussion of evidence relating to the purported neurophysiological mechanisms of action underlying these effects. Focus will be placed on research examining the effects of tDCS and tRNS on cognitive function and neurophysiological activity in MDD, as this represents the focus of this thesis. However, as research applying these techniques in MDD is limited, the following section will also include a brief overview of evidence from studies using the related technique of rTMS in MDD. Although this is not a primary aim of this thesis, evidence drawn from clinical rTMS studies has provided valuable information regarding the effects of non-invasive transcranial brain stimulation in depression and has played a key role in informing the subsequent use of tES techniques in MDD.

4.2. Repetitive Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique which utilises electromagnetic induction to depolarise cortical neurons (Hallett, 2007). TMS is delivered via a copper shielded coil which is placed on the scalp above the desired neural region of stimulation. During TMS, electrical currents are passed through the coil to produce a perpendicular magnetic current, known as a TMS pulse. The magnetic pulse passes through the skull to focally stimulate cortical regions and depolarise neurons (Hallett, 2007; Walsh & Cowey, 2000). rTMS involves the delivery of multiple pulses of TMS during a single session and can induce persistent changes in the cortical excitability of stimulated regions, which are believed to be dependent on the induction of LTP/LTD-like plasticity (Hoogendam, Ramakers, & Di Lazzaro, 2010; Ogiue-Ikeda, Kawato, & Ueno, 2003; Pascual-Leone et al., 2011; Siebner et al., 2004). The neurophysiological effects of rTMS are dependent on stimulation frequency: low-frequency rTMS (≤1 Hz) potentiates GABA neurotransmission and typically reduces cortical excitability, whereas high-frequency rTMS (≥5 Hz) facilitates glutaminergic synaptic activity and typically increases cortical excitability (Chen et al., 1997; Daskalakis, Levinson, & Fitzgerald, 2008; Fitzgerald, Fountain, & Daskalakis, 2006; Pascual-Leone et al., 1998). The intensity of the TMS pulse applied to treat depression typically ranges from 90-120% of the individual's resting motor threshold, defined as the minimal stimulation intensity required to produce a muscle twitch when applied over the corresponding node of the motor cortex (Wassermann & Lisanby, 2001). When applied as a treatment for MDD, rTMS is typically delivered five to six times a week for a four to six-week period (Kennedy et al., 2009; Lefaucheur et al., 2014).

The left dorsolateral prefrontal cortex (DLPFC) is the most common site of stimulation for delivery of rTMS in MDD, with several lines of evidence supporting this decision. Firstly, EEG research has repeatedly found that MDD is associated with an

asymmetry in frontal alpha power, which has been conceptualised as indicating hypoactivity in the left frontal cortex and hyperactivity in the right frontal cortex (e.g. Cantisani et al., 2015; Chang et al., 2012; Henriques & Davidson, 1991; Jaworska, Blier, Fusee, & Knott, 2012; Kemp et al., 2010). This is supported by functional neuroimaging research demonstrating that acute depressive episodes are associated with hypoactivity of the left DLPFC (Koenigs & Grafman, 2009; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007), with increases in left DLPFC activity typically observed following successful antidepressant treatment (Brody et al., 2001; Mayberg et al., 2000, 2005). Secondly, the DLPFC is a crucial node within neurocircuitry that supports both cognition and emotional control (Davidson, 2000; MacDonald et al., 2000; Ochsner, Bunge, Gross, & Gabrieli, 2002). Hypoactivation of the DLPFC in MDD is believed to reflect a failure of this region to exert top-down cognitive control (i.e. inhibition) over excessive and maladaptive emotional thoughts induced by hyperactivity of subcortical limbic regions (Koenigs & Grafman, 2009; Ochsner et al., 2002; Ochsner & Gross, 2005). There is evidence that dysfunctional cognitive control in MDD contributes to the development and maintenance of rumination and information processing bias towards negative emotional stimuli (Beckwé, Deroost, Koster, De Lissnyder, & De Raedt, 2014; Browning, Holmes, Murphy, Goodwin, & Harmer, 2010). DLPFC dysfunction has also been implicated in the pathophysiology of cognitive impairment in MDD, with neuroimaging repeatedly showing that WM impairments in MDD are associated with aberrant activation of the DLPFC during WM processing (Barch et al., 2003; Townsend, Bookheimer, Foland–Ross, Sugar, & Altshuler, 2010; Vasic, Walter, Sambataro, & Wolf, 2009). These converging findings indicate that abnormal prefrontal activity plays a role in the pathogenesis of depression and have led researchers to suggest that normalisation of frontal activity via rTMS of the DLPFC may therefore offer therapeutic benefits in MDD. Importantly, due to the important functional role that the DLPFC plays in cognitive control,

affective processing, and higher-order cognition, modulation of this regions using rTMS, as well as other forms of non-invasive brain stimulation, offers the potential to target both the affective and cognitive symptoms of MDD.

4.2.1. Antidepressant efficacy of rTMS

rTMS has repeatedly demonstrated antidepressant superiority over sham stimulation in reducing depression severity and the risk of relapse for individuals with MDD. In an early large-scale multi-site treatment study, O'Reardon et al. (2007) evaluated the antidepressant efficacy of a six-week course of rTMS in 301 medication-free patients with TRD, finding that individuals receiving active stimulation displayed significantly greater response rates as well as a twofold increase in remission rates, as compared to sham stimulation. Subsequent meta-analyses of sham-controlled rTMS treatment studies have repeatedly revealed moderate effect sizes for the superiority of active over sham rTMS, with estimates of response rates ranging from 25-46% for active stimulation and 9-11% for sham stimulation, and estimates of remission rates ranging from 11-31% for active stimulation and 5-6% for sham stimulation (Berlim, Van den Eynde, Tovar-Perdomo, & Daskalakis, 2014; Lam, Chan, Wilkins-Ho, & Yatham, 2008; Schutter, 2009). The antidepressant efficacy of rTMS appears to be higher when stimulation is delivered in combination with pharmacological treatments (Bretlau et al., 2008; Rumi et al., 2005; Schüle et al., 2003), highlighting rTMS as a potential efficacious adjunct to traditional first-line treatments. Further, emerging research suggests that the risk of relapse following successful a successful course of rTMS may be reduced via the administration of ongoing rTMS 'maintenance' sessions, whereby individuals receive clustered sessions of rTMS every month following the end of the initial treatment course (Fitzgerald, Grace, Hoy, Bailey, & Daskalakis, 2013; Philip et al., 2016; Richieri et al., 2013). Taken together, these results support the efficacy of rTMS as a treatment to reduce depressive symptomology and increase remission rates in MDD.

4.2.2. Cognitive effects of rTMS in MDD

Notable variability exists regarding the efficacy of rTMS to improve the cognitive symptoms of MDD. There is evidence of significant increases in neuropsychological performance following rTMS for MDD, including improvements in attention (Höppner et al., 2003; Huang et al., 2012; Shajahan et al., 2002), psychomotor processing speed (Höppner et al., 2003), learning and memory (Hoy, Segrave, Daskalakis, & Fitzgerald, 2012; Padberg et al., 1999; Schulze-Rauschenbach et al., 2005), and aspects of executive function (Martis et al., 2003; Moser et al., 2002; Nadeau et al., 2014; Schulze et al., 2016; Spampinato et al., 2013). In contrast, a considerable number of studies have failed to find evidence of cognitive improvement following rTMS, despite observing significant reductions in depressive symptomology (Demirtas-Tatlidede et al., 2008; Isenberg et al., 2005; Speer et al., 2001; Tovar-Perdomo, McGirr, Van den Eynde, dos Santos, & Berlim, 2017; Wajdik et al., 2014). While the variability between these studies is likely influenced by methodological factors, such as the cognitive domains assessed and the sensitivity and comparability of the cognitive tasks, this dissociation provides evidence that effects of rTMS on affective and cognitive symptoms are dependent on different yet overlapping mechanisms.

The results of recent meta-analyses suggest that rTMS may improve performance in specific neuropsychological domains, rather than exerting an overall increase in cognitive ability. In a meta-analysis of 30 clinical trials which included cognitive evaluation before and after rTMS, Martin, McClintock, Forster, and Loo (2016) found no significant improvement in overall cognitive performance after pooling results from different cognitive domains. However, a subsequent meta-analysis by the same group examined the impact of rTMS on individual cognitive tasks (11 in total), finding that active stimulation was associated with significant improvements in performance on the Trail Making Test (TMT) Part A and B, but not in any of the other cognitive tasks (Martin, McClintock, Forster, Lo, & Loo, 2017). The

TMT Part B is particularly sensitive to frontal-lobe dysfunction in MDD (e.g. Gooren, Schlattmann, & Neu, 2013; Mahurin et al., 2006), and performance on this task is associated with increased activation of the left DLPFC (Moll, Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002; Zakzanis, Mraz, & Graham, 2005). The selective increase in performance on the TMT Part B, but not on other tasks which feature less prefrontal involvement, supports the notion that rTMS may improve cognitive performance by facilitating activity in prefrontal regions. Taken together, the results of these meta-analyses suggest that rTMS does not produce generalised cognitive enhancement in MDD, but may improve specific aspects of neuropsychological performance, particularly for cognitive domains which rely heavily upon frontal-lobe function.

4.2.3. Mechanisms underlying the antidepressant effects of rTMS

Functional neuroimaging studies suggest that successful antidepressant treatment with rTMS involves a cascade of neurophysiological changes within the DLPFC and functionally connected regions. Consistent with the traditional aim of rTMS to normalise dysfunctional activity within prefrontal regions, studies have observed that high-frequency rTMS to the left DLPFC is associated with increases in metabolic activity within the DLPFC and wider prefrontal cortex (Loo et al., 2003; Mottaghy et al., 2002; Teneback et al., 1999). Further, rTMS results in widespread modulation of activity across connected cortical and sub-cortical regions distal to the site of stimulation. For instance, delivery of rTMS to the left DLPFC in MDD also exerts effects in the orbitofrontal cortex and anterior cingulate cortex (Loo et al., 2003; Nadeau et al., 2002; Nahas et al., 2001; Teneback et al., 1999), as well as in sub-cortical regions such as the amygdala, hypothalamus, and hippocampus (Kito, Fujita, & Koga, 2008; Kito, Hasegawa, & Koga, 2011; Loo et al., 2003; Nadeau et al., 2002; Nahas et al., 2001; Teneback et al., 1999). Importantly, many neuroanatomical regions which demonstrate metabolic changes following rTMS are involved in mood regulation and

emotional processing and are typically dysfunctional in MDD, thereby suggesting that the antidepressant effects of rTMS arise from normalising of activity within neuronal circuits that are dysfunctional in MDD. Consistent with this, functional neuroimaging studies have found that rTMS treatment efficacy may be predicted by baseline activity within these functionally connected regions, with greater modulation of activity within prefrontal regions predicting improved treatment outcome (Baeken et al., 2009, 2015; Drevets, Price, & Furey, 2008; Langguth et al., 2007; Paus, Castro-Alamancos, & Petrides, 2001; Teneback et al., 1999).

In summary, rTMS has demonstrated efficacy in reducing depressive symptomology for moderate-to-severe cases of MDD and represents a promising treatment modality for individuals with TRD who have failed to respond to first-line antidepressant medications. Evidence supports the ability of rTMS to improve aspects of cognitive dysfunction in MDD, particularly for cognitive functions subsumed by prefrontal regions, such as WM. While rTMS is a powerful addition to the therapeutic armamentarium for MDD, several practical limitations currently limit the widespread therapeutic application of rTMS. For instance, the relatively high cost of TMS machines renders treatment expensive for many individuals, and treatment is time intensive as patients are required to travel to hospitals or clinics for multiple sessions of rTMS. Moreover, rTMS treatment is associated with a significant, yet relatively low, risk of inducing seizures in some individuals (< 1% incidence) (Boes et al., 2016; Machii et al., 2006; Maizey et al., 2013). These practical limitations have driven research investigating whether other forms of non-invasive brain stimulation may induce comparable therapeutic effects to rTMS whilst overcoming these barriers.

4.3. Transcranial Direct Current Stimulation

There has recently been considerable interest in the application of tDCS to treat MDD. In contrast to the practical limitations of rTMS discussed above, tDCS devices are relatively inexpensive, portable, and have a high safety profile, thereby making tDCS well-suited for widespread clinical application and at-home treatment in MDD. Moreover, several studies have demonstrated beneficial antidepressant effects of tDCS when delivered in combination with pharmacological treatment for MDD, thereby highlighting the potential of tDCS as an adjunct to standard first-line antidepressant treatments. Similar to rTMS, the theoretical rationale for the use of tDCS to treat MDD involved remediating dysfunctional prefrontal activity (Ironside & Perlo, 2018). Given evidence that anodal tDCS of the DLPFC can modulate cognitive functioning in healthy individuals (see Chapter Three), combined with evidence implicating aberrant DLPFC activity in the pathophysiology of affective and cognitive symptomology in MDD (Koenigs & Grafman, 2009; Vasic et al., 2009), most studies in MDD have delivered anodal tDCS to the left DLPFC. These studies have typically placed the cathodal electrode over the contralateral orbit, although some studies have utilised a bifrontal montage in which the anodal and cathodal electrodes are placed over the left and right DLPFC, respectively (for a review see Meron, Hedger, Garner, & Baldwin, 2015). While some clinical research in MDD provided promising evidence for reductions in depression severity following anodal tDCS to the left DLPFC (Dedoncker et al., 2016; Rigonatti et al., 2008), several large-scale clinical trials have found that tDCS failed to produce clinically meaningful antidepressant effects (Blumberger, Tran, Fitzgerald, Hoy, & Daskalakis, 2012; Loo et al., 2018, 2010). Interpretation of these findings is complicated by broad heterogeneity in stimulation protocols and participant characteristics between studies, with tDCS treatment studies including large variation in depression severity, current density

(0.03 - 0.08 mA/cm^2), stimulation duration (20 - 30 minutes), and the total number of sessions (5 - 15 sessions) (Brunoni, Moffa, et al., 2016; Shiozawa et al., 2014).

4.3.1. Antidepressant efficacy of tDCS

tDCS treatment dose is a critical parameter in determining the antidepressant outcome of stimulation. While an early study by Fregni et al. (2006) noted a significant reduction in the severity of depressive symptoms following a five-day course of anodal tDCS to the left DLPFC using a low current density (0.029 mA/cm^2), a later study by the same group reported a greater magnitude of improvement in depressive symptoms when delivering the same stimulation montage using a higher current density (0.057 mA/cm^2) (Boggio et al., 2008). Similarly, an early by Loo et al. (2010) failed to find evidence of clinical improvement following a 10-session treatment course of tDCS using a low-current density (0.029 mA/cm^2), while a subsequent study by the same group observed improved clinical outcomes when applying a greater treatment dose which included a higher current density (0.057 mA/cm^2) and a longer 15-session treatment course (Loo et al., 2012). Consistent with these findings, a recent meta-analysis of six tDCS treatment studies including 289 patients with MDD revealed that tDCS dosage was positively associated with antidepressant efficacy, whereby increased response and remission rates were observed in studies using higher current density, longer stimulation duration, or an increased number of stimulation sessions (Brunoni, Moffa, et al., 2016). These studies highlight the important role that stimulation dosage plays determining the antidepressant outcome of tDCS.

Several sham-controlled clinical trials have provided evidence that tDCS exerts antidepressant effects of a similar magnitude to some first-line antidepressant medications. In a large-scale sham-controlled RCT including 120 individuals with moderate-to-severe MDD, Brunoni et al. (2013) compared the effects of bifrontal tDCS to the DLPFC (left anode, right cathode), the antidepressant sertraline, and combination of both treatments. Following 10

consecutive days of stimulation, the authors found that tDCS and sertraline resulted in a similar magnitude of improvement in depressive symptoms, and both were significantly more effective than sham stimulation. Interestingly, significantly higher antidepressant efficacy was noted when bifrontal tDCS and sertraline were administered in combination, highlighting a potential role for tDCS as an adjunct to standard pharmacological treatment. A subsequent sham-controlled study by the same group compared the antidepressant efficacy of bifrontal tDCS (anode over left DLPFC, cathode over right DLPFC) to that of escitalopram or placebo medication over a 15-week treatment course (Brunoni et al., 2017). The authours found that both tDCS and escitalopram resulted in greater reduction in depressive symptoms as compared to placebo medication, with no significant differences noted between the two active treatments. Similarly, one study found that tDCS produced a similar magnitude of clinical improvement as standard treatment with fluoxetine, however the antidepressant effects of tDCS were observed to manifest earlier than for fluoxetine (Rigonatti et al., 2008). These studies provide preliminary support for the use of tDCS as an adjunct to standard pharmacological treatment in MDD.

While significant antidepressant effects of prefrontal tDCS have been reported by several open label (Brunoni, Valiengo, et al., 2013; Ferrucci, Bortolomasi, Vergari, et al., 2009) and sham-controlled trials (Boggio et al., 2008; Loo et al., 2012), meta-analyses of clinical trials in MDD have highlighted that effects of tDCS, although statistically significant, are clinically sub-optimal (Berlim, Van den Eynde, & Daskalakis, 2013; Kalu, Sexton, Loo, & Ebmeier, 2012; Shiozawa et al., 2014). For instance, Berlim et al., (2013) conducted a meta-analysis of data from six randomised controlled trials delivering tDCS in MDD, finding that while response rates were significantly higher for active (23.3%) as compared to sham tDCS (12.2%), overall clinical outcomes were equivalent for active and sham tDCS. When viewed together, this evidence suggests that anodal tDCS of the DLPFC has antidepressant

potential, but that effects are of a clinically modest nature. As such, there is a need to investigate the neurophysiological mechanisms responsible for the antidepressant effects of tDCS, which will assist in determining whether other stimulation protocols which induce more pronounced and reliable antidepressant effects in MDD.

4.3.2. Cognitive effects of tDCS in MDD

Much of the evidence regarding the cognitive effects of tDCS in MDD has been provided by clinical trials that assessed changes in cognitive performance following a treatment course of anodal tDCS to the left DLPFC. While an early pilot study by Fregni, Boggio, Nitsche, Rigonatti, and Pascual-Leone (2006) reported that individuals with MDD displayed improved performance on the digit-span forwards and backwards tasks following five sessions of tDCS, subsequent large-scale RCTs have failed to replicate these improvements in digit-span performance (Brunoni, Tortella, et al., 2016; Brunoni, Valiengo, et al., 2013; Loo et al., 2012, 2010). Improvements in working memory (WM) have been reported following a single session of tDCS in depressed individuals (Moreno et al., 2015; Oliveira et al., 2013), and in two RCTs examining the antidepressant effects of tDCS (Salehinejad, Ghanavai, Rostami, & Nejati, 2017; Salehinejad, Rostami, & Ghanavati, 2015). In contrast, several other large-scale RCTs have failed to observe any significant changes in WM performance (Brunoni, Tortella, et al., 2016; Ferrucci, Bortolomasi, Vergari, et al., 2009; Palm et al., 2012). A series of studies by Loo and colleagues found no evidence of improvement in performance across a range of neuropsychological domains following 10 sessions of low current density anodal tDCS (0.029 mA/cm^2) over the left DLPFC (Loo et al., 2010), or after using of a higher dosage with 15 sessions of high current density anodal tDCS (0.057 mA/cm^2) delivered using the same montage (Loo et al., 2012). Similarly, other RCTs which included a broad battery of neuropsychological assessment have failed to observe significant improvements across any cognitive domains following anodal tDCS of the left

DLPFC (Brunoni, Tortella, et al., 2016; Ferrucci, Bortolomasi, Vergari, et al., 2009; Palm et al., 2012). Overall, while some studies have provided evidence of cognitive improvement following clinical trials of tDCS in MDD, particularly for WM, findings are inconsistent, and interpretation is complicated by broad heterogeneity in stimulation protocols and cognitive outcome measures.

4.3.3. Mechanisms underlying the antidepressant effects of tDCS

There is very limited research regarding the neurophysiological effects of tDCS in MDD, however, several lines of evidence suggest that stimulation exerts antidepressant effects by facilitating DLPFC activity and enhancing aspects of cognitive control. Depression is associated with an attentional bias towards negatively-valanced stimuli (Leppänen, 2006), which is believed to reflect impaired cognitive control over negative emotional representations (Gotlib, Krasnoperova, Yue, & Joormann, 2004; Joormann & Gotlib, 2007), and has been linked to dysfunctional activity within the DLPFC (Fales et al., 2008; Harvey et al., 2005). Several studies have demonstrated that delivering anodal tDCS to the left DLPFC in depressed individuals ameliorates or even eliminates this negative attentional bias on WM paradigms which feature emotionally-valanced stimuli or distractors (Boggio et al., 2007; Brunoni et al., 2014; Moreno et al., 2015; Segrave, Arnold, Hoy, & Fitzgerald, 2014; Wolkenstein & Plewnia, 2013). These findings suggest that the antidepressant effects of tDCS may primarily dependent on the enhancement of the cognitive components of emotional regulations rather than exerting direct effects on mood. Convergent support for this notion has been provided in studies of healthy individuals. Namely, evidence suggests that delivery of anodal tDCS to the left DLPFC does not acutely affect mood in healthy individuals (Morgan, Davis, & Bracewell, 2014; Nitsche et al., 2012; Plazier, Joos, Vanneste, Ost, & De Ridder, 2012), but rather increases the ability to suppress self-referential ruminative thoughts and negative emotional responses (Baeken et al., 2017; Feeser, Prehn,

Kazzer, Mungee, & Bajbouj, 2014). Taken together, these findings suggest that targeting the DLPFC to modulate cognitive control and affective bias is a promising way to treat both the affective and cognitive symptoms of MDD. However, tDCS as it is currently being applied is not yet robustly or reliably effective for improving symptomology in MDD. Obtaining a greater understanding of the neurophysiological mechanisms through which tDCS modulates affective and cognitive symptoms is an important first step towards improving the reliability and efficacy of this technique as a potential treatment for MDD.

EEG is a powerful yet under-utilised tool to examine the neural correlates of tDCS-induced modulation in cognitive function. Research in healthy individuals has demonstrated that tDCS can alter neural oscillatory activity and cognition in healthy individuals (Hsu et al., 2014; Zaehle et al., 2011) and has linked tDCS-induced modulation of neural oscillations to enhanced WM performance (Zaehle et al., 2011). There is, however, minimal research examining the potential of tDCS to modulate the abnormal neural oscillatory activity associated with cognitive impairment in MDD. This is somewhat surprising given evidence linking cognitive dysfunction in MDD to widespread abnormalities in resting and task-related neural oscillations (Arns et al., 2015; Bailey et al., 2014; Cantisani et al., 2015; Henriques & Davidson, 1991; Segrave et al., 2010). Preliminary evidence for the ability of tDCS to modulate abnormal neural oscillatory activity in MDD was provided in single-case study by Palm et al. (2009), who reported increased verbal fluency as well as pronounced decreases in resting frontal alpha and theta power in a 66-year old female with TRD who received a 16-session course of anodal tDCS to the left DLPFC (0.029 mA/cm^2, cathode over contralateral orbit). Given evidence linking MDD to abnormally high resting alpha and theta power in frontal regions (Arns et al., 2015; Broadway et al., 2012; Henriques & Davidson, 1991), these reductions in frequency-band power may reflect a shift towards normalisation of neural oscillatory activity. However, the absence of task-related EEG in these studies prevents

investigation of whether the observed cognitive improvements were associated with alterations in depression-related abnormalities in task-related neural oscillatory activity.

To date, only one study has directly investigated the effects of tDCS on task-related EEG in individuals with MDD. Using a sham-controlled crossover design, Powell, Boonstra, Martin, Loo, and Breakspear (2014) assessed visual WM performance and concurrent task-related EEG in 18 depressed individuals following a single session of anodal tDCS to the left DLPFC (0.057 mA/cm^2, 20-minutes duration, cathode over contralateral orbit). Although no significant differences in visual WM performance were observed between the active and sham conditions, active tDCS was associated with a significant reduction in posterior alpha power during the maintenance phase of the WM task, in addition to decreased FMT power during the retrieval phase. As some studies have found evidence that MDD is associated with abnormally high posterior alpha power during the maintenance phase of WM processing (Segrave et al., 2010), the observed increase in posterior alpha following active tDCS may reflect a shift towards normalisation of activity within these regions. Moreover, as FMT power typically increases during the retrieval phase of WM processing (e.g. Hsieh & Ranganath, 2014; Itthipuripat, Wessel, & Aron, 2013), decreases in FMT power following tDCS may reflect a shift towards more efficient cognitive processing, whereby the same level of cognitive performance was achieved with reduced effort. Taken together, these findings highlight the potential of tDCS to modulate aspects of neural oscillatory activity which have been linked to the pathophysiology of MDD. Further, the observed dissociation between changes in neural oscillatory power and WM performance suggest that EEG measures can be more sensitive to the effects of tDCS than behavioural measures. However, it is important to note that the study by Powell et al. did not assess behavioural or neurophysiological outcomes until approximately one-hour after the cessation of tDCS, thereby limiting their ability to examine the acute effects of tDCS.

The importance of assessing the underlying neurophysiological effects of tDCS in MDD is emphasised by recent research suggesting that stimulation may exert different effects in healthy and depressed individuals. Several studies in healthy individuals have observed that higher dosages of tDCS can exert non-linear effects on cortical excitability (Bastani & Jaberzadeh, 2013; Batsikadze et al., 2013) and WM performance (Hoy et al., 2013). In contrast, as discussed above, emerging research suggests that higher stimulation dosage is associated with greater improvement in affective and cognitive symptoms in MDD (Boggio et al., 2008; Fregni, Boggio, Nitsche, Rigonatti, et al., 2006; Loo et al., 2012, 2010). In addition, a recent meta-analysis of 16 tDCS studies observed that healthy and depressed individuals differed in the optimal timing of tDCS for cognitive enhancement, whereby depressed individuals displayed improved WM performance when anodal tDCS was delivered concurrent with task completion, but healthy individuals displayed enhanced performance when stimulation was delivered prior to the completion of the task (Hill et al., 2016). Taken together, evidence suggest that tDCS exerts differing effects in healthy and depressed individuals, highlighting that stimulation protocols which demonstrated efficacy in modulating neurophysiological or cognitive outcomes in healthy individuals cannot be assumed to demonstrate equivalent outcomes when applied in depressed individuals.

There are several factors likely to influence this dissociation in outcome between healthy and depressed individuals. Firstly, as discussed in Chapter Three, the non-linear effects of tDCS in healthy individuals are believed to occur as a result of activation of homeostatic mechanisms which counter-regulate persistent changes in neural activation (Fertonani & Miniussi, 2017; Fertonani et al., 2011). However, several studies have found that MDD is associated with dysfunction in synaptic homeostatic mechanisms (Duman & Aghajanian, 2012; Thickbroom & Mastaglia, 2009), hence these mechanisms may be perturbed and have a higher threshold for activation in MDD. Further, it cannot be assumed

that outcomes observed in healthy individuals will display a direct one-to-one transferability in MDD due to interactions between tDCS and depression-related abnormalities in cortical activation, neural oscillatory activity, and functional connectivity (Fingelkurts & Fingelkurts, 2014; Greicius et al., 2007; Segrave et al., 2010; Siegle, Thompson, et al., 2007). Finally, many pharmacological treatments for MDD influence neuroplasticity and neurotransmitter function and have been shown to significantly alter or even eliminate the neuromodulatory effects induced by tDCS (Kuo et al., 2016; Liebetanz, Nitsche, Tergau, & Paulus, 2002; Nitsche et al., 2004, 2009), making the outcome of tDCS more uncertain in depressed individuals taking these medications, particularly when patients are taking multiple psychoactive medications. The uncertain outcome of applying tDCS in MDD highlights the importance of further research including measures capable of examining the neurophysiological effects of stimulation. Neurophysiological measurement techniques, such as EEG, can provide valuable information regarding the underlying neural changes responsible for improvements in affective and cognitive symptoms, as well as inform potential reasons why stimulation protocols failed to induce the desired outcomes (i.e. failure of a tDCS protocol to induce effects on underlying neurophysiology, or a failure of neurophysiological changes to translate into affective or cognitive improvement).

Overall, there is evidence supporting the ability of tDCS of reduce depression severity and improve cognitive function in MDD, however effects tend to be modest in size and variable between studies. Obtaining a greater understanding of the neurophysiological mechanisms through which tDCS modulates affective and cognitive symptoms is an important first step towards determining the true therapeutic potential of this technique. Current evidence regarding the neurophysiological effects of applying tDCS to the depressed brain is limited, particularly regarding the mechanisms underlying cognitive improvement, although very preliminary evidence supports its potential to modulate aspects of neural

oscillatory activity associated with cognitive impairment in MDD. Further research is required to directly compare differences in the neurophysiological and cognitive outcomes of tDCS between healthy and depressed individuals using well-matched samples and applying a standardised methodology for both populations.

4.4. Transcranial Random Noise Stimulation

While there is promising support for the efficacy of tRNS as a neuromodulatory tool for enhancing cortical excitability and cognitive performance in healthy individuals (Fertonani et al., 2011; Pirulli, Fertonani, & Miniussi, 2013; Snowball et al., 2013; Terney, Chaieb, Moliadze, Antal, & Paulus, 2008), there has yet to be any sham-controlled studies delivering tRNS in MDD. Despite this, preliminary evidence from healthy individuals suggests that tRNS may exert greater facilitatory effects on cortical excitability than anodal tDCS (Inukai et al., 2016), and may be more effective at enhancing behavioural performance (Fertonani et al., 2011; Moliadze, Fritzsche, & Antal, 2014; although see Mulquiney, Hoy, Daskalakis, & Fitzgerald, 2011). Further, tRNS has demonstrated efficacy in reducing symptom severity for schizophrenia (Haesebaert, Mondino, Saoud, Poulet, & Brunelin, 2014; Palm, Hasan, Keeser, Falkai, & Padberg, 2013), multiple sclerosis (Palm et al., 2016), and neuropathic pain (Alm & Dreimanis, 2013), and was found to be more effective than anodal tDCS in ameliorating the symptoms of tinnitus (Vanneste, Fregni, & De Ridder, 2013). In addition, studies have found that when compared to tDCS, tRNS has a higher cutaneous perception threshold and is associated with fewer negative sequelae (i.e. itching, burning sensations) (Ambrus, Paulus, & Antal, 2010; Fertonani et al., 2011), thus making it more tolerable and supporting its potential clinical viability as a treatment in MDD. These studies highlight tRNS as a promising therapeutic technique and warrant investigation of whether tRNS may demonstrate beneficial effects when applied in MDD.

4.4.1. Affective and cognitive effects of tRNS in MDD

The potential efficacy of tRNS in treating the affective or cognitive symptoms of MDD has not yet been investigated in any sham-controlled studies. However, a single case study has provided very preliminary support for antidepressant effects. Chan et al. (2012) reported the case of a 35-year-old woman with a seven-year history of depression who received a 15-session course of tDCS (0.057 mA/cm^2, anode over left DLPFC, cathode over right frontotemporal region), followed by a 20-session course of tRNS completed four-months later using the same montage (2 mA tRNS with a 1 mA DC offset). When compared to tDCS, the course of tRNS was associated with a greater reduction in depression severity, measured as a 63% reduction in the Montgomery-Asberg Depression Rating Scale score (as compared to 31% following tDCS) and an 87.5% reduction in Quick Inventory of Depressive Symptoms score (as compared to a 67% reduction following tDCS). Although the use of a single non-blinded participant and the possibility of cumulative effects makes this highly speculative evidence, when coupled with the theoretical capacity of tRNS to overcome homeostatic neuroplastic response to tDCS, the prospect of antidepressant tRNS is intriguing. Further sham-controlled studies using larger samples are warranted to examine the comparative efficacy of tDCS and tRNS in treating symptoms of MDD. Given evidence supporting the cognitive enhancing effects of tRNS in healthy (Fertonani et al., 2011; Pirulli et al., 2013; Snowball et al., 2013) and clinical populations (Palm et al., 2013), it would be particularly beneficial to examine the potential of this technique to ameliorate the cognitive impairments associated with MDD. Moreover, given evidence that delivering tRNS with a direct-current offset (DC-offset) can induce more pronounced neurophysiological effects than tRNS without an offset (Ho et al., 2015), it is worthwhile to examine whether tRNS + DC-offset may also prove more effective as a means to enhance cognitive performance in clinical populations such as MDD.

4.5. Summary and Conclusions of Literature Review

MDD is a highly prevalent mental illness associated with significant functional impairment and reductions in quality of life. Impairments in WM are a core neuropsychological feature of MDD which can persist following the remission of affective symptoms and strongly contribute to reductions in functional abilities. A significant proportion of individuals with MDD fail to respond to established treatment modalities, and cognitive impairments remain largely refractory to these conventional treatments. Established antidepressant treatments can also induce notable side-effects which limit treatment compliance, highlighting the need for development of alternative treatment modalities which are more effective, tolerable, and accessible for individuals with MDD. To do so will require a greater understanding of how the neurobiological processes underlying cognition are altered in MDD, and how these neurobiological changes relate to cognitive functioning.

tES techniques have demonstrated the potential to enhance cognitive functioning and possess several characteristics which makes them attractive candidates for therapeutic application, including a relatively high safety profile, portability, and low cost. Evidence suggests that tDCS can enhance cognition in healthy individuals and various clinical conditions. However, enhancements in cognition are variable between individuals and an understanding of the precise neurophysiological changes underlying cognitive enhancement is lacking. tRNS has demonstrated an ability to enhance cognitive performance in healthy individuals, ameliorate symptom severity in various clinical conditions, and may induce more pronounced neurophysiological and behavioural effects than anodal tDCS. However, the cognitive effects of tRNS in MDD are largely unknown, and the neurophysiological mechanisms poorly understood. A greater understanding is required of how stimulation alters the neurobiological processes which support WM processing and how these changes translate in improved cognitive performance. To this end, assessment of WM task-related

neurophysiological activity with EEG offers the potential to provide valuable information regarding how stimulation interacts with ongoing neural activity in the healthy and depressed brain and may assist in elucidating the neurophysiological changes associated with cognitive improvement in these populations.

4.6. Thesis Aims

Given these limitations in our current understanding, the broad purpose of the current thesis is to compare the cognitive and neurophysiological effects of tDCS and tRNS in healthy individuals and in MDD, and to better characterise the pattern of neural oscillatory activity associated with WM processing in MDD. More specifically, this thesis aimed to:

1. Directly compare the effect of single session tDCS and tRNS on WM performance in healthy individuals and MDD;
2. Examine whether a single session of tDCS or tRNS alters oscillatory activity during WM encoding and online information maintenance, and whether these neurophysiological changes are related cognitive enhancements in in healthy individuals and MDD.
3. Characterise the pattern of neural oscillatory activity associated with WM encoding and online information maintenance in MDD.

Three studies were conducted to address these aims:

- Study One used task-related EEG to investigate the presence of alterations in oscillatory activity during WM encoding and online maintenance in MDD, as compared to a sample of healthy individuals closely balanced on potentially confounding demographic and cognitive variables.

- Study Two compared the effects of a single session of tDCS or tRNS on cognitive and neurophysiological measures of WM in healthy individuals, using task-related EEG recording to examine effects of tES on oscillatory activity during WM encoding and online information maintenance.
- Study Three compared the effects of a single session of tDCS or tRNS on cognitive and neurophysiological measures of WM in MDD, using task-related EEG recording to examine effects of tES on oscillatory activity during WM encoding and online information maintenance.

CHAPTER FIVE

Study One - Individuals with depression display abnormal modulation of neural oscillatory activity during working memory encoding and maintenance

5.1. Explanatory Notes

The first study in this thesis aimed to characterise the pattern of oscillatory activity associated with WM processing in MDD. This was achieved using task-related EEG to examine whether individuals with MDD displayed alterations in theta, upper alpha, or gamma activity during WM encoding and maintenance when compared to a sample of healthy individuals closely balanced on potentially confounding demographic and cognitive variables. By balancing participant groups on baseline WM ability, this study aimed to examine whether individuals with MDD display altered patterns of oscillatory activity even when no cognitive impairments are observed. The Sternberg WM task was chosen as the cognitive task during which EEG was recorded as it temporally separates the initial encoding, short-term maintenance, and retrieval of information and thereby allows examination of oscillatory activity associated with each component of WM processing. Further, the use of this task allows the current study to clarify past MDD research which provided conflicting evidence regarding the presence and directions of altered upper alpha power during the maintenance phase of the Sternberg WM task (Bailey et al., 2018, 2014; Segrave et al., 2010).

The pattern of WM-related oscillatory activity associated with MDD is poorly characterised and improving the understanding of these neurobiological changes may inform the processes underlying altered WM processing in MDD. Moreover, this study forms an initial step towards the overall aims of this thesis by improving understanding of the neural state in which tES would be applied to improve WM performance in MDD. Given that the effects of tES are known to be dependent on the state of the brain during stimulation, understanding the neurobiological underpinnings of WM processing in MDD may thereby inform the optimal stimulation protocols for modulating cognitive function in this population.

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Individuals with depression display abnormal modulation of neural oscillatory activity during working memory encoding and maintenance

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ABSTRACT

Purpose: To investigate neural oscillatory activity supporting working memory (WM) processing in depressed individuals and healthy controls.
Methods: Forty-six participants with Major Depressive Disorder (MDD) and 41 healthy controls balanced on age, gender, and WM ability completed a Sternberg verbal WM task with concurrent electroencephalography recording. Oscillatory activity was calculated for upper alpha, theta, and gamma frequency bands during WM encoding and maintenance.
Results: WM performance did not differ between groups. When compared to healthy controls, depressed individuals displayed reduced frontal-midline theta power and increased occipital upper alpha power during WM encoding, and reductions in frontal-midline theta power and occipital gamma and upper alpha power during WM maintenance. Higher depression severity was associated with greater reductions upper alpha and gamma power during WM maintenance.
Conclusions: Depressed individuals displayed prominent alterations in oscillatory activity during WM encoding and maintenance, indicating that the neural processes which support WM processing are altered in MDD even when no cognitive impairments are observed.

1. Introduction

Working memory (WM) is a limited-capacity cognitive system encompassing the encoding, short-term maintenance, and manipulation of mental representations related to goal-oriented behaviour (Baddeley, 2002). Impairments in WM are a core neuropsychological feature of major depressive disorder (MDD) which contribute to significant functional limitations (Cotrena, Branco, Kochhann, Shansis, & Fonseca, 2016; Lam, Kennedy, McIntyre, & Khullar, 2014; Snyder, 2013), and can persist following remission of affective symptoms (Conradi, Ormel, & De Jonge, 2011; Herrera-Guzmán et al., 2010). Neuroimaging studies in MDD have repeatedly demonstrated abnormal activation of prefrontal and parietal regions during the maintenance period of WM tasks (Barch, Sheline, Csernansky, & Snyder, 2003; Matsuo et al., 2007; Walsh et al., 2007), indicating that individuals with MDD utilise different neural processes and regions to the support short-term maintenance of information. Furthermore, electroencephalography (EEG) studies of MDD have observed altered neural responses in occipital regions during the initial encoding of information into WM (Coullaut-Valera, Arbaiza, Coullaut-Valera, & Ortiz, 2007), indicating that deficits in sensory processing may also contribute to WM deficits. Despite this, relatively little is known about the neural processes associated with WM dysfunction in MDD and it is unclear whether inefficient WM processing is contributed to equally by alterations in neural processes during the initial encoding or maintenance of information.

EEG allows examination of neural activity during different stages of WM, including encoding and maintenance. In healthy individuals, WM encoding and maintenance are supported by reliable and robust modulations of neural oscillatory activity within the theta (4–8 Hz), upper alpha (10–12.5 Hz), and gamma (30–100 Hz) frequency ranges (Jensen & Tesche, 2002; Jensen, Gelfand, Kounios, & Lisman, 2002; Roux,

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Wibral, Mohr, Singer, & Uhlhaas, 2012). Theta oscillations recorded over the frontal-midline (frontal-midline theta; FMT) are amongst the most reliable neural markers of attentional control (Sauseng, Hoppe, Klimesch, Gerloff, & Hummel, 2007; Sauseng, Griesmayr, Freunberger, & Klimesch, 2010). Oscillations within the gamma frequency range are believed to contribute to sensory integration and the active maintenance of WM representations (Fries, Reynolds, Rorie, & Desimone, 2001; Jensen, Kaiser, & Lachaux, 2007; Roux & Uhlhaas, 2014). Finally, upper alpha oscillations are believed to reflect the expression of functional inhibition over neural regions in response to changing task-demands (Klimesch, Sauseng, & Hanslmayr, 2007). Increasing WM load has repeatedly been shown to elicit more pronounced modulation of theta, upper alpha, and gamma power during the maintenance phase of WM processing (Axmacher et al., 2007; Howard, 2003; Jensen & Tesche, 2002; Jensen et al., 2002; van Vugt, Schulze-Bonhage, Litt, Brandt, & Kahana, 2010), and a greater magnitude of theta and gamma power during encoding has been shown to predict higher accuracy of subsequent recall (Sederberg, Kahana, Howard, Donner, & Madsen, 2003; White et al., 2013), thereby indicating a crucial role for neural oscillations in supporting efficient WM processing.

The pattern of oscillatory activity associated with WM processing in MDD, however, is poorly characterised. For example, studies examining WM maintenance have reported that MDD is associated with increased (Segrave et al., 2010) or decreased (Bailey, Segrave, Hoy, Maller, & Fitzgerald, 2014) upper alpha power when compared to healthy controls, whereas others have failed to find evidence of differences in upper alpha power (Bailey et al., 2018). These inconsistent findings are likely contributed to by small sample sizes as well as heterogeneity of WM task characteristics, participant demographics, and depression severity between studies. Previous research has also largely failed to account for the confounding influence that differences in WM performance may exert on oscillatory activity (Palva, Monto, Kulashekhar, & Palva, 2010), as studies have typically compared the oscillatory activity associated with WM impairment in MDD to that recorded from healthy controls who display intact WM performance (e.g. Bailey et al., 2014; Segrave et al., 2010). Given this, it is possible that previous evidence of aberrant WM-related oscillatory activity in MDD was the result of differences in WM performance between the MDD and control groups, rather than reflecting altered neural processing related to the pathophysiology of MDD. Previous research in MDD has largely focussed on upper alpha power during WM maintenance, and there is limited information regarding potential alterations in theta or gamma activity. While recent research by Bailey et al. (2018) provided preliminary evidence that individuals with MDD display less theta power than healthy controls during WM maintenance, these reductions in theta power were only observed in a subset of individuals with MDD who failed to respond to subsequent treatment with repetitive transcranial magnetic stimulation (rTMS). Finally, despite behavioural evidence that MDD is associated with inefficient encoding of information (Bearden et al., 2006; Rock, Roiser, Riedel, & Blackwell, 2014), there is a paucity of research examining whether MDD involves alterations in oscillatory activity during WM encoding.

The current study firstly aimed to improve characterisation of oscillatory activity associated with WM encoding and maintenance in MDD by examining oscillatory activity during a verbal WM task in a large cohort of individuals with MDD and age- and gender-matched healthy controls. To control for the confounding influence of WM performance on oscillatory activity, the current study closely balanced the MDD and control groups on baseline WM ability. It was hypothesised that when compared to healthy controls balanced on age, gender, and WM ability, participants with MDD would display less FMT power during WM encoding and maintenance, as well as significant differences in gamma and upper alpha power over occipital regions during WM encoding and maintenance. Given inconsistencies in past research examining upper alpha activity in MDD (Bailey et al., 2018; Bailey, Segrave, Hoy, Maller, & Fitzgerald, 2014; Segrave et al., 2010), and the paucity of relevant research concerning WM-related gamma activity in MDD, we did not hypothesise the direction of groups differences in these frequency bands.

2. Methods

2.1. Participants

Forty-nine individuals with MDD and 51 healthy controls were recruited into the study. All participants were aged between 18 and 65 years, had normal or corrected-to-normal vision, were right-handed, and reported no history of brain injury, neurological illness, mania or hypomania, post-traumatic stress disorder, diagnosed learning difficulty, or attention-deficit hyperactivity disorder. Participants who reported a formal diagnosis of borderline personality disorder were also excluded, given evidence of WM impairments in this condition (LeGris & van Reekum, 2006; Stevens, Burkhardt, Hautzinger, Schwarz, & Unckel, 2004). Participants in the MDD group met criteria for a current DSM-IV defined Major Depressive Episode. While no minimum level of depression severity was required for inclusion into the study, baseline scores for the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960) ranged between 14 and 28, which is indicative of moderate to severe depression. Twenty-five participants in the MDD group were taking antidepressant medication at the time of testing (Table 1). None had changed the type or dose of antidepressant medication in four-weeks prior to the study, and none were taking benzodiazepines, antipsychotics, or mood stabilisers. Participants in the control group were excluded if they met criteria for current or prior DSM-IV psychiatric illness or were currently taking any psychoactive medication. No participants had a history of substance abuse or dependence in the preceding year and none reported recreational drug use within one month prior to testing.

Data from 13 participants were excluded due to: excessive noise in EEG data (5 healthy controls, 1 MDD), equipment fault (3 healthy controls), and performing at near-chance level on the Sternberg WM task (represented by an accuracy score of ≤59.49%) (2 MDD, 2 healthy controls). Consistent with previous WM research (e.g. Reed, Gallagher, Sullivan, Callicott, & Green, 2017), we defined near-chance level performance as any accuracy score falling within one standard deviation from chance (i.e. 50% ± 9.49%). Thus, the final data set comprised 46 participants with MDD (27 female, mean age ± SD = 28.11 ± 9.54

Table 1
Participant demographic and psychological characteristics (mean ± SD).

	Control	MDD	t
Gender (F/M)	29/12	27/19	
Age (years)	28.76 ± 10.32	28.11 ± 9.54	0.30
Formal education (years)	14.58 ± 1.67	13.95 ± 1.66	1.83
WAIS-IV WMI	110.17 ± 11.62	107.57 ± 11.89	1.03
STAI – State	28.76 ± 7.09	41.78 ± 10.75	−6.58**
STAI – Trait	34.85 ± 7.52	55.72 ± 10.66	−10.43**
HAM-D		17.13 ± 2.51	
QIDS		13.80 ± 2.30	
Years since diagnosis		9.59 ± 8.38	
Medications			
None		20	
SSRI		15	
SNRI		5	
Tricyclic Antidepressant		2	
Atypical Antidepressant		4	
n	41	46	

Degrees of freedom = 85 for all comparisons. *$p < .05$; **$p < .01$.
Note: WAIS-IV WMI = Wechsler Adult Intelligence Scale, Fourth Edition – Working Memory Index; STAI = State-Trait Anxiety Inventory; HAM-D = Hamilton Depression Rating Scale; QIDS = Quick Inventory of Depressive Symptomology; SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor.

years) and 41 healthy controls (29 female, mean age ± SD = 28.76 ± 10.32 years). Control and MDD groups were closely balanced on age, years of formal education, and WM ability at baseline, as confirmed by independent samples *t*-tests (all $p > .10$) (see Table 1 for demographic and clinical characteristics of the participants).

Participants provided written confirmation of informed consent prior to engaging in the study. The study received approval from the Alfred Human Research Ethics Committee and the Monash University Human Ethics Committee.

2.2. Procedure

Data was collected during a single experimental session conducted at the Monash Alfred Psychiatry Research Centre, Melbourne. All participants underwent the same experimental protocol which began with a clinical interview to collect demographic and psychological data. The Mini International Neuropsychiatric Interview for the DSM-IV (Hergueta, Baker, & Dunbar, 1998) was used to either confirm (MDD participants) or exclude (control participants) the presence of a current Major Depressive Episode and to screen for additional psychopathology. Depression severity was assessed using the Hamilton Depression Rating Scale, 17-item (HAM-D_{17}) (Hamilton, 1960) and the Quick Inventory of Depressive Symptomology – Clinician Rated, 16-item (QIDS-C) (Rush et al., 2003; Trivedi et al., 2004). Right-handed preference was determined using the Edinburgh Handedness Inventory (Oldfield, 1971). State and trait anxiety levels were assessed using the State-Trait Anxiety Inventory (STAI) (Spielberger, Gorsuch, Lushene, & Vagg, 2010). Baseline WM ability was assessed using the Working Memory Index from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (Wechsler, 2008). All clinical interviews and cognitive tasks were administered by a single researcher trained in standardised administration. Following the clinical interview, all participants completed the Sternberg verbal WM task with concurrent EEG recording (described below).

2.3. WM task and stimuli

WM was assessed using a Sternberg verbal WM task presented with Neuroscan Stim2 software (Compumedics, Melbourne, Australia). The Sternberg WM task was chosen as it temporally separates the encoding, maintenance, and retrieval of information and thereby allows examination of neural activity associated with each phase of WM processing. The task involves presentation of a memory set containing eight letters, followed by a maintenance period in which the letters are removed. Participants are then presented with a probe letter and indicate using a button press whether the probe was present or absent in the memory set (see Fig. 1 for Sternberg WM task design and stimuli timing). Responses made outside of the 2000 ms probe window were considered incorrect. Memory stimuli consisted of a selection of fifteen consonants (B, C, D, F, H, J, K, L, N, R, S, T, Y, W, Z) pseudo-randomised so that no letter appeared in the same location consecutively. Probe letters were present in the memory set at 50% probability and no letter was presented as the probe twice in succession. The trial sequence was the same for all participants. Participants completed a total of 52 trials presented in two blocks with a short break between blocks. Prior to beginning the task, participants completed several practice trials and were encouraged to repeat this sequence until they felt comfortable with the task. The instructions for the task were standardised across all participants, and a researcher was present throughout task completion to monitor participant engagement and ensure participant's attention was focused on the task. To control for the potentially confounding effect that closing the eyes can have on alpha power (e.g. Barry, Clarke, Johnstone, Magee, & Rushby, 2007), all participants were instructed to keep their eyes open during the maintenance period of the task. Accuracy and response times were recorded for each participant.

2.4. Electrophysiological recording and pre-processing

EEG recording was conducted in a darkened, electrically-shielded, and sound-attenuated room. Thirty-four single Ag/AgCl scalp electrodes recorded EEG activity to Neuroscan Acquire software using a Synamps 2 amplifier (Compumedics, Melbourne Australia). Recordings were obtained from electrodes positioned according to the 10–20 system (AF3, AF4, F5, F3, F1, FZ, F2, F4, F6, FC5, FC1, FCZ, FC2, FC6, C3, C1, CZ, C2, C4, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO3, POZ, PO4, O1, OZ, O2). Four facial electrodes were positioned adjacent to the left and right outer canthus of each eye and above and below the left orbit to measure eye movement. Electrodes were grounded to AFz and referenced online to an electrode between Cz and CPz. Impedances were kept below 5 kΩ prior to recording. EEG was sampled at 1000 Hz with a bandpass of 0.1–100 Hz.

Data was analysed offline in MATLAB (The Mathworks, Natick, MA) using EEGLAB for pre-processing (sccn.ucsd.edu/eeglab) (Delorme & Makeig, 2004) and fieldtrip for frequency analysis (http://www.ru.nl/donders/fieldtrip) (Oostenveld, Fries, Maris, & Schoffelen, 2011). A second-order Butterworth filter was applied to the data with a bandpass of 1–80 Hz and a band-stop filter of 45–55 Hz (12 dB/octave roll-off). Data was then epoched into 11,500 ms segments extending from the onset of the fixation cross to the middle of the blank screen for each trial. Only correct trials were included in further analysis. Single electrodes containing artifacts in more than 5% of the trials were rejected (indicated by variations in voltage larger than 250μv, kurtosis values > 5, or values exceeding -100 or 30 dB in the 25–45 Hz range). Epochs containing artifacts were also rejected (indicated by kurtosis values > 5 for all electrodes, and more than −100 to 30 dB in the 25–45 Hz range). Artifact rejections were then manually checked by a trained researcher. Fast independent component analysis (FastICA) using 'symmetric approach' and the 'tanh' contrast function was then used to manually select and remove remaining artifacts related to eye movements and muscle activity. The criteria used for visual identification of artifacts was based on previous research (e.g. Chaumon, Bishop, & Busch, 2015; Delorme & Makeig, 2004), and is consistent with previous studies examining WM-related oscillatory activity in healthy and depressed individuals (Bailey et al., 2018). Missing

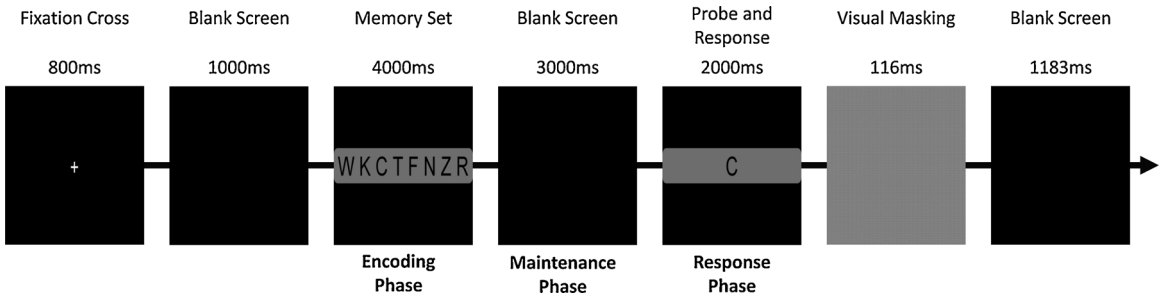

Fig. 1. Sternberg WM task stimuli, timing, and corresponding WM phase. Memory set contained eight letters which were presented simultaneously.

channels were interpolated using the 'spherical' function and recordings were re-referenced offline to an average reference. Following cleaning of EEG data and removal of epochs with excessive artifacts, all remaining participants had a minimum of 20 noise-free epochs available for ERS/ERD% analysis. No significant differences were detected between groups in the number of epochs accepted in the final analysis ($p > .05$).

2.5. Spectral analysis

All valid epochs were submitted to a Morlet Wavelet Transform (3.5 oscillation cycles with steps of 1 Hz) to calculate neural oscillatory power within the theta (5–8 Hz), upper alpha (10–12.5 Hz), and gamma (30–45 Hz) frequency ranges. Frequency ranges for each band were chosen to correspond with previous research examining oscillatory activity during the Sternberg WM task (e.g. Bailey et al., 2018, 2014; Roberts, Hsieh, & Ranganath, 2013; Segrave et al., 2010). Additional comparisons of oscillatory activity within adjacent frequency ranges were conducted upon reviewer request, including the lower alpha (8–10 Hz), full alpha spectrum (8–13 Hz), and beta range (14–28 Hz). Results from these analyses are presented in supplementary materials. Modulation of oscillatory power was calculated as event-related synchronisation/desynchronisation (ERS/ERD%) using the formula: (Active - Reference)/Reference) x 100). This formula provides positive values when oscillatory power increases in the active test period compared to the reference period (i.e. neural synchronisation) and negative values when power decreases in the active test period compared to the reference period (i.e. neural desynchronisation). The reference period used for baseline correction was defined as the middle 600 ms of the blank screen between the fixation cross and memory set, during which time no task-related cognitive processing was required.

For all frequency bands, the active period used for calculating ERS/ERD% during WM maintenance was defined as the 2900 ms window extending from 100 ms after memory set offset until the onset of the letter probe. This period was selected based on research showing sustained synchronisation of alpha, gamma, and theta activity throughout the entire maintenance phase (Jensen & Tesche, 2002; Jensen et al., 2002; Tallon-Baudry, Bertrand, Peronnet, & Pernier, 1998). Upper alpha and gamma ERS/ERD% for the encoding period was calculated using 3500 ms active period beginning 200 ms after the presentation of the memory set and ending 300 ms before memory set offset. This period was chosen as parieto-occipital regions typically display sustained modulations of upper alpha and gamma activity during the encoding phase of WM processing (Tallon-Baudry et al., 1998). Theta ERS/ERD% during the encoding period was calculated using a shorter active period which captured the 600 ms period immediately following the onset of the memory set. This active period was chosen based on previous research demonstrating large increases in FMT power occurring in the 600 ms period immediately following the presentation of WM stimuli (Klimesch et al., 2001; White et al., 2013). This early peak in FMT power during encoding of information is thought to reflect increased allocation of attentional resources towards sensory processing (Klimesch et al., 2001; White et al., 2013), which is supported by evidence that a greater magnitude of FMT power during early periods of WM encoding predicts higher accuracy of subsequent recall (White et al., 2013). ERS/ERD% for each frequency band was first calculated across the entire encoding and maintenance periods, then ERS/ERD% data from the active period was extracted and averaged over trials for each participant. This analytical method using Morlet Wavelet Transformation provides sufficient data on each side of the active period to avoid edge effects when estimating low-frequency oscillations such as theta (Sederberg et al., 2003).

2.6. Statistical analysis

2.6.1. Sample size estimation

The minimum required sample size was calculated using GPower software (Erdfelder, Faul, & Buchner, 1996). Previous research showing group differences in upper alpha activity between healthy and MDD groups reported an average effect size of $f = 0.36$ (Bailey et al., 2014; Segrave et al., 2010), however, given the absence of relevant evidence for estimating the effect size of potential group differences in theta or gamma activity, a more conservative effect size of $f = 0.30$ was used to estimate the minimum required sample size. Using an effect size of $f = 0.30$, a minimum total sample size of 76 would be required to detect an effect of this magnitude with 95% power and $\alpha = 0.05$ (GPower: Erdfelder et al., 1996).

2.6.2. Demographic and behavioural analyses

Independent samples *t*-tests were performed to confirm balancing of MDD and control groups for age, years of education, and WM ability. Behavioural data was analysed using independent samples *t*-test to compare accuracy and response time on the Sternberg WM task.

2.6.3. EEG analyses

Upper alpha ERS/ERD% was calculated for channels O1 and O2 as topographical analysis revealed that modulation of upper alpha activity was maximal at these electrodes (Fig. 2), and previous research has observed that individuals with MDD and healthy controls differ in maintenance period upper alpha power in these regions (Bailey et al., 2014; Segrave et al., 2010). Gamma ERS/ERD% was calculated for O1 and O2 given previous research showing that gamma synchronisation is maximal over occipital regions during the maintenance phase of WM tasks featuring visual stimuli (Jokisch & Jensen, 2007; Tallon-Baudry et al., 1998), and because participants in the current study demonstrated prominent modulation of gamma activity over these electrodes (Fig. 3). Theta ERS/ERD% was calculated for Fz and FCz based on topographical analysis of the current data (Fig. 4), as well as previous research showing that FMT power is most prominent at these electrodes (Gevins, Smith, McEvoy, & Yu, 1997; Onton, Delorme, & Makeig, 2005). To reduce the number of multiple comparisons, ERS/ERD% for each frequency band was averaged across the two electrodes selected for analysis. Shapiro-Wilks test and visual inspection of P-P plots revealed that residuals for upper alpha ERS/ERD% data were non-normally distributed; hence a logarithmic transformation was applied to normalise data. As logarithmic transformation cannot be performed on negative values, a value of 100 was added to data for all frequency bands. This transformation preserves the essential relationships between data points. ERS/ERD% data for theta and gamma activity was normally distributed hence no transformation was applied to these frequency bands.

To ensure that potential group differences in ERS/ERD% during WM encoding and maintenance were not simply driven by differences in oscillatory activity during the reference period used for baseline correction, independent-samples *t*-tests analyses were conducted comparing the control and MDD groups in absolute theta, upper alpha, and gamma power during the reference period (i.e. the middle 600 ms of the blank screen between the fixation cross and memory set). These comparisons revealed that the healthy and MDD groups did not significantly differ in absolute theta ($p = .663$), upper alpha ($p = .181$), or gamma power ($p = .190$) during the reference period (degrees of freedom = 85 for all comparisons).

ERS/ERD% for each frequency band was analysed using a two-way mixed ANOVA with group (control and MDD) as the between subjects factor and WM phase (encoding and maintenance) as the within-subjects factor. Gender was included as a covariate in these analyses, given evidence that males and females display significant differences in oscillatory activity at rest and during task performance (Güntekin & Başar, 2007; Wada, Takizawa, Zheng-Yan, & Yamaguchi, 1994).

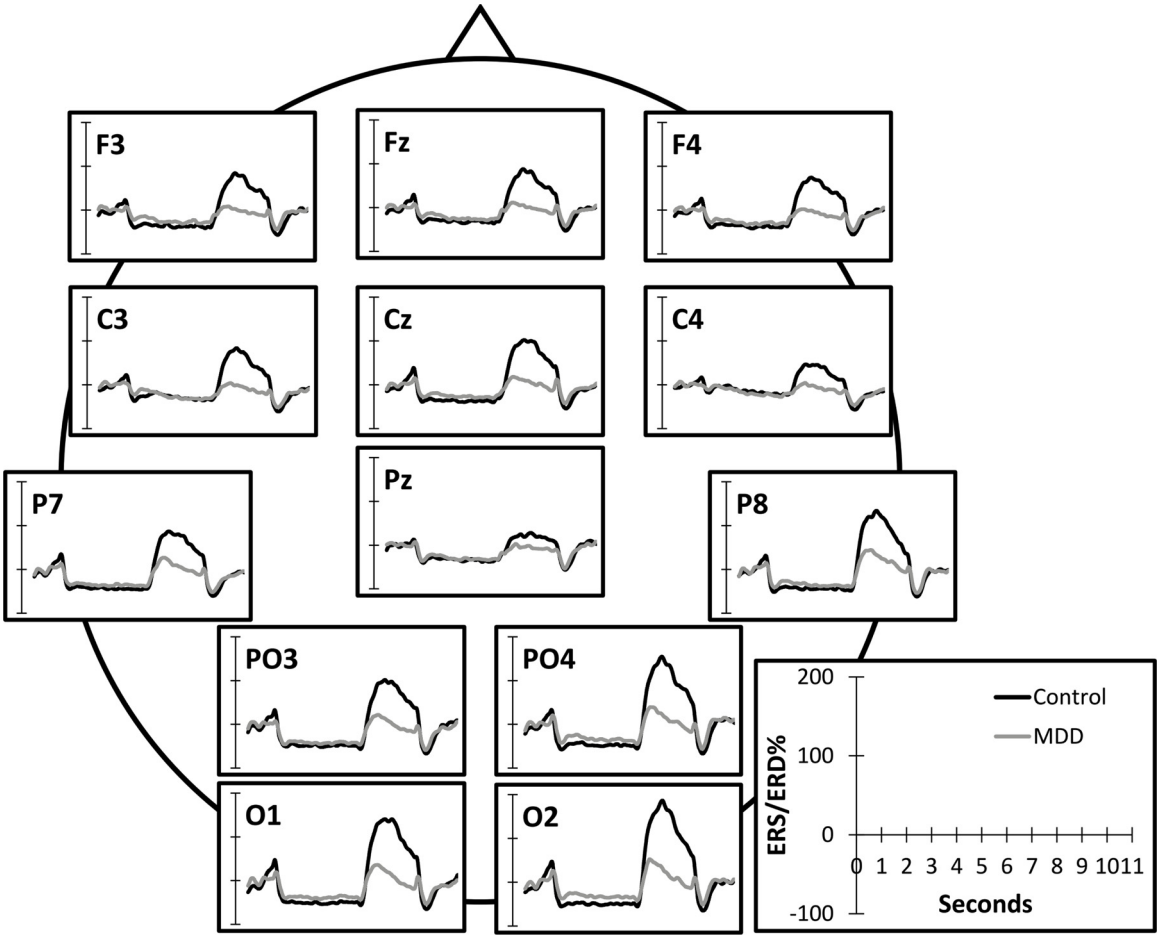

Fig. 2. Average upper alpha ERS/ERD% for each group in selected electrodes during the Sternberg WM task.

Significant interaction effects were further examined in post-hoc independent samples *t*-tests with group as the between-subjects variable. To confirm that potential group differences were not simply due to the psychoactive effects of antidepressant medication use, two-way mixed model ANOVAs were repeated separately for the MDD group using medication status (medicated and unmedicated) as the between subjects factor and WM phase (encoding and maintenance) as the within-subjects factor.

To explore potential relationships between WM task performance and oscillatory activity, Spearman's correlations were conducted separately for each group between WM task accuracy and ERS/ERD% variables. To explore potential relationships between depression severity and oscillatory activity, Spearman's correlations were conducted for the MDD group between HAM-D score and ERS/ERD% variables. Spearman's correlation was chosen over parametric correlation techniques because it is robust to violations of linearity.

3. Results

3.1. Sternberg WM task behavioural data

Healthy controls and participants with MDD did not significantly differ in WM task accuracy (t(85) = 0.334, p = .740), response time (t(85) = 0.69, p = .491), or the number of trials considered incorrect due to exceeding the time limit (t(85) = 1.72, p = .089) (Table 2). For the MDD group, higher depression severity was associated with lower WM task accuracy (r = −0.306, p = .019).

3.2. Upper alpha activity

Analysis of upper alpha activity revealed a significant WM phase by group interaction (F(1,84) = 37.92, p < .001, η_p^2 = 0.31). Post-hoc analysis of this interaction revealed that participants with MDD displayed more upper alpha activity than healthy controls during the encoding period (t(74.41) = 2.99, p = .004, d = 0.65), whereas participants with MDD displayed less upper alpha activity than healthy controls during the maintenance period, (t(54.21) = 5.68, p < .001, d = 1.24) (Table 3). A significant main effect was observed for WM phase (F(1,84) = 18.34, p < .001, η_p^2 = 0.18), with pairwise comparisons revealing that upper alpha activity was higher during the maintenance period (2.12 ± 0.02) than the encoding period (1.71 ± 0.02) (Fig. 5). No main effect was observed for group (F(1,84) = 0.97, p = .33, η_p^2 = 0.01). Gender was not a significant covariate for any comparisons of upper alpha activity (p = .655).

Higher depression severity in the MDD group was associated with less upper alpha activity during the maintenance period (r = −0.311, p = .036), whereas depression severity was not related to upper alpha activity during the encoding period (r = −0.063, p = .675). For MDD, WM task accuracy was not related to upper alpha activity during the encoding period (r = −0.144, p = .452), or maintenance period (r = 0.152, p = .313). For controls, WM task accuracy was not related to upper alpha activity during the encoding period (r = 0.030, p = .854), or maintenance period (r = 0.091, p = .572).

3.3. Gamma activity

Analyses of gamma activity revealed a significant WM phase by

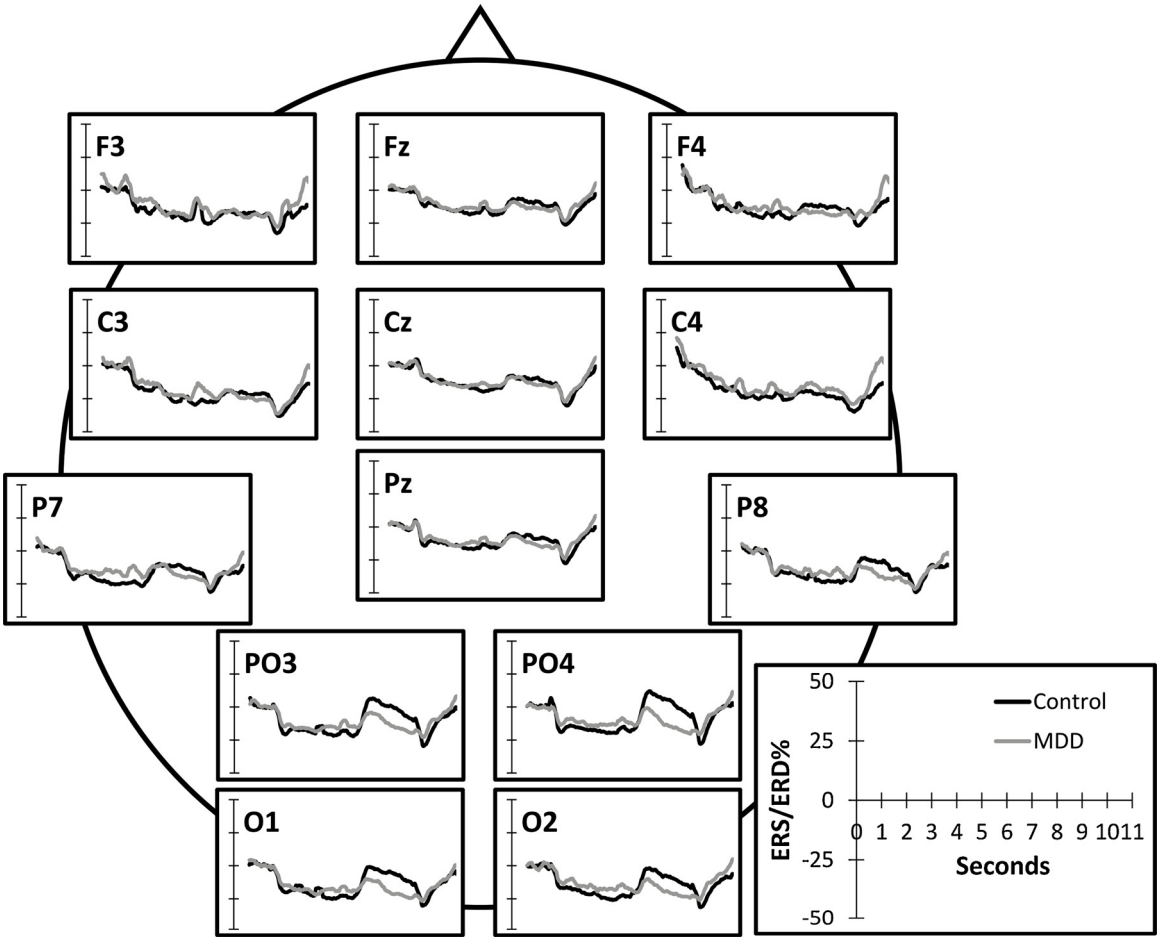

Fig. 3. Average gamma ERS/ERD% for each group in selected electrodes during the Sternberg WM task.

group interaction ($F(1,84) = 13.61$, $p < .001$, $\eta_p^2 = 0.14$). Post-hoc analysis of the interaction revealed that participants with MDD displayed less gamma activity than healthy controls during the maintenance period ($t(85) = 2.45$, $p = .017$, $d = 0.52$), whereas no group differences were observed in gamma activity during the encoding period ($t(85) = 1.32$, $p = .190$, $d = 0.28$) (Table 4). No significant main effects were observed for WM phase ($F(1,84) = 0.53$, $p = .467$, $\eta_p^2 = 0.01$), or group ($F(1,84) = 0.84$, $p = .363$, $\eta_p^2 = 0.01$) (Fig. 6). Gender was not a significant covariate for any comparisons of gamma activity ($p = .987$).

Higher depression severity in the MDD group was associated with less gamma activity during the maintenance period ($r = -0.305$, $p = .039$), whereas depression severity was not related to gamma activity during the encoding period ($r = -0.179$, $p = .234$). For MDD, WM task accuracy was not related to gamma activity during the encoding period ($r = -0.161$, $p = .284$), or maintenance period ($r = 0.100$, $p = .510$). For controls, WM task accuracy was not related to gamma activity during the encoding period ($r = -0.110$, $p = .495$), or maintenance period ($r = -0.172$, $p = .282$).

3.4. Theta activity

Analysis of FMT activity did not reveal a significant WM phase by group interaction ($F(1,84) = 0.56$, $p = .457$, $\eta_p^2 = 0.007$) (Table 5). However, a significant main effect was observed for group ($F(1,84) = 6.67$, $p = .012$, $\eta_p^2 = 0.074$), with pairwise comparisons revealing that participants with MDD (121.38 ± 3.98) displayed significantly less FMT activity across the encoding and maintenance periods when compared to healthy controls (136.77 ± 4.21). A significant main effect was also observed for WM phase ($F(1,84) = 6.53$, $p = .012$, $\eta_p^2 = 0.072$), with pairwise comparisons revealing that FMT activity was higher during the encoding period (145.79 ± 4.98) than during the maintenance period (112.37 ± 2.79) (Fig. 7). Gender was not a significant covariate for any comparisons of theta activity ($p = .762$).

Depression severity in the MDD group was not related to FMT activity during the encoding period ($r = 0.088$, $p = .561$), or maintenance period ($r = -0.101$, $p = .503$). For MDD, WM task accuracy was not related to FMT activity during the encoding period ($r = -0.039$, $p = .796$), or maintenance period ($r = 0.057$, $p = .707$). For controls, WM task accuracy was not related to FMT activity during the encoding period ($r = -0.025$, $p = .875$) or maintenance period ($r = 0.100$, $p = .534$).

3.5. Influence of antidepressant medications on oscillatory activity

To confirm that alterations in WM-related oscillatory activity were not simply due to effects of antidepressant medications, further analyses were conducted to compare upper alpha, gamma, and theta ERS/ERD% between medicated ($n = 26$) and unmedicated ($n = 20$) participants with MDD. There was no effect of antidepressant medication use on WM task accuracy ($p = .885$) or response time ($p = .919$), nor were there any effects on oscillatory activity during the encoding or maintenance phases (Table 6).

4. Discussion

We examined oscillatory activity during WM encoding and maintenance in a large sample of healthy and depressed participants who

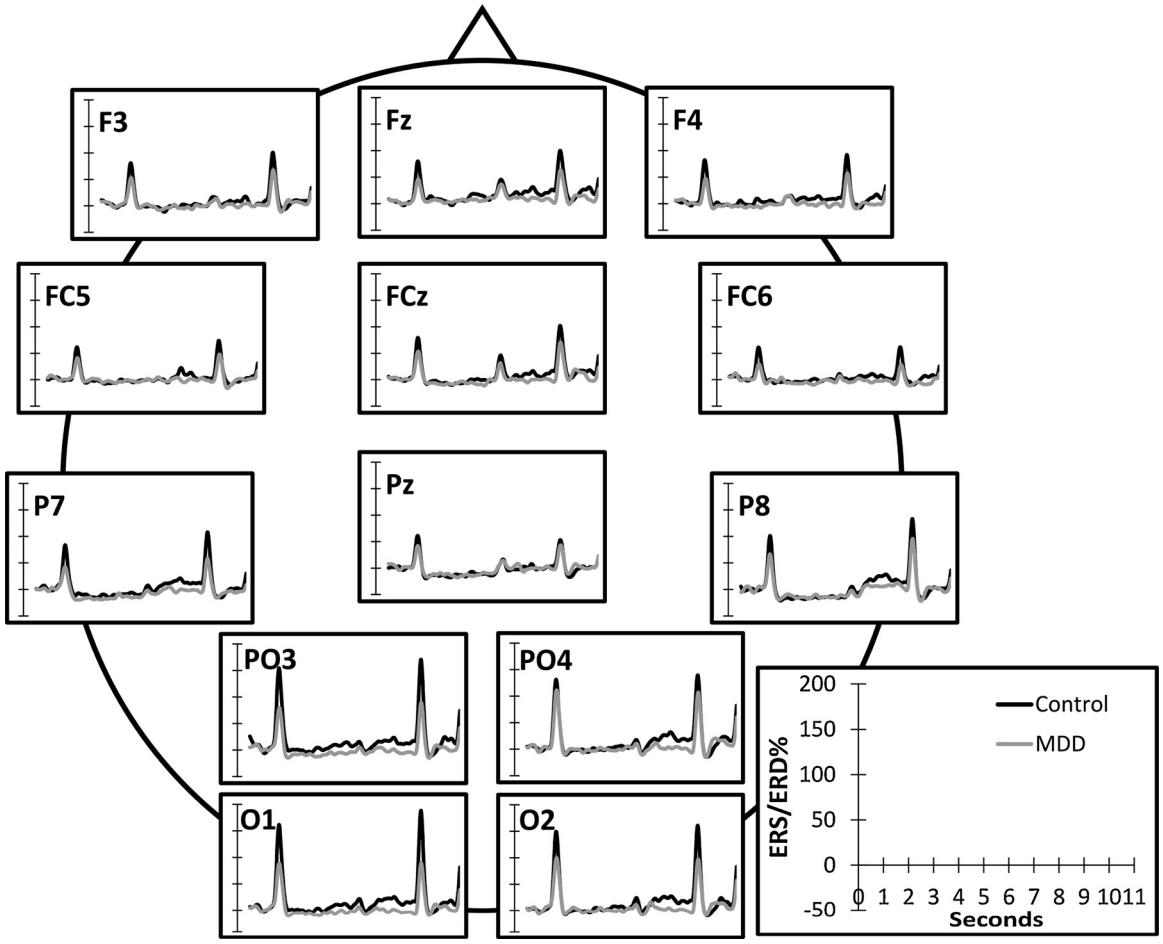

Fig. 4. Average theta ERS/ERD% for each group in selected electrodes during the Sternberg WM task.

Table 2
Accuracy, response time, and number of missed trials for the Sternberg WM task (mean ± SD).

	Control	MDD
Accuracy (%)	78.47 ± 8.58	77.88 ± 7.78
Response time (ms)	1175.88 ± 164.50	1145.55 ± 154.90
Missed trials %	8.16 ± 6.77	5.98 ± 5.02

Note: Accuracy % = Proportion of trials answered correctly. Missed trials = Percentage of trials in which participants did not provide a response within the 2000 ms response period.

Table 3
Upper alpha ERS/ERD% during the encoding and maintenance periods of the Sternberg task, averaged across electrodes O1 and O2 (mean ± SD).

	Encoding Period		Maintenance Period	
	Controls	MDD	Controls	MDD
Upper alpha ERS/ERD%	1.63 ± 0.25	1.78 ± 0.19	2.22 ± 0.21	2.01 ± 0.10

Data was log transformed. Toenable log transform, 100 was added to every value so that all values were positive.

were closely balanced on age, gender, and WM ability. During encoding of WM stimuli, participants with MDD displayed significantly less FMT power and significantly more upper alpha power over occipital regions. During WM maintenance, participants with MDD displayed significantly less FMT power as well as significantly less upper alpha and gamma power over occipital regions. For participants with MDD, higher depression severity was significantly associated with greater reductions in upper alpha and gamma power during WM maintenance. Importantly, these findings were observed despite the control and MDD groups being closely balanced on demographic variables and displaying comparable performance on the WM task. Further, alterations in WM-related oscillatory activity were present in both medicated and unmedicated individuals with MDD, indicating that these findings are not attributable to the effects of antidepressant medications. These findings extend upon previous research and demonstrate that the neural processes associated with WM processing are altered in MDD even when individuals do not display behavioural evidence of WM impairments. Moreover, to our knowledge, these data present the first evidence that WM encoding in MDD is associated with alterations in oscillatory activity linked to efficient encoding of information.

4.1. Upper alpha activity during WM encoding and maintenance

When compared to healthy controls, participants with MDD displayed significantly less upper alpha power over occipital regions during the maintenance phase of WM processing (see Fig. 5). Synchronisation of upper alpha power in parieto-occipital regions is believed to facilitate WM maintenance by inhibiting posterior cortical regions associated with sensory processing (Jensen et al., 2002; Klimesch et al., 2007). Thus, our findings indicate that participants with MDD display less inhibition of posterior cortical regions during the WM maintenance phase. Importantly, however, participants with MDD achieved intact WM performance despite displaying altered patterns of upper alpha power during WM encoding and maintenance, indicating

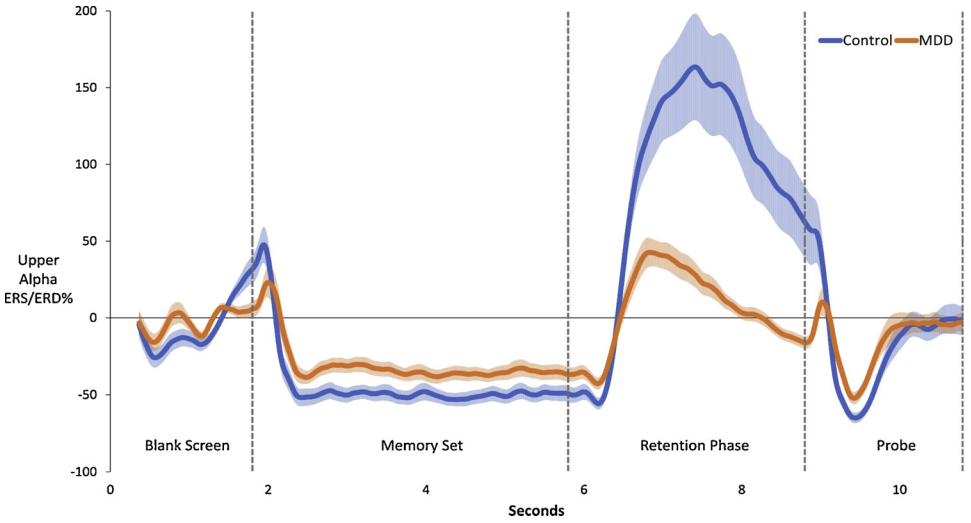

Fig. 5. Upper alpha ERS/ERD% during the Sternberg task for control and MDD groups. Data was pooled across O1 and O2 and averaged over correct trials for each participant. The shaded area around the line indicates the standard error the mean. Note that positive values reflect ERS and negative values reflect ERD.

Table 4
Gamma ERS/ERD% during the encoding and maintenance periods of the Sternberg task, averaged across electrodes O1 and O2 (mean ± SD).

	Encoding Period		Maintenance Period	
	Controls	MDD	Controls	MDD
Gamma ERS/ERD %	79.70 ± 14.40	83.72 ± 14.02	91.40 ± 22.48	81.79 ± 13.50

that these changes in oscillatory dynamics did not impair performance on the WM task used in the current study.

Our finding that individuals with MDD display less upper alpha power than healthy controls during WM maintenance is consistent with previous research by Bailey et al. (2014), however, these results directly contrast with the results of Segrave et al. (2010) who found that individuals with MDD displayed greater parieto-occipital upper alpha power than controls during WM maintenance. There are several methodological differences between the studies which may contribute to these contrasting findings. Firstly, Segrave et al. tested only females whereas Bailey et al. and the current study included both males and females. However, it appears unlikely that gender differences fully explain these contrasting findings, as including gender as a covariate did not significantly alter the results of analysis for any group comparisons of oscillatory activity. Secondly, Segrave et al. examined upper alpha using an individualised alpha frequency for each participant, whereas analyses by Bailey et al. and the current study used a fixed frequency band (10–12.5 Hz). However, previous research suggests that both methods of analysis produce similar values for alpha power (Segrave et al., 2011), hence it is unlikely that this methodological difference would be sufficient to produce conflicting findings between studies. Finally, the current study examined upper alpha activity associated with intact WM performance in healthy and depressed individuals, whereas Segrave et al. and Bailey et al. compared intact WM performance in healthy controls to impaired WM performance in MDD. Research in healthy individuals has shown that high and low WM performers display significant differences in oscillatory power during WM encoding and maintenance (Pahor & Jaušovec, 2017), hence it is possible that variation in WM performance between the MDD and control groups in Segrave et al. and Bailey et al. may have influenced group differences in upper alpha power. In contrast, the control and MDD groups in the current study were closely balanced on WM ability at

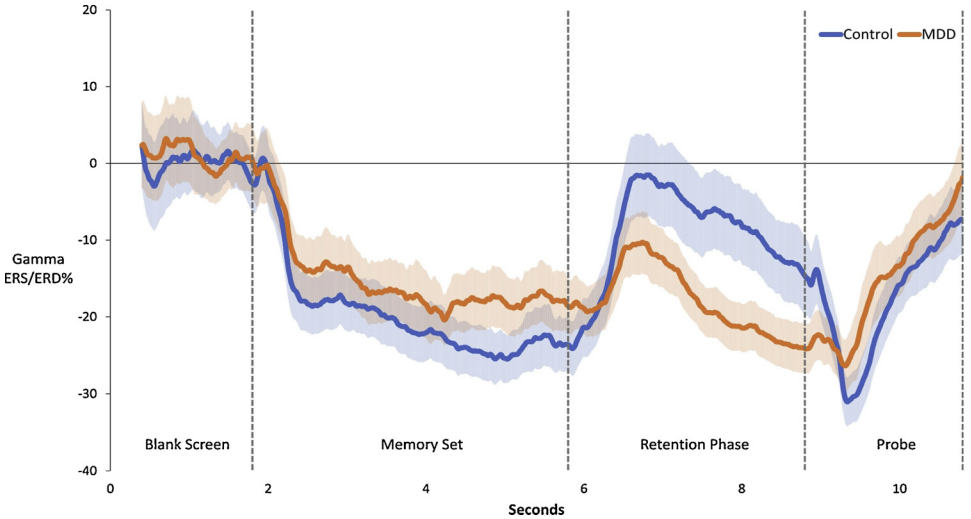

Fig. 6. Gamma ERS/ERD% during the Sternberg task for control and MDD groups. Data was pooled across O1 and O2 and averaged over correct trials for each participant. The shaded area around the line indicates the standard error the mean. Note that positive values reflect ERS and negative values reflect ERD.

Table 5
Theta ERS/ERD% during the encoding and maintenance periods of the Sternberg task, averaged across electrodes Fz and FCz (mean ± SD).

	Encoding Period		Maintenance Period	
	Controls	MDD	Controls	MDD
Theta ERS/ERD%	155.81 ± 49.39	135.76 ± 43.28	117.72 ± 32.09	107.01 ± 18.92

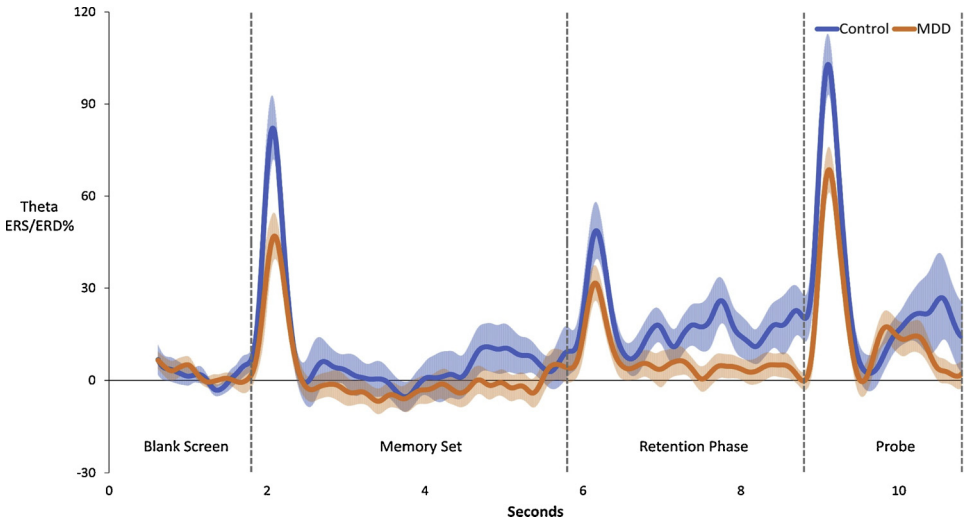

Fig. 7. Theta ERS/ERD% during the Sternberg task for control and MDD groups. Data was pooled across Fz and FCz and averaged over correct trials for each participant. The shaded area around the line indicates the standard error the mean. Note that positive values reflect ERS and negative values reflect ERD.

baseline and displayed comparable performance on the Sternberg WM task, thereby increasing confidence that reductions in upper alpha activity during WM maintenance are related to the pathophysiology of MDD rather than being driven by differences in WM performance. These findings highlight the importance of future research closely balancing participant groups on demographic and cognitive characteristics which may influence oscillatory activity during WM processing.

To our knowledge, this study provides the first evidence that individuals with MDD display attenuated desynchronisation of upper alpha activity during WM encoding. Desynchronisation of parieto-occipital alpha power upon the presentation of a visual stimulus is among the most stereotypical and robust patterns of alpha modulation observed in healthy adult humans and is thought to reflect decreased functional inhibition of posterior cortical regions associated with sensory processing and encoding of visual stimuli (Doppelmayr, Klimesch, Hödlmoser, Sauseng, & Gruber, 2005; Hanslmayr, Staudigl, & Fellner, 2012; Jensen & Mazaheri, 2010). Greater desynchronisation of upper alpha activity during stimulus presentation has been shown to predict increased accuracy of encoding and subsequent recall in healthy individuals (Jaušovec & Jaušovec, 2004; Klimesch, Doppelmayr, Pachinger, & Ripper, 1997; Mölle, Marshall, Fehm, & Born, 2002). Given this functional role, diminished desynchronisation of upper alpha power during encoding indicates that WM processing in MDD involves alterations in neural processes supporting sensory encoding of information. These findings are consistent with behavioural evidence of inefficient WM encoding in MDD (Bearden et al., 2006; Rock et al., 2014), as well as EEG studies showing that individuals with MDD display altered neural responses in occipital regions during the initial encoding of WM information (Coullaut-Valera et al., 2007).

4.2. Gamma activity during WM maintenance

Individuals with MDD displayed less gamma power in occipital regions during the maintenance phase of WM processing (see Fig. 6). Gamma oscillations are believed to support the active maintenance of WM representations in the absence of external stimuli (Fries et al., 2001; Jensen et al., 2007; Roux & Uhlhaas, 2014), and synchronisation of gamma activity has been shown to predict individual WM capacity (Palva et al., 2010; Palva, Kulashekhar, Hamalainen, & Palva, 2011). While oscillations within the gamma range can also be elicited by eye movements and muscle activity across the scalp (Hipp & Siegel, 2013; Jerbi et al., 2009), intracranial EEG research has shown that gamma power increases parametrically alongside WM load (Axmacher et al., 2007; van Vugt et al., 2010), thereby indicating an important role for gamma activity in supporting the maintenance of WM representations. The current findings would suggest that the neural processes which support WM maintenance are altered in MDD as compared to healthy

Table 6
Upper alpha, gamma, and theta ERS/ERD% during the Sternberg WM task for medicated and unmedicated participants with MDD (mean ± SD).

	Encoding Period			Maintenance Period		
	Medicated	Unmedicated	*p*	Medicated	Unmedicated	*p*
Upper Alpha ERS/ERD%	1.80 ± 0.21	1.76 ± 0.18	.527	2.02 ± 0.10	2.01 ± 0.09	.857
Gamma ERS/ERD%	83.94 ± 15.72	83.44 ± 11.85	.908	80.85 ± 15.56	83.02 ± 10.50	.594
Theta ERS/ERD%	138.83 ± 49.46	131.75 ± 34.46	.588	104.59 ± 17.26	110.14 ± 20.92	.330

Note: Degrees of freedom = 44 for all comparisons. Upper alpha ERS/ERD% data was log transformed.

individuals. To our knowledge this study provides the first evidence that individuals with MDD display altered gamma activity during WM processing. These findings add to the growing body of research showing abnormal gamma activity during WM performance across a broad range of clinical conditions, including schizophrenia (Barr et al., 2010; Basar-Eroglu et al., 2007), Alzheimer's disease and mild cognitive impairment (König et al., 2005), and attention-deficit hyperactivity disorder (Yordanova, Banaschewski, Kolev, Woerner, & Rothenberger, 2001).

4.3. Frontal-midline theta activity during WM encoding and maintenance

To our knowledge we provide the first evidence that individuals with MDD display less FMT power than controls during the encoding and maintenance phases of WM processing (see Fig. 7). FMT oscillations are believed to reflect activation of prefrontal regions associated with attentional control and the allocation of neural resources towards task-relevant neural processes (Sauseng et al., 2007, 2010). Increases in FMT power occurring 100–500 ms following the presentation of WM stimuli are thought to facilitate efficient encoding of information via increased allocation of attentional resources towards sensory processing (Klimesch et al., 2001; White et al., 2013), whereas sustained increases in FMT power during WM maintenance is typically conceptualised as a neural marker of sustained and internally-focussed attention (Gevins et al., 1997; Jensen & Tesche, 2002; Raghavachari et al., 2001). Less FMT power during WM encoding and maintenance may therefore be indicative of reduced attentional control in MDD, albeit these alterations were not sufficient to impair behavioural performance on the WM task. Moreover, evidence suggests that FMT power is inversely related to activity within the default mode network (DMN), whereby increased FMT power is proposed to reflect greater top-down suppression of the DMN via frontal executive regions. (Michels et al., 2010; Scheeringa et al., 2008, 2009; White et al., 2013). Given this, the current FMT findings may also be indicative of reduced suppression of DMN activity during WM processing, which is consistent with previous neuroimaging studies of WM processing in MDD (Bartova et al., 2015).

4.4. Implications

Results of the current study have practical and theoretical implications for understanding the nature of altered WM processing in MDD. These findings extend upon previous research in MDD showing altered neural responses in occipital regions during information encoding (Coullaut-Valera et al., 2007), and suggests that MDD involves alterations in sensory processes which support encoding of information into WM. Previous studies have found that impaired WM performance in MDD is associated with prominent alterations in oscillatory activity during WM maintenance ([Bailey et al.,2018], Bailey, Segrave, Hoy, Maller, & Fitzgerald, 2014; Segrave et al., 2010), which has led to speculation that abnormal modulation of oscillatory activity may underlie aspects of WM dysfunction (e.g. Bailey et al., 2014). However, using a large and well-balanced cohort of individuals with MDD and healthy controls, our findings show that MDD is associated with widespread alterations in oscillatory activity during WM encoding and maintenance even when no behavioural impairment is present. These findings indicate that the neural processes supporting WM encoding and maintenance are altered in MDD, but also demonstrate that prominent alterations in oscillatory activity were not sufficient to impair WM performance in the current cohort. In addition to group differences in oscillatory activity, we observed relationships between depression severity and gamma and upper alpha power during WM maintenance. These findings indicate that pathophysiological processes underlying the affective symptoms of MDD also influence neural processing within WM-related neurocircuitry. Further research is required to investigate the underlying pathophysiological mechanisms which lead to these observed alterations in oscillatory activity.

These findings may have broader implications for understanding the nature of altered cognitive processing in MDD. Although there is substantial evidence in healthy individuals that theta, upper alpha, and gamma activity are related to efficient WM processing (Jensen & Tesche, 2002; Jensen et al., 2002; Roux et al., 2012; Sauseng et al., 2009), individuals with MDD in the current study were able to achieve intact WM performance despite displaying prominent alterations in oscillatory activity within these frequency bands. For instance, while a greater magnitude of theta and gamma power has been found to predict higher WM capacity and task performance (Sederberg et al., 2003; van Vugt et al., 2010), individuals with MDD displayed significantly lower power in these frequency bands during WM processing but maintained intact WM performance. Moreover, a greater magnitude of alpha power in parieto-occipital regions during WM maintenance been found to predict higher WM task performance (Bonnefond & Jensen, 2012), indicating an important functional role for alpha activity in supporting the short-term maintenance of information in healthy individuals. Despite this, the presence of prominent reductions in upper alpha power during WM maintenance did not significantly impair WM performance for individuals with MDD in the current study, and the magnitude of upper alpha activity was not related to WM performance for either the healthy or MDD groups. One possible explanation for these seemingly contrasting findings is that individuals with MDD achieved intact WM performance by relying upon different neural mechanisms to healthy individuals. Although speculative, research in other neurological and psychiatric conditions which feature WM dysfunction have observed compensatory recruitment of different neural resources to healthy individuals during WM processing, including in schizophrenia (Kim et al., 2010), multiple sclerosis (Audoin et al., 2003), and traumatic brain injury (D'esposito, Cooney, Gazzaley, Gibbs, & Postle, 2006). Alternatively, it is possible that the observed alterations in oscillatory activity reflect non-specific neural changes related to depression, such as differences in the subjective experience of completing the task, rather than reflecting potential inefficiencies in the underlying neural processes which support WM processing. Further research is required to better characterise the neural processes which support WM processing in MDD, and to investigate the potential functional significance of altered oscillatory activity in MDD.

4.5. Limitations

The current findings should be considered with several limitations in mind. Firstly, the MDD and control groups were closely balanced on baseline WM ability in order to control for the confounding influence that group differences in WM performance could exert on oscillatory activity. While this was necessary to allow investigation of whether MDD displayed altered oscillatory activity even when no WM impairments are present, a result of this is that the pattern of alterations in oscillatory activity observed in the current cohort may not be directly applicable to individuals with MDD who display WM impairment. Secondly, the current sample of participants with MDD was relatively young with a mean age of 28.11 years. Further research is required to better characterise the pattern of WM-related oscillatory activity in MDD across the lifespan, particularly given evidence that the cognitive symptoms and alterations in oscillatory activity associated with MDD may become more pronounced during older age (Adler, Bramesfeld, & Jajcevic, 1999; Thomas et al., 2009). Thirdly, the Sternberg WM task used in the current study provides a robust measure of performance and oscillatory activity related to the temporary encoding, short-term maintenance, and retrieval components of WM, however, this measure does not tap into the manipulation aspect of WM processing. Further research is therefore required to expand upon the current evidence of altered oscillatory activity during WM encoding and maintenance and examine whether MDD also involves alterations in WM-related oscillatory activity related to the manipulation component of WM processing. Finally, while significant correlations between depression severity and WM-related oscillatory power suggests a potential shared

pathophysiological mechanism influencing both affective symptoms and cognitive processing in MDD, the current study design does not inform the neurobiological substrates which contribute to altered modulation of oscillatory activity in MDD. Further research is required to investigate the underlying pathophysiological mechanisms which lead to alterations in WM-related oscillatory and to investigate whether these changes in neural oscillations may potentially relate to WM dysfunction in MDD.

4.6. Conclusions

The current study provides evidence that individuals with MDD display quantitative abnormalities in oscillatory activity during WM encoding and maintenance, even when WM performance is comparable to age- and gender-matched healthy controls. The presence of prominent alterations in WM-related oscillatory activity in the absence of WM impairment would suggest that WM processing in MDD may rely upon different neurophysiological mechanisms to healthy individuals. These findings highlight the utility of using oscillatory activity as a neurobiological marker to investigate the pathophysiology of cognitive dysfunction in MDD and other neuropathological conditions. While the current study focussed on oscillatory activity associated with intact WM processing in MDD and controls, these findings warrant further research to explore potential relationships between altered WM-related oscillatory activity and WM impairment in MDD.

Declaration of Competing Interest

Nothing to report.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopsycho.2019.107766.

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5.2. Supplementary Materials

Statistical Analysis

Statistical analysis of lower alpha (8-10 Hz), full alpha (8-13 Hz), and beta (14-28 Hz) activity were conducted in accordance with the methods described for upper alpha activity in the accompanying manuscript. In brief, ERS/ERD% for each frequency band was analysed using a two-way mixed ANOVA with group (control and MDD) as the between subjects factor and WM phase (encoding and maintenance) as the within-subjects factor. Gender was included as a covariate in these analyses.

5.2.1. Lower Alpha Activity

Analysis of lower alpha activity revealed a significant WM phase by group interaction ($F(1,84) = 23.05$, $p < .001$, $\eta_p^2 = .21$). Post-hoc analysis of this interaction did not reveal significant differences in lower alpha activity between the healthy and MDD groups during WM encoding ($t(74.40) = 1.81$, $p = .073$, $d = 0.39$), whereas participants with MDD displayed less lower alpha activity than healthy controls during the maintenance period, ($t(54.94) = 5.03$, $p < .001$, $d = 1.10$) (Table S5.1). A significant main effect was observed for WM phase ($F(1,84) = 9.98$, $p = .002$, $\eta_p^2 = .11$), with pairwise comparisons revealing that lower alpha activity was higher during the maintenance period (2.08 ± 0.02) than the encoding period (1.81 ± 0.02). No main effect was observed for group ($F(1,84) = 2.48$, $p = .119$, $\eta_p^2 = .03$). Gender was not a significant covariate for any comparisons of lower alpha activity ($p = .696$).

Table S5.1.

Lower alpha ERS/ERD% during the encoding and maintenance periods of the Sternberg task, averaged across electrodes O1 and O2 (mean ± SD).

	Encoding Period		Maintenance Period	
	Controls	MDD	Controls	MDD
Lower alpha ERS/ERD%	1.77 ± 0.23	1.85 ± 0.18	2.17 ± 0.20	2.00 ± 0.09

Data was log transformed. To enable log transform, 100 was added to every value so that all values were positive.

5.2.2. Full Alpha Spectrum Activity

Analysis of alpha activity revealed a significant WM phase by group interaction ($F(1,84) = 33.15$, $p < .001$, $\eta_p^2 = .28$). Post-hoc analysis of this interaction revealed that participants with MDD displayed more alpha activity than healthy controls during the encoding period ($t(74.74) = 2.55$, $p = .013$, $d = 0.55$), whereas participants with MDD displayed less alpha activity than healthy controls during the maintenance period, ($t(53.27) = 5.53$, $p < .001$, $d = 1.21$) (Table S5.2). A significant main effect was observed for WM phase ($F(1,84) = 15.53$, $p < .001$, $\eta_p^2 = .16$), with pairwise comparisons revealing that alpha activity was higher during the maintenance period (2.11 ± 0.02) than the encoding period (1.75 ± 0.02). No main effect was observed for group ($F(1,84) = 1.74$, $p = .191$, $\eta_p^2 = .02$). Gender was not a significant covariate for any comparisons of alpha activity ($p = .637$).

Table S5.2.

Alpha ERS/ERD% during the encoding and maintenance periods of the Sternberg task, averaged across electrodes O1 and O2 (mean ± SD).

	Encoding Period		Maintenance Period	
	Controls	MDD	Controls	MDD
Alpha ERS/ERD%	1.70 ± 0.23	1.81 ± 0.18	2.20 ± 0.20	2.01 ± 0.09

Data was log transformed. To enable log transform, 100 was added to every value so that all values were positive.

5.2.3. Beta Activity

Analysis of beta activity revealed a significant WM phase by group interaction ($F(1,84) = 36.94$, $p < .001$, $\eta_p^2 = .31$). Post-hoc analysis of this interaction revealed that participants with MDD displayed more beta activity than healthy controls during the encoding period ($t(85) = 3.30$, $p = .002$, $d = 0.70$), whereas participants with MDD displayed less beta activity than healthy controls during the maintenance period, ($t(58.67) = 5.35$, $p < .001$, $d = 1.17$) (Table S5.3). A significant main effect was observed for WM phase ($F(1,84) = 15.63$, $p < .001$, $\eta_p^2 = .157$), with pairwise comparisons revealing that beta activity was higher during the maintenance period (2.03 ± .01) than the encoding period (1.83 ± 0.01). No main effect was observed for group ($F(1,84) = 3.04$, $p = .085$, $\eta_p^2 = .035$). Gender was not a significant covariate for any comparisons of beta activity ($p = .700$).

Table S5.3.

Beta ERS/ERD% during the encoding and maintenance periods of the Sternberg task, averaged across electrodes O1 and O2 (mean ± SD).

	Encoding Period		Maintenance Period	
	Controls	MDD	Controls	MDD
Beta ERS/ERD%	1.80 ± 0.11	1.87 ± 0.08	2.09 ± 0.13	1.97 ± 0.07

Data was log transformed. To enable log transform, 100 was added to every value so that all values were positive.

Medication Effects

There was no difference in lower alpha, full alpha, or beta activity between medicated and unmediated MDD participants during WM encoding or maintenance (all $p > .05$).

CHAPTER SIX

Study Two - Transcranial random noise stimulation is more effective than transcranial direct current stimulation for enhancing working memory in healthy individuals: behavioural and electrophysiological evidence

6.1. Explanatory Notes

Given the limited understanding of the neurobiological effects of tDCS on WM in healthy individuals, and the absence of previous research examining the effects of tRNS on the neurobiological activity underlying WM processing, the aim of this study was to compare the efficacy of these techniques as a means to enhance WM performance in healthy individuals and to better characterise the neurophysiological changes underlying potential cognitive improvements. This study is an extension of Study One in that the same cohort of healthy individuals were included and allocated to receive either anodal tDCS, tRNS + DC-offset, or sham stimulation to the left DLPFC. Effects of tES on WM performance were examined using the Sternberg WM task completed before and at 5- and 25-minutes post-stimulation. Given that the cognitive effects of tDCS are known to be highly variable, the current study also aimed to compare the consistency of WM improvements induced by tDCS and tRNS + DC-offset. To examine the neurobiological effects of these tES techniques, concurrent EEG recording during the Sternberg WM task was analysed to calculate event-related synchronisation / desynchronisation for theta, upper alpha, and gamma activity during the encoding and maintenance phases of WM processing. Finally, this study included exploratory correlational analysis between changes in WM performance and task-related oscillatory activity to examine whether tES-induced modulation of oscillatory activity contribute to the observed cognitive improvements.

Transcranial Random Noise Stimulation is More Effective than Transcranial Direct Current Stimulation for Enhancing Working Memory in Healthy Individuals: Behavioural and Electrophysiological Evidence

(Running title: Effects of tDCS and tRNS on WM and Oscillatory Activity in Healthy Individuals)

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6.2. Abstract

Background: Transcranial direct current stimulation (tDCS) has been shown to improve working memory (WM) performance in healthy individuals, however effects tend to be modest and variable. Transcranial random noise stimulation (tRNS) can be delivered with a direct-current offset (DC-offset) to induce equal or even greater effects on cortical excitability than tDCS. To-date, no research has directly compared the effects of these techniques on WM performance or underlying neurophysiological activity.

Objective: To compare the effects of anodal tDCS, tRNS + DC-offset, or sham stimulation over the left dorsolateral prefrontal cortex (DLPFC) on WM performance and task-related EEG oscillatory activity in healthy adults.

Methods: Using a between-subjects design, 49 participants were allocated to receive either anodal tDCS (N = 16), high-frequency tRNS + DC-offset (N = 16), or sham stimulation (N = 17) to the left DLPFC. Changes in WM performance were assessed using the Sternberg WM task completed before and 5- and 25-minutes post-stimulation. Oscillatory activity recorded by EEG during WM encoding and maintenance was also examined.

Results: tRNS induced more pronounced and consistent enhancements in WM accuracy when compared to both tDCS and sham stimulation. Improvements in WM performance following tRNS were accompanied by increased theta and gamma activity during WM encoding, which were significantly greater than those observed following anodal tDCS or sham stimulation.

Conclusions: These findings demonstrate the potential of tRNS + DC-offset to modulate cognitive and electrophysiological measures of WM and raise the possibility that tRNS + DC-offset may be more effective and reliable than tDCS for enhancing WM performance in healthy individuals.

6.3. Introduction

There is significant interest in the use of non-invasive transcranial electrical stimulation (tES) techniques to modulate a wide range of cognitive functions in both healthy and clinical populations (Fertonani & Miniussi, 2017). The working memory (WM) system is among the most common targets for neuromodulation as it is central to a range of higher-order cognitive functions and is frequently impaired in many neurological and psychiatric conditions (Rose & Ebmeier, 2006; Santarnecchi et al., 2015). Delivery of anodal transcranial direct current stimulation (tDCS) to the left dorsolateral prefrontal cortex (DLPFC), a brain region crucially involved in WM processing (Barbey et al., 2013; Petrides, 2000), has been shown to significantly improve WM performance in healthy individuals (Fregni et al., 2005; Ohn et al., 2008; Teo et al., 2011). However, recent systematic reviews and meta-analyses have highlighted that the effects of tDCS on WM performance are typically modest and heterogenous between studies (Brunoni & Vanderhasselt, 2014; Dedoncker et al., 2016; Hill et al., 2016; Mancuso, Ilieva, Hamilton, & Farah, 2016). There is also evidence that effects of tDCS are highly variable between individuals with regard to modulation of cognitive performance (Jacobson, Koslowsky, et al., 2012; Mancuso et al., 2016) and underlying brain activity (Nikolin et al., 2018). These findings highlight the need to improve understanding of how tDCS influences the neurophysiological activity underlying WM and suggests the need for further research examining whether other forms of tES may induce more consistent effects on cognitive performance.

One factor thought to limit the effectiveness of tDCS is the activation of homeostatic neural mechanisms which counter-regulate the persistent changes in neuronal membrane potentials induced by direct current stimulation (Fertonani & Miniussi, 2017; Fertonani et al., 2011). While tDCS delivers a direct electrical current with a constant intensity and fixed polarity at each electrode, transcranial random noise stimulation (tRNS) is another form of

tES which delivers an alternating current with a randomly fluctuating frequency and intensity. In contrast to tDCS, it has been proposed that tRNS may induce more pronounced and reliable neuromodulatory effects by delivering a randomly fluctuating electrical field which prevents activation of homeostatic mechanisms (Fertonani et al., 2011). tRNS can also be delivered with a direct current offset (DC-offset) to produce a unidirectional current flow analogous to tDCS, thereby combining the characteristics of tDCS (i.e. net polarisation of neuronal membrane potentials) and tRNS (i.e. introducing noise into the neural system) (Ho et al., 2015). While several studies have found that delivering tRNS without a DC-offset can produce similar or even greater neuromodulatory effects on cortical excitability than anodal tDCS (Inukai et al., 2016; Laczó, Antal, Rothkegel, & Paulus, 2014; Moliadze, Fritzsche, & Antal, 2014), recent evidence suggests that tRNS + DC-offset can induce more pronounced enhancements (Ho et al., 2015). This raises the possibility that tRNS + DC-offset may prove more effective as a means to enhance cognitive performance; however, we are not aware of any research examining the effects of tRNS + DC-offset on WM performance or WM-related neurophysiological activity in healthy individuals.

Neurophysiological measures derived from electroencephalography (EEG) can provide an objective and temporally-precise means to examine the neuromodulatory effects of tES. WM processing in healthy individuals is supported by reliable and robust modulations of neural oscillatory activity within the theta (4 – 8 Hz), upper alpha (10 – 12.5 Hz), and gamma (30 – 100 Hz) frequency ranges (Jensen et al., 2002; Jensen & Tesche, 2002; Roux et al., 2012). Several studies have observed that enhancements in WM performance following anodal tDCS were accompanied by modulation of task-related oscillatory activity, indicating that modulation of oscillatory activity may reflect a potential neurophysiological process underlying the cognitive-enhancing effects of stimulation (Choe et al., 2016; Hoy et al., 2013; Zaehle et al., 2011). Further, electrophysiological effects of tDCS have been observed in the

absence of improvements in cognitive performance (Nikolin et al., 2018), indicating that neurophysiological measures derived from EEG may be more sensitive than cognitive measures alone.

The current study aimed to directly compare the neuromodulatory effects of anodal tDCS and tRNS + DC-offset on WM performance and WM-related oscillatory activity in healthy adults. We hypothesised that both tDCS and tRNS would induce greater enhancements in WM performance when compared to sham stimulation. We further hypothesised that tRNS + DC-offset would induce greater increases in WM performance than anodal tDCS. We also hypothesised that, when compared to anodal tDCS, tRNS + DC-offset would induce more consistent improvements in WM performance. Exploratory analyses were also performed to investigate effects of tES on oscillatory activity recorded during completion of the WM task. We did not construct specific hypotheses regarding the direction of changes in oscillatory activity due to the paucity of relevant previous research.

6.4. Methods

6.4.1. Participants

Forty-nine healthy adults were recruited into the study. Written informed consent was obtained from all participants prior to engaging in the study. The experimental protocol was approved by the Alfred Human Research Ethics Committee and Monash University Human Ethics Committee and was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12612001061820). All participants were aged between 18 and 65 years, fluent in English, had normal or corrected-to-normal vision, and were confirmed as right-handed using the Edinburgh Handedness Inventory (Oldfield, 1971). Prior to inclusion, participants were screened for current psychopathology using the Mini International

Neuropsychiatric Interview for the DSM-IV (Hergueta et al., 1998), and a safety-screen was completed to identify and exclude any participants with contraindicators to tES. No participants were taking psychoactive medication at the time of testing, and none reported recreational drug use in the previous month. Using a parallel-group study design, participants were allocated to receive either tDCS, tRNS+ DC-offset, or sham stimulation. Stratified randomisation was used to allocate participants to each condition based on age, gender, and WM ability as assessed using the Working Memory Index from the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (Wechsler, 2008). The stimulation groups did not significantly differ in age, years of formal education, or WM ability (all $p > .10$) (see Table 6.1 for demographic and clinical characteristics of the participants). All clinical interviews and cognitive tasks were administered by a single researcher trained in standardised administration.

Table 6.1.

Participant demographic characteristics (mean ± SD).

	Sham	tDCS	tRNS	F-statistic	*p*-value
Sample (*n*)	17	16	16		
Gender (F/M)	12 / 5	11 / 5	10 / 6		
Age (years)	31.05 ± 13.06	30.43 ± 12.01	27.60 ± 8.60	0.42	.659
Years of education	14.35 ± 1.69	14.75 ± 1.84	15.00 ± 1.41	0.64	.532
WAIS-IV WMI	108.59 ± 13.37	108.50 ± 9.56	111.06 ± 11.75	0.25	.778

Degrees of freedom = 48 for all comparisons.

6.4.2. Design and procedure

Data was collected during a single experimental session conducted at the Monash Alfred Psychiatry Research Centre, Melbourne. Participants first completed a clinical interview to collect demographic data and assess WM ability, and were then allocated to receive either sham stimulation, tDCS, or tRNS. The Sternberg WM task with concurrent EEG recording was administered at BASELINE, as well as approximately 5 min (POST-1) and 25-min (POST-2) following the end of stimulation (see Figure 6.1 for illustration of study procedure and protocol). While not reported in the current study, effects of tES were also assessed using combined transcranial magnetic stimulation and EEG (TMS-EEG), recorded at BASELINE, as well as approximately 15-min (POST-1) and 35-min (POST-2) following the end of stimulation.

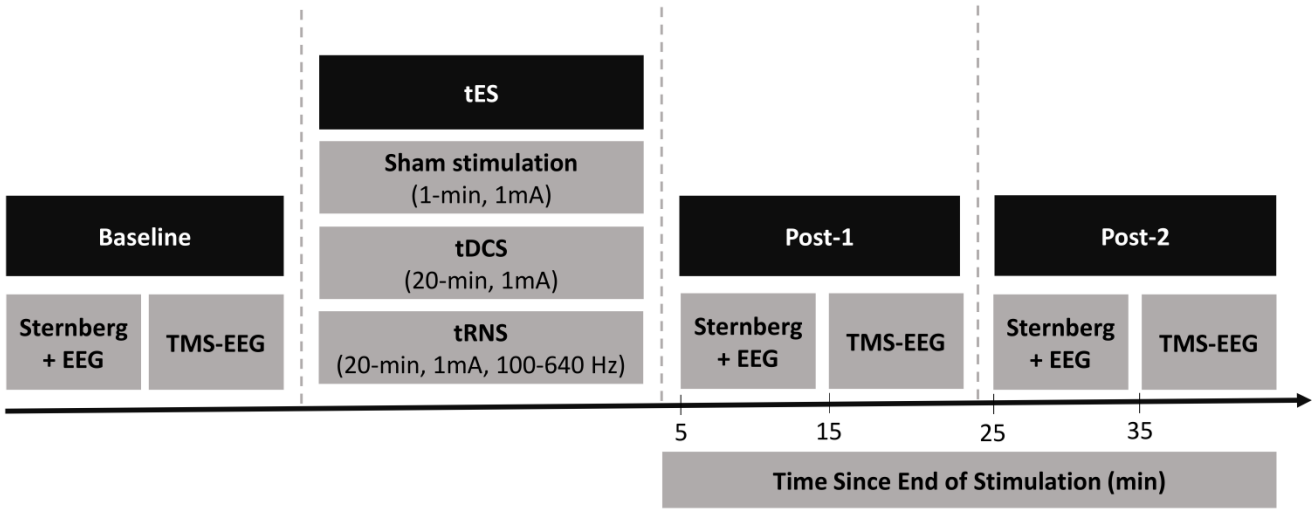

Figure 6.1. Overview of experimental design and protocol.

6.4.3. Transcranial electric stimulation

tES was delivered while participants completed the Paced Auditory Serial Addition Task (PASAT) (described below), given evidence that engaging in concurrent cognitive activity whilst receiving tDCS can produce more pronounced after-effects (Andrews et al., 2011). Stimulation was delivered using an Eldith Stimulator Plus (NeuroConn, Germany) and a pair of rectangular 5x7 cm electrodes (35cm^2) attached to the scalp using Ten20 conductive paste (Weaver and Co., Colorado, USA). For all stimulation conditions, the anodal electrode was placed over the left DLPFC (F3 using the 10-20 system of electrode placement) and the cathodal electrode was placed over the right supraorbital area. tDCS was delivered at 1 mA (current density = 0.029 mA/cm^2) for a duration of 22 minutes (60 s ramp-up, 60 s ramp-down). High-frequency tRNS (100-640 Hz) was delivered with an intensity of 1 mA and a DC-offset of 1 mA for a duration of 22 minutes (60 s ramp-up, 60 s ramp-down). A high-frequency range was chosen based on previous research that the neuromodulatory effects of tRNS are primarily driven by oscillations in the upper end of the frequency range (100-640 Hz) (Fertonani et al., 2011). Delivering tRNS + DC-offset with these parameters ensures that each electrode maintains a consistent polarity produces a unidirectional current flow analogous to tDCS (Ho et al., 2015), whereby the current passes from the positively-charged anode (over the left DLPFC, current intensity fluctuates between +0.5 mA and +1.5 mA) to the negatively-charged cathode (over the right supraorbital area, current intensity fluctuates between -0.5 mA and -1.5 mA). Importantly, the stimulation parameters chosen for tDCS and tRNS + DC-offset ensures that both techniques deliver an approximately equivalent net charge over the course of the stimulation session (mean charge of +1 mA at anode and -1 mA at cathode) and is therefore appropriate for directly comparing effects of tES techniques. Sham stimulation involved delivery of active tDCS for a total of 2.5 minutes (60s ramp-up, held constant for 30s, 60s ramp-down). This sham procedure elicits initial itching sensation

under the electrodes to aid blinding, but participants receive no current for the remaining stimulation period, and has been shown to result in successful participant blinding (Boggio et al., 2008; Ferrucci, Bortolomasi, Brunoni, et al., 2009). Immediately following the end of stimulation, participants completed a questionnaire to evaluate whether tES caused any discomfort or adverse effects. The integrity of stimulation blinding was also assessed at this time by asking participants to report whether they believed they had received active or sham stimulation.

6.4.4. Working memory tasks

6.4.4.1. Paced Auditory Serial Addition Task (PASAT)

Participants completed three 5-minute blocks of the PASAT whilst receiving tES. The PASAT is a challenging mental arithmetic task which has been shown to engage fronto-parietal regions involved in WM processing, including the DLPFC (Lazeron, Rombouts, de Sonneville, Barkhof, & Scheltens, 2003; Lockwood, Linn, Szymanski, Coad, & Wack, 2004). We used an adaptive version of the PASAT in which interstimulus interval between the presentation of numbers adjusted based on the participants performance, thereby ensuring that the task remained challenging but achievable for all participants (Gronwall, 1977; Siegle, Ghinassi, & Thase, 2007). Participants began the first block of the PASAT after the initial ramping-up period for tES had ended, and each block was separated by a one-minute break. Further details of task administration and structure are presented in supplementary materials.

6.4.4.2. Sternberg working memory task

Effects of tES on WM performance were assessed using a Sternberg WM task presented with Neuroscan Stim2 software (Compumedics, Melbourne, Australia). The task simultaneously presented eight letters to remember which were randomly selected from a set of 15 consonants. Following a retention period, participants were presented with a probe

letter and responded as to whether it was present in the memory set. Sternberg task design and stimuli timing are presented in Figure 6.2, and additional task detail are described in supplementary materials.

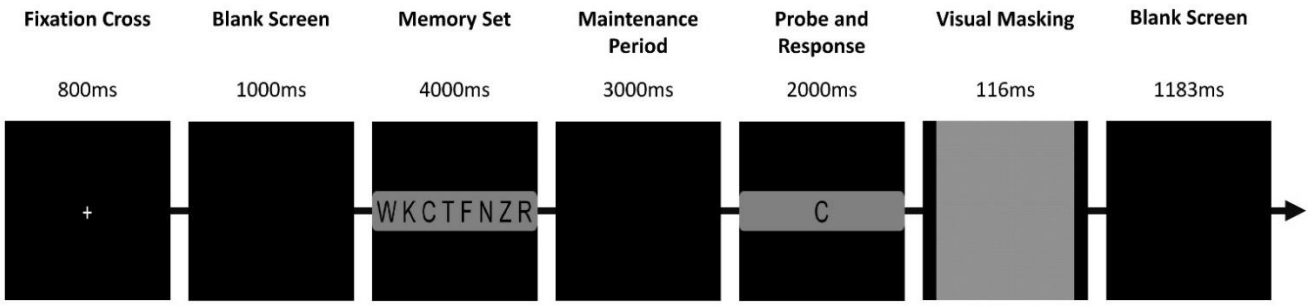

Figure 6.2. Sequence and timing of stimuli for the Sternberg WM task.

6.4.5. Electrophysiological recording and pre-processing

A detailed methodological description of EEG setup, recording, and pre-processing is provided in the supplementary materials. Briefly, 34 single Ag/AgCl scalp electrodes recorded EEG activity to Neuroscan Acquire software using a Synamps 2 amplifier (Compumedics, Melbourne Australia). Impedances were kept below 5 kΩ prior to recording. EEG was sampled at 1000 Hz with a bandpass of 0.1-100 Hz. EEG data was analysed offline in MATLAB (The Mathworks, Natick, MA) using EEGLAB for pre-processing (sccn.ucsd.edu/eeglab) (Delorme & Makeig, 2004) and fieldtrip for frequency analysis (http://www.ru.nl/donders/fieldtrip) (Oostenveld et al., 2011).

6.4.6. Spectral analysis

EEG data was converted into the frequency domain using Morlet Wavelet Transform (3.5 oscillation cycles with steps of 1 Hz). Neural oscillatory power was calculated within the theta (4 - 7 Hz), upper alpha (10 - 12.5 Hz), and gamma (35 - 45 Hz) frequency bands, with

the frequency ranges chosen to correspond with previous research examining oscillatory activity during WM and the Sternberg task (Bailey et al., 2014; Hill, Rogasch, Fitzgerald, & Hoy, 2017; Howard, 2003; Hsieh, Ekstrom, & Ranganath, 2011; Roberts et al., 2013; Segrave et al., 2010). Modulation of oscillatory power was calculated as event-related synchronisation / desynchronisation (ERS/ERD%), which provides positive values when oscillatory power increases in the active test period compared to the reference period. The reference period used for baseline correction was defined as the middle 600ms of the blank screen between the fixation cross and memory set. Average power for each frequency band was calculated across the encoding (1800-5800 ms) and maintenance (5800-8800 ms) periods and then averaged over trials for each participant.

6.4.7. Statistical analysis

All statistical analyses were performed using either IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY) or MATLAB. Chi-square tests were used to assess the effectiveness of stimulation blinding between groups.

6.4.7.1. Cognitive data

Accuracy and response time on the Sternberg WM task were used as the primary WM outcome measures. One-way ANOVAs were used to confirm that stimulation conditions did not significantly differ in accuracy or response time at BASELINE (both $p > .05$). Effects of tES on accuracy and response time were first assessed separately using 3x3 mixed ANOVAs with CONDITION (sham, tDCS, and tRNS) as the between subjects factor and TIME (BASELINE, POST-1, and POST-2) as the within-subjects factor. Significant interaction effects were further explored via separate repeated measures ANOVAs for each stimulation condition to examine changes over TIME (BASELINE, POST-1, POST-2). Additionally, one-way ANOVAs were used to compare change-from-baseline (i.e., POST-1 - BASELINE,

POST-2 - BASELINE) scores (Δ-scores) between stimulation conditions at each time-point (Δ-POST-1, Δ-POST-2). Analysis of Δ-scores allows for a direct comparison of whether changes in WM performance significantly differed between stimulation conditions, and is consistent with previous research examining tES-induced changes in WM performance (Hill, Rogasch, Fitzgerald, & Hoy, 2018; Zaehle et al., 2011). Pairwise comparisons with Bonferroni correction were used to explore any significant main effects. Mauchly's test was used to evaluate the assumption of sphericity, with Greenhouse-Geisser corrections applied where appropriate. Finally, for WM performance variables which displayed significant changes over time, we examined the consistency of improvement induced by tDCS and tRNS by comparing the proportion of participants in each stimulation group who demonstrated improvements in accuracy which were greater than simple practice effects, defined as the mean change in performance displayed by the sham group from BASELINE to POST-1 or POST-2. A chi-square test was used to compare whether the proportion of participants displaying improvements greater than practice effects significantly differed between the tDCS and tRNS groups at POST-1 or POST-2.

6.4.7.2. EEG data

EEG data from 5 participants were excluded due to technical errors (2 participants) and excessive artefact in the EEG recording (3 participants), resulting in a total of 44 participants with valid EEG data (sham n =16, tDCS n = 14, tRNS n = 14). Effects of tES on task-related oscillatory activity were examined via non-parametric cluster-based permutation analyses using the Fieldtrip toolbox (Oostenveld et al., 2011). This technique allows examination of global changes in oscillatory activity across all EEG electrodes whilst also controlling for multiple comparisons (Maris & Oostenveld, 2007) and has been used in previous studies examining the effects of tES on WM-related oscillatory activity (Hill et al., 2017, 2018). Clusters were defined as two or more neighbouring electrodes with a t-statistic

< .05. Monte Carlo *p*-values (two-tailed) were then subsequently calculated using 2000 iterations. Effects of tES on oscillatory activity were first examined separately for each group using a repeated measures ANOVA design to compare changes in oscillatory activity over time from BASELINE to POST-1 or POST-2. When any significant changes in oscillatory activity were observed over time, further comparisons were conducted using Δ-scores to compare whether the three stimulation conditions significantly differed in their effects on oscillatory activity, consistent with previous research examining effects of tES on WM-related oscillatory activity (Hill et al., 2018; Zaehle et al., 2011).

6.5. Results

6.5.1. Working memory performance

6.5.1.1. Accuracy

A significant time by stimulation condition interaction was observed for Sternberg task accuracy ($F(4,92) = 3.855$, $p = .006$, $\eta_p^2 = .144$). Post-hoc analyses revealed that accuracy significantly increased following tRNS ($F(2,30) = 26.716$, $p < .001$, $\eta_p^2 = .640$), with pairwise comparisons showing that accuracy significantly increased from BASELINE to POST-1 (mean difference = 11.06, $p < .001$), and from BASELINE to POST-2 (mean difference = 7.09, $p = .002$) (Figure 6.3). No significant changes in accuracy were observed following either sham ($F(2,32) = 2.965$, $p = .066$, $\eta_p^2 = .156$) or tDCS ($F(2,30) = 0.023$, $p = .977$, $\eta_p^2 = .002$) (Figure 6.3).

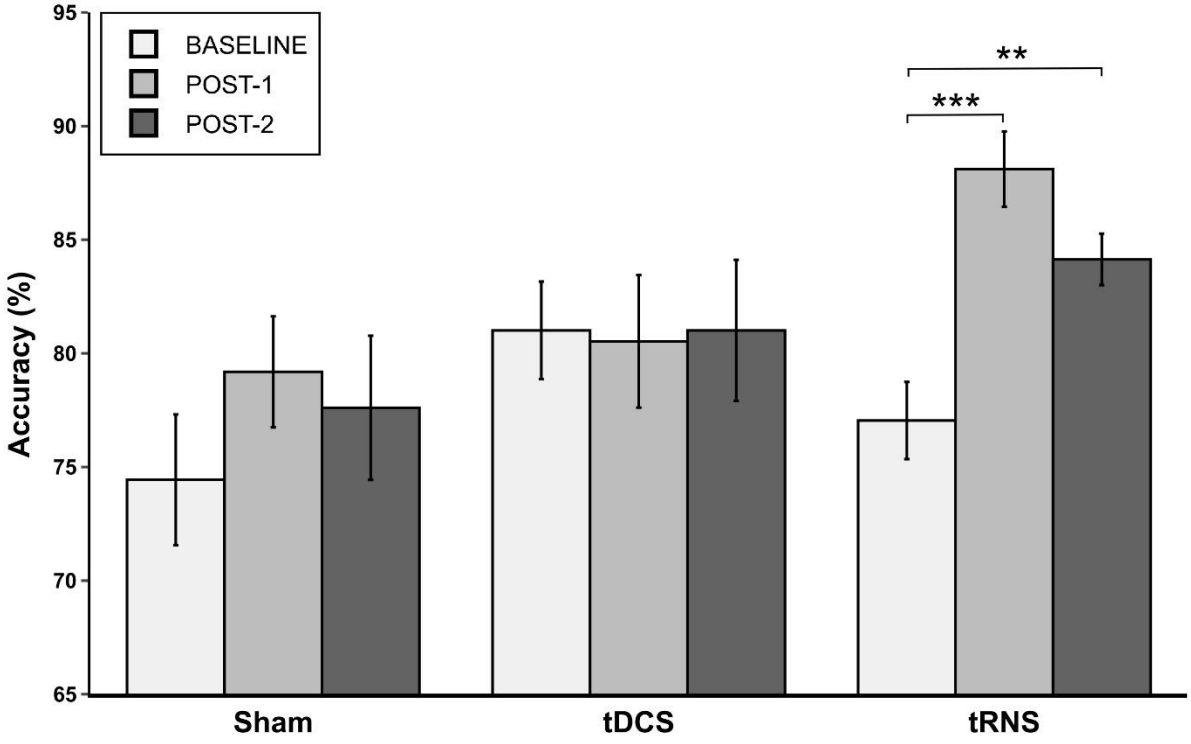

Figure 6.3. Accuracy on the Sternberg WM task across the three time points (BASELINE, POST-1, POST-2). Error bars denote standard error of the mean. * $p < .05$. ** $p < .01$. *** $p < .001$.

Direct comparison of stimulation conditions using accuracy Δ-scores revealed significant group differences at POST-1 ($F(2,48) = 11.148$, $p < .001$, $\eta_p^2 = .326$), with pairwise comparisons revealing that tRNS displayed significantly larger improvements in accuracy when compared to both sham (mean difference = 6.31, $p = .036$) and tDCS (mean difference = 11.54, $p < .001$), whereas no significant difference was observed between sham and tDCS (mean difference = 5.23, $p = .106$) (Figure 6.4). As illustrated in Figure 6.4, participants receiving tRNS displayed a more consistent pattern of improvement from BASELINE to POST-1, with 13 of the 16 participants in the tRNS group demonstrating improvements in accuracy that were larger than the mean improvement following sham (i.e. simple practice effects), whereas only 5 of the 16 participants in the tDCS group met this

criterion. The proportion of participants in the tRNS group who displayed improvements in accuracy from BASELINE to POST-1 which were larger than simple practice effects (81.25% of tRNS group) was significantly greater than observed in the tDCS group (31.25% of tDCS group) (χ^2 (2, N = 49), = 8.20, p = .017).

Comparison of accuracy Δ-scores at POST-2 did not reveal significant differences between stimulation conditions (F(2,48) = 2.341, p = .108, η_p^2 = .092). Similar to the pattern of results observed at POST-1, participants receiving tRNS displayed a more consistent pattern of improvement from BASELINE to POST-2, with 11 of the 16 participants in the tRNS group demonstrating improvements in accuracy that were larger than the mean improvement following sham, whereas only 6 of the 16 participants in the tDCS group met this criterion. However, the proportion of participants who demonstrated improvements in accuracy which were greater than practice effects at POST-2 did not significantly differ between the tDCS (37.50% of tDCS group) and tRNS groups (68.75% of tRNS group) (χ^2 (2, N = 49), = 3.14, p = .208).

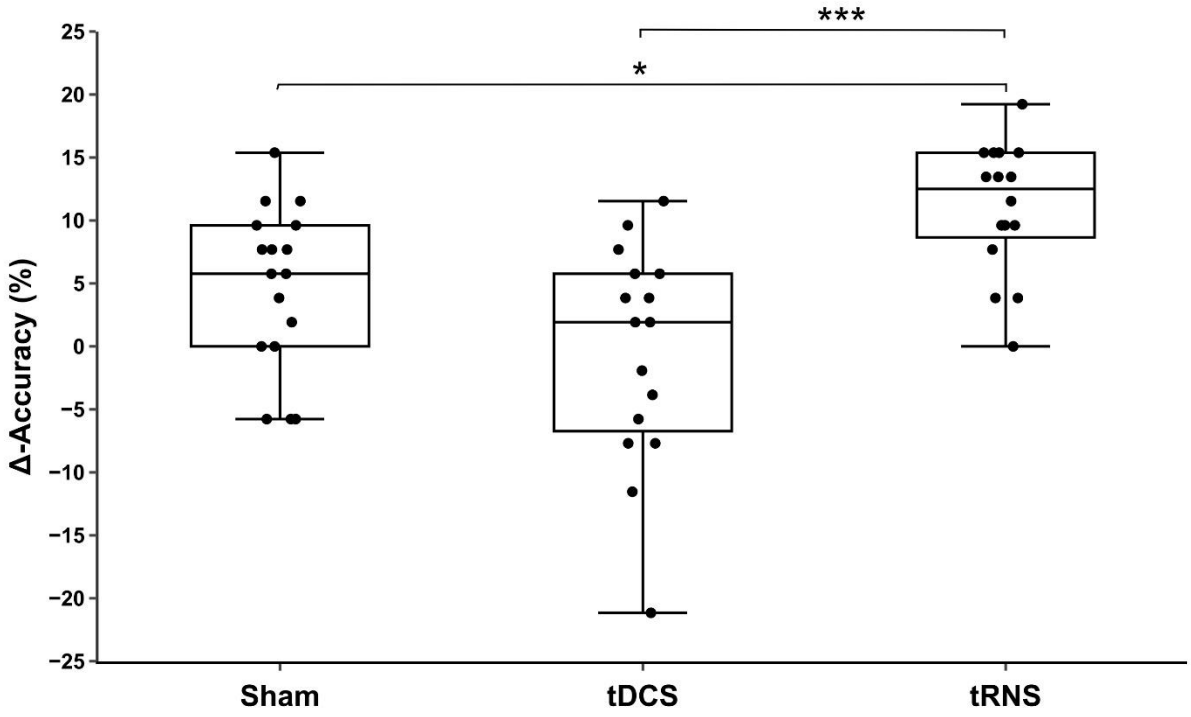

Figure 6.4. Box-and-whisker plots with individual participant values overlaid (circles) showing changes in Sternberg task accuracy from BASELINE to POST-1 (Δ-scores). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Whiskers extend from the minimum to maximum values. * $p < .05$. * $p < .01$. *** $p < .001$.

6.5.1.2. Response time

No significant time by stimulation condition interaction was observed for response time ($F(3.53,81.25) = 1.589$, $p = .191$, $\eta_p^2 = .065$) (Figure 6.5). As the interaction term for response time was non-significant, no further analyses were performed for this variable.

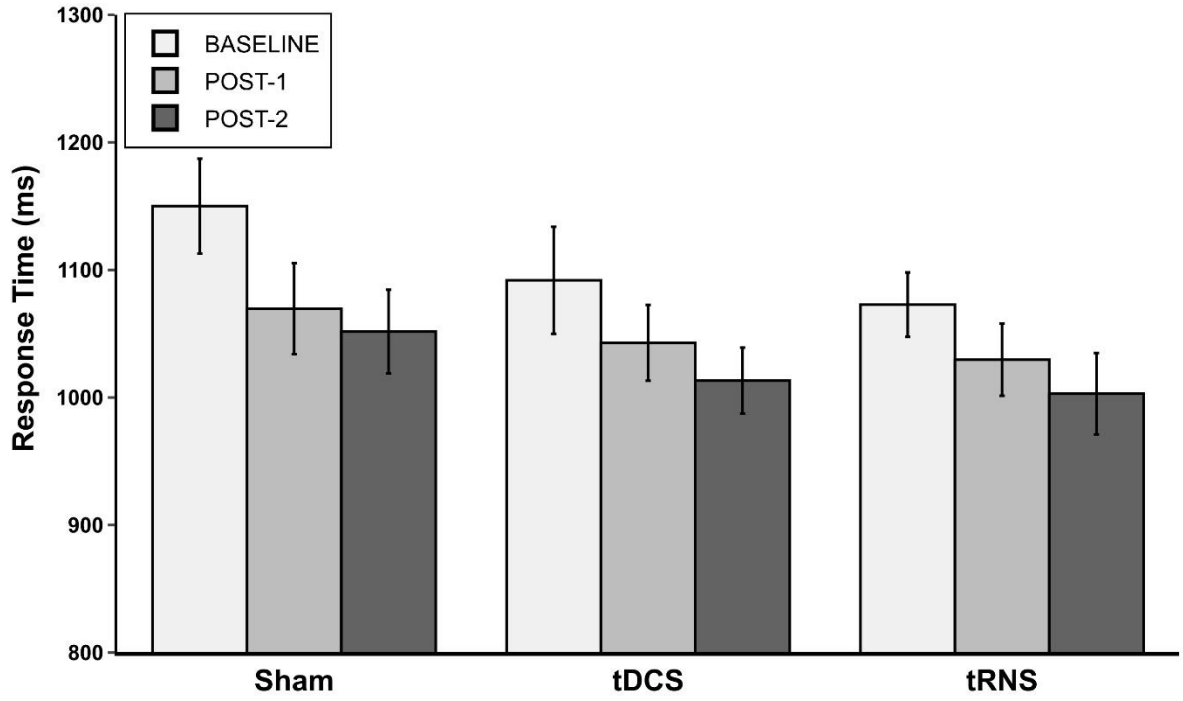

Figure 6.5. Response time (ms) on the Sternberg WM task across the three time points (BASELINE, POST-1, POST-2). Error bars reflect the standard error of the mean.

6.5.2. Oscillatory activity during working memory processing

6.5.2.1. Within-group comparisons

Exploratory analysis of oscillatory activity for the tRNS group revealed a significant increase in encoding period theta activity from BASELINE to POST-1, which was present over left frontal regions (p = .008) and left parieto-occipital regions (p = .042) (Figure 6.6). The tRNS group also displayed an increase in encoding period gamma power over left frontal regions from BASELINE to POST-1 (p = .023) (Figure 6.6). The tRNS group did not display any significant changes in encoding period upper alpha power from BASELINE to POST-1 (p > .05), nor were any significant changes observed in maintenance period theta, upper alpha, or gamma activity from BASELINE to POST-1 (all p > .05). The tRNS group did not

display any significant changes in theta, upper alpha, or gamma activity from BASELINE to POST-2 (all $p > .05$).

Exploratory analysis of oscillatory activity for the tDCS group did not reveal any significant changes in encoding or maintenance period theta, upper alpha, or gamma activity from BASELINE to POST-1 (all $p > .05$). The tDCS group displayed a significant decrease in encoding period theta power over parieto-occipital regions from BASELINE to POST-2 ($p = .037$). The tDCS group did not display any significant changes in encoding period upper alpha or gamma activity from BASELINE to POST-1 (both $p > .05$), nor were any significant changes observed in maintenance period theta, upper alpha, or gamma activity from BASELINE to POST-2 (all $p > .05$).

Exploratory analysis of oscillatory activity for the sham group did not reveal any significant changes in encoding or maintenance period theta, upper alpha, or gamma activity from BASELINE to POST-1 or POST-2 (all $p > .05$).

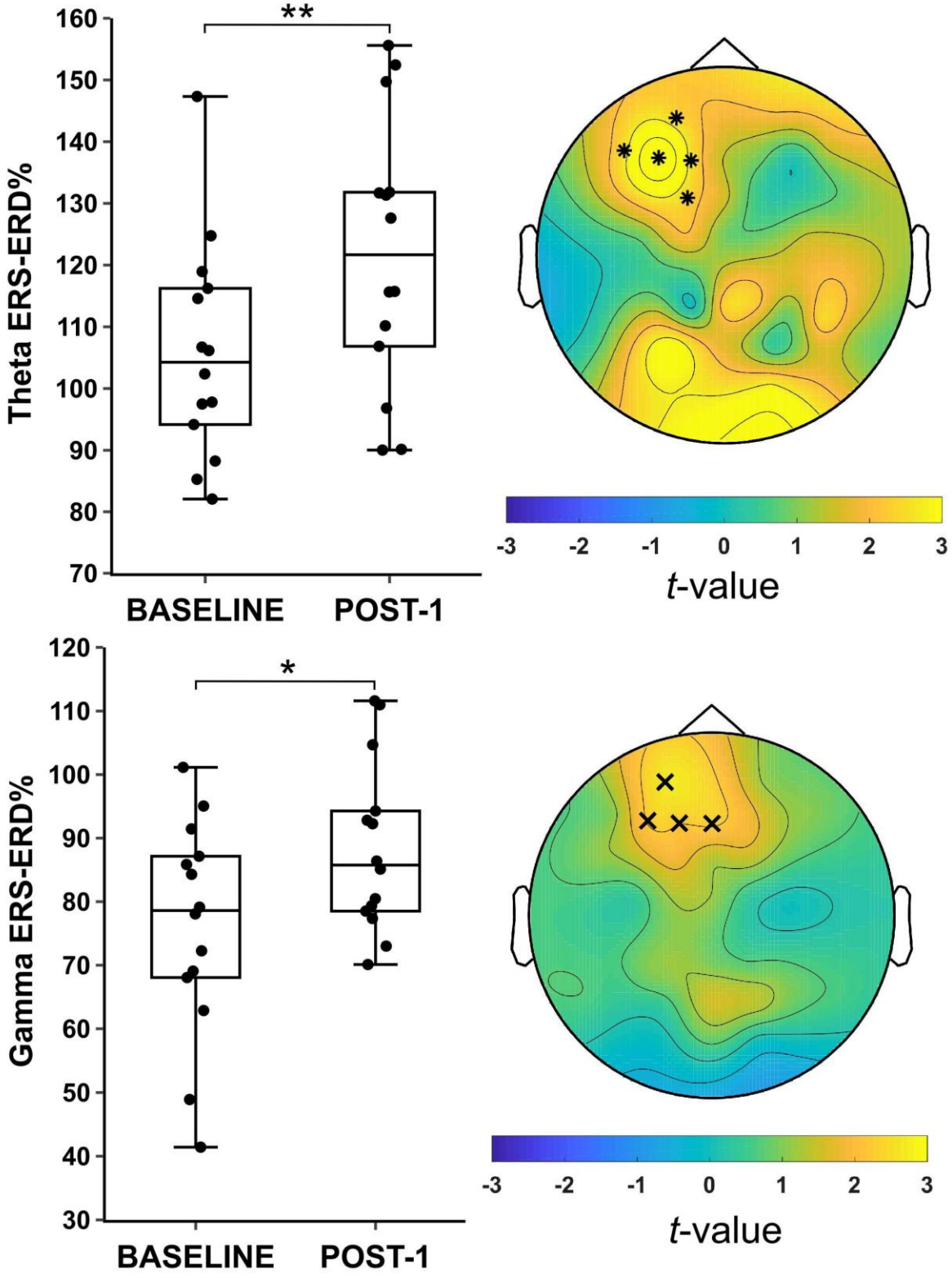

Figure 6.6. Difference in encoding period theta and gamma power from BASELINE to POST-1 for the tRNS group. Box-and-whisker plot displays theta and gamma power at BASELINE and POST-1 (*p < .05, **p < .01), with individual participant data points

overlaid (black circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Whiskers extend from the minimum to maximum values. Topographical map displays differences in oscillatory power (POST-1 - BASELINE), with EEG electrodes forming significant clusters marked by black crosses ($p < .05$) and stars ($p < .01$). Data displayed in the box-and-whisker plot reflects the average of electrodes marked in the topographical map.

6.5.2.2. Between-group comparisons

Direct comparison of stimulation conditions using change-from-baseline-scores (Δ-scores) revealed that the tRNS group displayed significantly larger increases in theta activity from BASELINE to POST-1 when compared to both sham (left frontal cluster: $p = .021$, parieto-occipital cluster: $p = .004$) and tDCS groups (left frontal cluster: $p = .003$; parieto-occipital cluster: $p = .005$) (Figure 6.7). Further, the tRNS group displayed a significantly larger increase in frontal gamma activity from BASELINE to POST-1 when compared to both sham ($p = .021$) and tDCS ($p = .025$) (Figure 6.8). Changes in theta activity from BASELINE to POST-2 did not significantly differ between stimulation conditions (all $p > .05$). Exploratory correlations did not reveal any significant relationships between Δ-scores for accuracy and oscillatory activity (all $p > .05$).

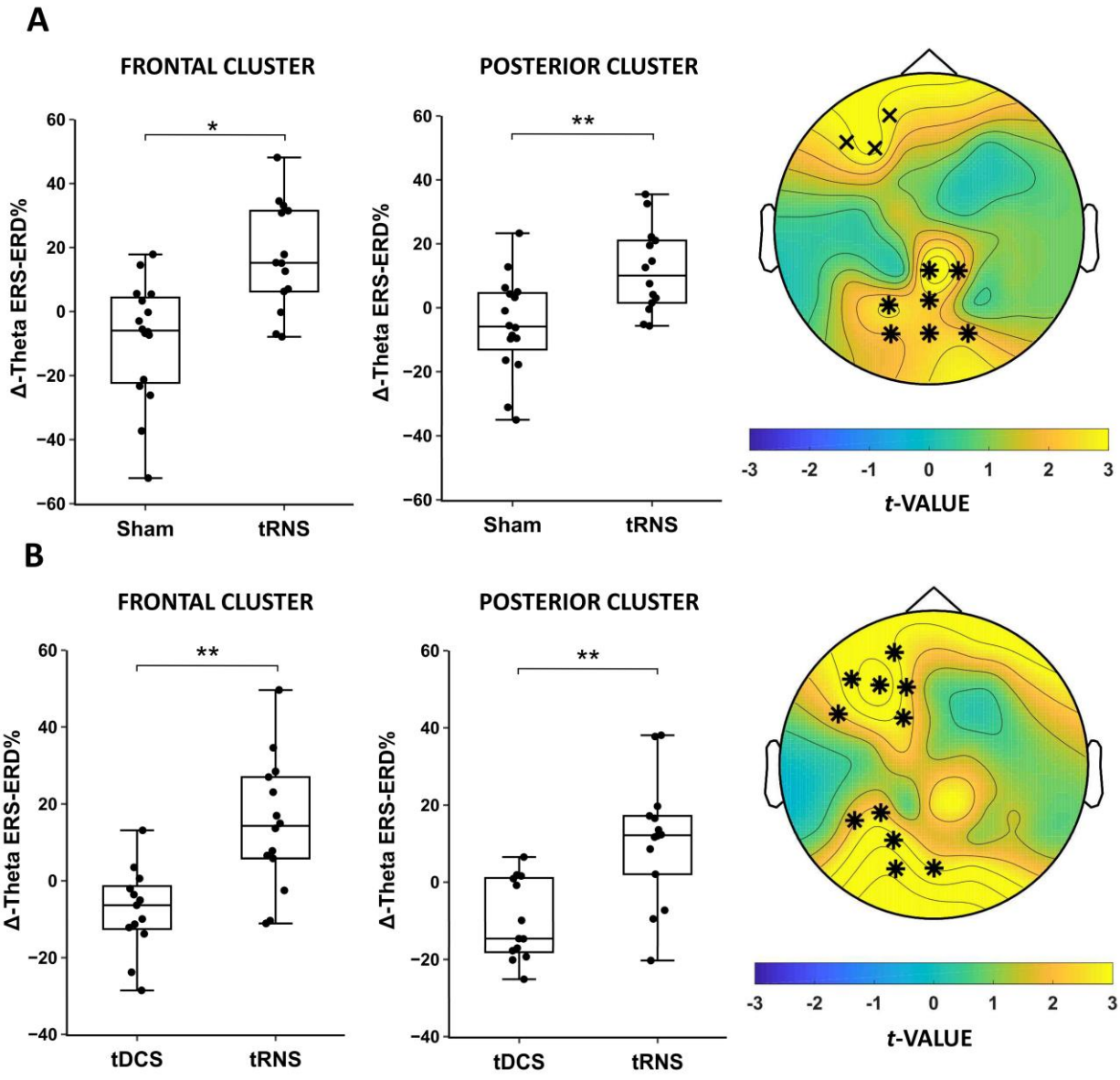

Figure 6.7. Comparison of encoding period Δ-theta power at POST-1 between the tRNS and sham conditions (A), and between the tRNS and tDCS conditions (B). Box-and-whisker plot displays Δ-theta oscillatory power (*p < .05, **p < .01), with individual participant data points overlaid (black circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Whiskers extend from the minimum to maximum values. Topographical map displays differences in oscillatory power when comparing tRNS to Sham (A) and tRNS to tDCS (B), with EEG electrodes forming significant clusters marked by black crosses (p < .05) and stars (p < .01). Data displayed in the box-and-whisker plot reflects the average of electrodes marked in the topographical map.

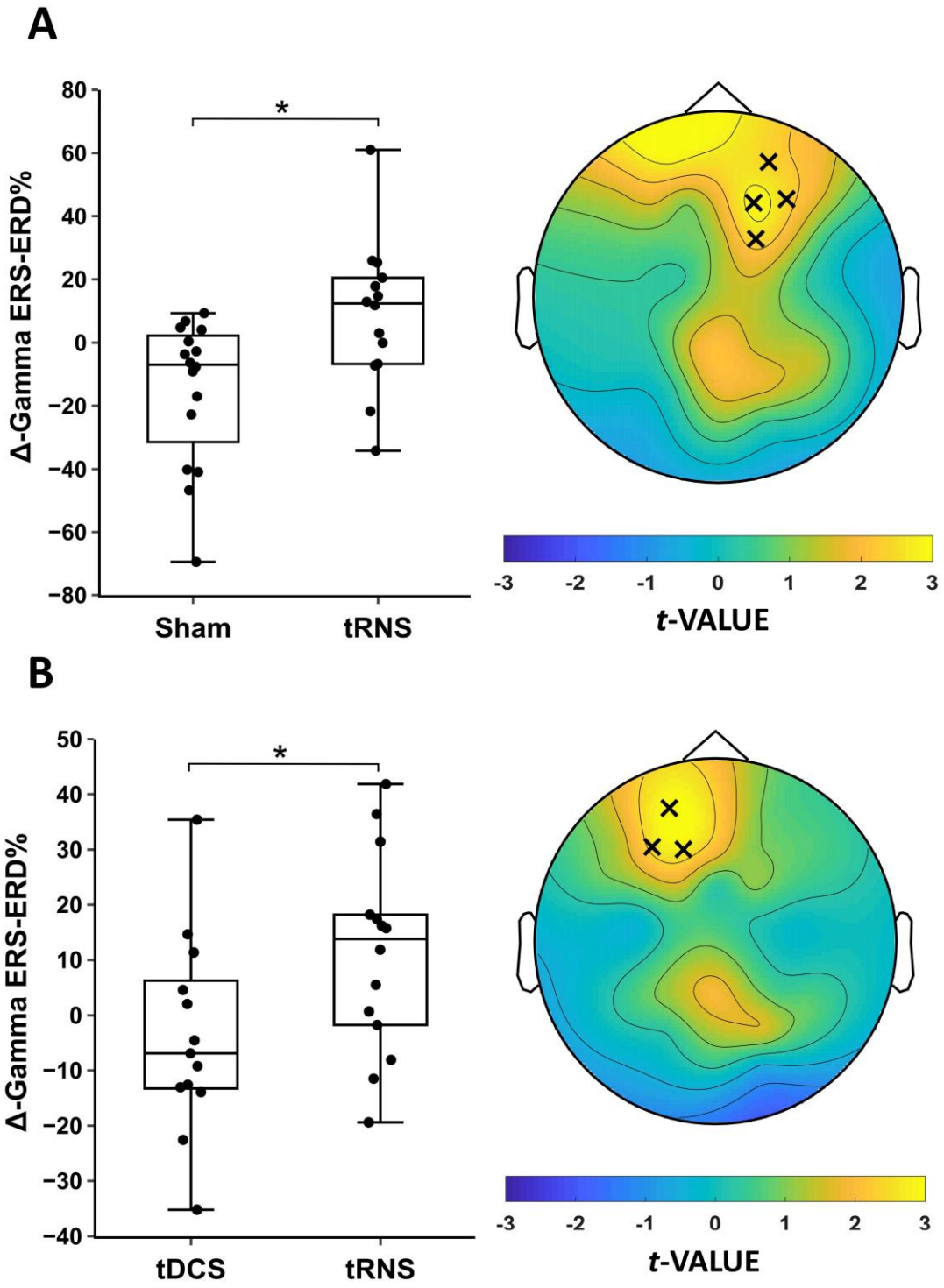

Figure 6.8. Comparison of encoding period Δ-gamma power at POST-1 between the tRNS and sham conditions (A), and between the tRNS and tDCS conditions (B). Box-and-whisker plot displays Δ-gamma oscillatory power (*p < .05, **p < .01), with individual participant data points overlaid (black circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Whiskers extend from the minimum to maximum

values. Topographical map displays differences in oscillatory power when comparing tRNS to Sham (A) and tRNS to tDCS (B), with EEG electrodes forming significant clusters marked by black crosses ($p < .05$). Data displayed in the box-and-whisker plot reflects the average of electrodes marked in the topographical map.

6.5.3. tES tolerability and blinding integrity

The experimental protocol was well tolerated, and no significant adverse effects were reported. Fifteen of the 49 participants (30.61%) reported minor adverse effects whilst receiving tES, including: slight itching or discomfort under the electrode (15 participants), mild burning sensation (1 participant), or a mild headache (1 participants). The incidence of minor adverse effects did not significantly differ between the three stimulation conditions (all $p > .10$). Blinding of stimulation conditions was maintained as participants were unable to guess at better than chance level whether they had received active or sham stimulation (χ^2 (1, N = 49), = 2.451, $p = .294$).

6.6. Discussion

The aim of the present study was to directly compare the cognitive and neurophysiological effects of tDCS and tRNS as neuromodulatory tools for enhancing WM in healthy adults. When delivered using the current stimulation parameters, we found that tRNS + DC-offset over the left DLPFC significantly improved WM task accuracy, whereas no significant cognitive effects were observed following anodal tDCS or sham stimulation. Moreover, tRNS induced more consistent improvements in WM accuracy as compared to tDCS. Enhancements in WM performance immediately following tRNS were accompanied by increases theta and gamma activity during WM encoding. In contrast, we did not observe

any immediate effects of anodal tDCS on WM-related oscillatory activity; a decrease in encoding period theta activity was observed 25-minutes post-stimulation, however these changes did not remain significant when compared to sham stimulation.

6.6.1. Cognitive effects of tES

To our knowledge, this reflects the first evidence showing tRNS to be more effective than anodal tDCS for enhancing WM performance in healthy adults. Results of the current study contrast with previous research by Mulquiney et al. (Mulquiney et al., 2011), who found that tDCS but not tRNS over the left DLPFC significantly improved WM performance in healthy adults. There are several methodological factors which may have contributed to these conflicting findings. Firstly, the current study examined effects of tRNS + DC-offset, whereas Mulquiney et al. delivered tRNS without a DC-offset. Delivering tRNS without a DC-offset results in stimulation electrodes rapidly changing polarity with a randomly fluctuating frequency, whereas tRNS + DC-offset produces a consistent unidirectional current flow analogous to tDCS as the current intensity fluctuates entirely within the positive range at the anodal electrode (between +0.5 and +1.5 mA using the current stimulation parameters) and entirely within the negative range at the cathodal electrode (-0.5 and -1.5 mA). tRNS + DC-offset has been shown to induce larger modulation of cortical excitability than tRNS without an offset (Ho et al., 2015), potentially because it combines the characteristics of tRNS (i.e. introducing noise into the neural system) with those of tDCS (i.e. consistent polarisation of neuronal membrane potentials). Given this, it is possible that the addition of a DC-offset may also increase the effectiveness of tRNS as a means to enhance cognitive performance in healthy adults. However, further research is needed to directly compare the neurophysiological and cognitive effects of delivering tRNS with and without a DC-offset. Secondly, the current study delivered tRNS for a duration of 20-minutes whereas Mulquiney et al. used a shorter duration of 10-minutes. Although delivery of tRNS for a duration of 10-

minutes has been shown to induce enhancements in motor cortex excitability for up to an hour after stimulation (Terney et al., 2008), it is possible that longer stimulation durations are required to modulate excitability and cognitive performance in non-motor regions such as the prefrontal cortex.

Contrary to our predictions, we did not observe significant improvements in WM performance following anodal tDCS. Existing evidence for the facilitatory effects of anodal tDCS over the DLPFC on WM performance in healthy individuals is inconsistent, with several recent meta-analyses findings that effects of anodal tDCS on WM performance are typically modest and variable (Brunoni & Vanderhasselt, 2014; Hill et al., 2016; Mancuso et al., 2016). Moreover, effects of tDCS appear to be highly variable at the individual level, with one meta-analysis finding that only 16% of participants displayed the desired outcome in cognitive studies (Jacobson, Koslowsky, et al., 2012). Consistent with this, we observed a high degree of variability in the effects of tDCS on WM performance, with only 31.25% of participants in the tDCS group displaying improvements in accuracy that were above-and-beyond what would be expected due to practice effects (i.e. greater than the average improvement shown by the sham group). In contrast, 81.25% of participants in the tRNS group demonstrated improvements in accuracy which were greater than practice effects. Taken together, our null findings are broadly consistent with previous research and suggest that a single session of anodal tDCS to the left DLPFC using the current stimulation parameters may not be sufficient to induce meaningful or consistent enhancements in WM performance in healthy adults. Furthermore, these findings indicate that tRNS + DC-offset may reflect a more effective and reliable means to enhance WM performance in healthy adults.

6.6.2. Effects of tES on oscillatory activity during working memory processing

Enhancements in WM performance following tRNS were accompanied by changes in measures of oscillatory activity which have been shown to support efficient WM processing (Jensen et al., 2002; Jensen & Tesche, 2002; Roux et al., 2012). Immediately following tRNS, we observed increases in theta and gamma activity during the encoding phase of the Sternberg task, including increased theta activity over left frontal and parieto-occipital regions, and increased gamma activity over left frontal regions. Consistent with the pattern of cognitive improvements, changes in oscillatory activity were maximal immediately following tRNS, but did not significantly differ when assessed at 25-minutes post-stimulation. Given evidence that higher WM performance is associated with a greater magnitude of theta and gamma activity during WM encoding (Hsieh et al., 2011; Roberts et al., 2013), the pattern of changes in oscillatory activity we observed following tRNS are consistent with increased efficiency of cognitive processing within fronto-parietal neurocircuitry which supports WM processing. Importantly, however, we did not observe any linear relationships between tRNS-induced enhancements of WM performance and increases in task-related theta and gamma activity, indicating that while changes in oscillatory activity may reflect sensitive neurophysiological markers of enhanced cognitive performance, modulation of task-related oscillatory activity does not appear to be a primary mechanism through which tRNS enhances WM performance.

The precise neurophysiological mechanisms through which tRNS alters oscillatory activity remain poorly understood, and less is known about the mechanisms underlying tRNS + DC-offset (Fertonani & Miniussi, 2017). One possible explanation relates to the stochastic resonance phenomenon, whereby the randomly fluctuating current delivered by tRNS introduces ‘noise’ into the neural system and thereby increases the synchronisation of neural firing via amplification of subthreshold oscillatory activity (Fertonani & Miniussi, 2017;

Fertonani et al., 2011). Within this context, effects of tRNS are state-dependent as the 'noise' introduced to the neural system primarily affects neurons which are close to the discharge threshold (i.e. task-dependent activity) (Miniussi, Harris, & Ruzzoli, 2013). As participants in the current study received tES whilst completing the PASAT, a cognitive task which has been shown to engage WM neurocircuitry (Lazeron et al., 2003; Lockwood et al., 2004), the 'noise' introduced by tRNS may have therefore amplified WM-related oscillatory activity in a manner consistent with the stochastic resonance phenomena. However, while this theoretical framework provides a potential explanation for the 'online' effects of tRNS on oscillatory activity, it remains unclear how tRNS-induced changes in oscillatory activity during stimulation are translated into long-term 'offline' effects which persist beyond the end of stimulation (Antal & Herrmann, 2016; Snowball et al., 2013).

We did not observe any effects of anodal tDCS on WM-related oscillatory activity immediately following stimulation. Although a small decrease in parieto-occipital theta activity was observed 25-minutes following tDCS, this change was not significant when compared to other stimulation conditions. Moreover, the absence of any changes in WM performance following tDCS limits our ability to interpret how these changes in oscillatory activity may relate to cognitive performance. There is limited research investigating the effects of anodal tDCS on WM-related oscillatory activity, however, our findings contrast with two previous studies which observed enhanced WM performance on a 2-back task and increased task-related theta activity following a single session of anodal tDCS to the left DLPFC (Hoy et al., 2013; Zaehle et al., 2011). One potential explanation for these conflicting findings relates to differences in the WM task used, as the *n*-back task requires simultaneous encoding, maintenance, and retrieval of information whereas the Sternberg WM task used in the current study temporally separates each phase of WM processing. Given this variation in cognitive demands, combined with evidence that the *n*-back and Sternberg tasks engage

different neural regions (Veltman et al., 2003), it remains possible that effects of tDCS on oscillatory activity were not observable when using the Sternberg task.

Given that recent research has raised concerns that commonly used sham tES protocols may induce active effects on neurophysiological and cognitive outcomes (Fonteneau et al., 2019; Nikolin et al., 2018), it is relevant to note that we did not observe any significant changes in WM performance or oscillatory activity following sham stimulation. While the sham group demonstrated subtle and non-significant improvements in WM performance over time, these improvements are consistent with practice effects and were significantly weaker than those observed following tRNS. Given evidence that neurophysiological measures derived from EEG may be more sensitive than cognitive measures for assessing the effects of tES (Nikolin et al., 2018), the absence of changes in oscillatory activity following sham stimulation further increases confidence that the current sham protocol reflects an accurate control condition for comparing effects of tES methods.

6.6.3. Limitations and future directions

The current findings should be considered with a number of study limitations in mind. Firstly, we used a between-groups design to prevent practice effects from repeated exposure to the WM task over multiple session, whereas evidence suggests that a within-groups design is most appropriate for minimising inter-individual response to tES (López-Alonso, Cheeran, Río-Rodríguez, & Fernández-del-Olmo, 2014). It is possible that the observed group differences in the cognitive and electrophysiological response to tES are primarily driven by inter-group variation in participant characteristics rather than reflecting the contrasting effects of stimulation condition. We utilised stratified randomisation to ensure close balancing of groups on factors known to influence effects of tES, including age, gender, and WM ability, and therefore aimed to reduce the inter-individual variability introduced by the between-group design used in this study. However, the use of a relatively small sample in conjunction

with a between-subjects design does increase the likelihood that potential participant variation in other characteristics may have influenced the study findings. Further large-scale research is therefore required to replicate the findings of the current study using a within-groups design to better control for potential confounding effects of individual characteristics. Secondly, while the current study examined the cognitive and neurophysiological effects of a single session of tES, further research is warranted to examine whether multiple sessions of tDCS or tRNS may induce more pronounced effects on behavioural and neurophysiological measures of WM. Finally, while the current study examined effects of tES in healthy individuals, these findings highlight the potential utility of tRNS + DC-offset as a therapeutic tool for ameliorating cognitive deficits associated with various neurological or psychiatric conditions. Future research should aim to investigate the efficacy of tRNS + DC-offset in improving WM performance in psychiatric conditions which feature prominent WM deficits, such as depression or schizophrenia (Cotrena et al., 2016; Lee & Park, 2005).

6.7. Concluding remarks

In conclusion, our findings show that a single session of tRNS + DC-offset over the left DLPFC can enhance WM performance and modulate task-related oscillatory activity in healthy adults. Delivery of tRNS + DC-offset induced more pronounced and consistent improvements in WM performance when compared to anodal tDCS, indicating that tRNS may overcome some of the factors contributing to high rates of inter-individual variability in the response to tDCS. These findings support the potential of tRNS as a neuromodulatory tool to alter behavioural and neurophysiological markers of WM in healthy adults. Future research is needed to investigate the therapeutic efficacy of tRNS + DC-offset for treatment of neurological and psychiatric conditions, particularly those which feature cognitive dysfunction.

6.8. Disclosures and conflicts of interest

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6.10. References

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6.1. Supplementary Method

6.1.1. Paced Auditory Serial Addition Task (PASAT)

The computerised version of the PASAT involved the presentation of single-digit numbers between one and (auditory presentation via computer and surround sound speakers) to participants who are required to calculate the sum of the two most recently presented numbers. Potential responses (digits ranging from 1 to 18) were presented on a computer monitor and participants were instructed to indicate their response via mouse click prior to the presentation of the next digit. An adaptive version of the PASAT was used in which the interstimulus interval (ISI) between the presentation of numbers adjusts based on participants performance (Siegle, Ghinassi, et al., 2007). The ISI was initially set at 3000 ms and decreased by 100 ms following four consecutive correct responses or increased by 100 ms following four consecutive incorrect responses.

6.1.2. Sternberg working memory task

The Sternberg WM task simultaneously presented eight letters to remember, followed by a retention period, then a probe letter. Participants indicated their response by pressing one button if the probe was present in the memory set and another button if the probe was not present. Responses made outside of the 2000ms probe window were considered incorrect. Memory stimuli consisted of a selection of fifteen consonants (B, C, D, F, H, J, K, L, N, R, S, T, Y, W, Z) which were pseudo-randomised so that no letter appeared in the same location consecutively. Probe letters were present in the memory set at 50% probability and no letter was presented as the probe twice in succession.

The trial sequence was the same for all participants. Trials began with the presentation of a fixation cross (800 ms) followed by a blank screen (1000 ms). The memory set (encoding period) was then presented (4000 ms), followed by the retention period

(maintenance period) (3000 ms). The probe letter was then presented (2000 ms) and participants indicated their response (retrieval period), followed by a visual mask (166 ms) and a blank screen (1883 ms). Participants completed a total of 52 trials presented in two blocks with a short break between blocks. Participants completed 10 practice trials before beginning the task and were encouraged to repeat this sequence until they felt comfortable with the task. Accuracy and response times were recorded for each participant.

6.1.3. EEG recording and pre-processing

Thirty-four single Ag/AgCl scalp electrodes recorded EEG activity to Neuroscan Acquire software using a Synamps 2 amplifier (Compumedics, Melbourne Australia). Electrodes were positioned according to the 10-20 system (AF3, AF4, F5, F3, F1, FZ, F2, F4, F6, FC5, FC1, FCZ, FC2, FC6, C3, C1, CZ, C2, C4, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO3, POZ, PO4, O1, OZ, O2). Four facial electrodes were positioned adjacent to the left and right outer canthus of each eye and above and below the left orbit to measure eye movement. Electrodes were grounded to AFz and referenced online to an electrode between Cz and CPz. Impedances were kept below 5 kΩ prior to recording. EEG was sampled at 1000 Hz with a bandpass of 0.1-100 Hz.

Data was analysed offline in MATLAB (The Mathworks, Natick, MA) using EEGLAB for pre-processing (sccn.ucsd.edu/eeglab) (Delorme & Makeig, 2004) and fieldtrip for frequency analysis (http://www.ru.nl/donders/fieldtrip) (Oostenveld et al., 2011). A second-order Butterworth filter was applied to the data with a bandpass of 1-80 Hz and a band-stop filter of 45-55 Hz. Data was then epoched into 11500ms segments extending from the onset of the fixation cross to the middle of the blank screen for each trial. Only correct trials were included in further analysis. Single electrodes containing artifacts in more than 5% of the trials were rejected (indicated by variations in voltage larger than 250μv, kurtosis values > 5, or values exceeding -100 or 30 dB in the 25-45Hz range). Epochs containing

artifacts were also rejected (indicated by kurtosis values > 5 for all electrodes, and more than -100 to 30 dB in the 25-45Hz range). Artifact rejections were then manually checked by a trained researcher. Fast independent component analysis (FastICA) using 'symmetric approach' and the 'tanh' contrast function was then used to manually select and remove eye movements and remaining muscle activity artifacts. Missing channels were interpolated using the 'spherical' function and recordings were re-referenced offline to an average reference. Participants were excluded if fewer than 20 correct and noise free epochs were available for analysis. No significant differences were detected between groups in the number of epochs accepted in the final analysis ($p > .05$).

6.1.4. Supplementary References

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CHAPTER SEVEN

Study Three - Effects of transcranial direct current stimulation and transcranial random noise stimulation on working memory in major depressive disorder: behavioural and electrophysiological outcomes

7.1. Explanatory Notes

Study One demonstrated that MDD involves widespread changes in WM-related oscillatory activity when compared to healthy controls, and Study Two indicated that tRNS + DC-offset may induce more pronounced and reliable enhancements in WM performance than tDCS in healthy individuals. Study Three aimed to extend upon these findings by directly comparing the effects of tDCS and tRNS on WM performance and WM-related oscillatory activity in MDD. In doing so, this reflects the first sham-controlled study to deliver tRNS in MDD (either with or without a DC-offset).

Study Three used the same cohort of participants with MDD who displayed widespread alterations in WM-related oscillatory activity in Study One, thereby allowing examination of whether the cognitive effects of tDCS or tRNS + DC-offset involved modulation of abnormal oscillatory activity. Participants were allocated to receive either anodal tDCS, tRNS + DC-offset, or sham stimulation; delivered using the same stimulation parameters as Study Two. Stimulation groups were closely balanced on potentially confounding variables, including age, gender, depression severity, and baseline WM ability. WM performance and task-related oscillatory activity were assessed using the same experimental protocol as Study Two, with Sternberg WM task and concurrent EEG recorded before and at 5- and 25-minutes post-stimulation. We are only aware of one previous study examining the effects of tDCS on WM-related oscillatory activity in MDD, however, WM performance and task-related EEG were not examined until approximately 60-minutes following the end of stimulation (Powell et al., 2014). The current study thereby provides valuable information regarding the acute neurophysiological and cognitive effects of tDCS in MDD.

Effects of Transcranial Direct Current Stimulation and Transcranial Random Noise Stimulation on Working Memory in Major Depressive Disorder: Behavioural and Electrophysiological Outcomes

(Running title: Effects of tDCS and tRNS on WM and Oscillatory Activity in MDD)

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7.2. Abstract

Background: Transcranial direct current stimulation (tDCS) has been shown to enhance working memory (WM) performance in Major Depressive Disorder (MDD), however effects tend to be modest and variable. Delivering transcranial random noise stimulation (tRNS) with a direct-current offset (DC-offset) may induce more pronounced and consistent enhancements in WM performance in healthy individuals when compared to tDCS. However, the effects of tRNS have yet to be systematically investigated in MDD.

Objective: We compared the effects of anodal tDCS, tRNS + DC-offset, and sham stimulation over the left dorsolateral prefrontal cortex (DLPFC) on WM performance and task-related electroencephalography (EEG) oscillatory activity in individuals with MDD.

Methods: Using a parallel-groups design, 49 currently depressed participants with MDD were allocated to receive anodal tDCS (N = 16), high-frequency tRNS + DC-offset (N = 16), or sham stimulation (N = 17) to the left DLPFC for 20-minutes. The Sternberg WM task was completed before and at 5- and 25-minutes post-stimulation, and task-related oscillatory activity was recorded throughout WM task execution using EEG.

Results: Neither tDCS nor tRNS improved WM performance to a significantly greater degree than sham stimulation. When compared to sham stimulation, tDCS significantly increased parieto-occipital upper alpha power during WM maintenance on EEG recorded 5- and 25-minutes post-stimulation. tRNS did not significantly alter WM-related oscillatory activity when compared to sham stimulation.

Conclusions: Neither tDCS nor tRNS induced reliable cognitive improvements in acutely depressed individuals with MDD when compared to sham. However, tDCS demonstrated the potential to alter the neurobiological activity underlying WM processing.

7.3. Introduction

Major Depressive Disorder (MDD) is a highly prevalent and frequently debilitating mental illness which is associated with significant rates of morbidity and mortality (Kessler et al., 2009, 2005a). Impairments in working memory (WM) are amongst the most common cognitive symptoms of MDD and are associated with increased rumination and poorer treatment outcomes (Dunkin et al., 2000; Joormann & Gotlib, 2010; Snyder, 2013). Current first-line psychopharmaceutical and counselling treatments have demonstrated effectiveness in reducing the affective symptoms of MDD but are less effective for treating cognitive impairments (Herrera-Guzmán et al., 2010; Raskin et al., 2007). Recent research has highlighted the potential of transcranial electrical stimulation (tES) techniques to enhance WM performance in both healthy and depressed individuals when delivered to the left dorsolateral prefrontal cortex (DLPFC) (Andrews et al., 2011; Boggio et al., 2007; Fregni et al., 2005; Moreno et al., 2015).

Transcranial direct current stimulation (tDCS) is the most widely studied form of tES and involves the delivery of a weak direct current to the cortex via electrodes placed on the scalp (Woods et al., 2016). While delivery of tDCS to the DLPFC has been shown to enhance WM performance in MDD (Boggio et al., 2007; Loo et al., 2012; Moreno et al., 2015; Oliveira et al., 2013; Wolkenstein & Plewnia, 2013), recent meta-analyses highlight that effects are often modest in size and variable between studies and individuals (Hill et al., 2016; Martin et al., 2018). Transcranial random noise stimulation (tRNS) is another form of tES which delivers an alternating current with a randomly fluctuating frequency and intensity (Terney et al., 2008). Delivering tRNS with a direct current offset (DC-offset) results in the delivery of a consistent polarity with a randomly fluctuating current intensity through electrodes, thereby combining the electrical characteristics of tDCS (i.e. net polarisation of neuronal membrane potentials) and tRNS (i.e. introducing noise into the neural system) (Ho et al., 2015).

Research in healthy individuals has demonstrated that tRNS without an offset can induce more pronounced neurophysiological and behavioural effects than anodal tDCS (e.g. Fertonani, Pirulli, & Miniussi, 2011; Inukai et al., 2016), and delivery of tRNS with a DC-offset has been shown to facilitate cortical excitability to a greater degree than tRNS without an offset (Ho et al., 2015). We recently found that tRNS + DC-offset induced more pronounced and consistent WM enhancements than anodal tDCS in healthy individuals (Murphy et al., in submission). These findings warrant investigation of whether tRNS + DC-offset may also prove more effective than anodal tDCS for enhancing WM performance in clinical conditions such as MDD. We are not aware of any previous sham-controlled research applying tRNS in this population.

While the summarized tES research is promising, a greater understanding of how stimulation influences underlying neurobiological activity and how these effects facilitate cognitive processing could help improve the reliability of cognitive outcomes. Electroencephalography (EEG) has been widely used to characterise the neurophysiological correlates of WM processing in healthy individuals, which include reliable and robust modulation of oscillatory activity within the theta (4 – 8 Hz), upper alpha (10 – 12.5 Hz), and gamma (30 – 100 Hz) frequency ranges (Jensen et al., 2002; Jensen & Tesche, 2002; Roux et al., 2012). Individuals with MDD have been shown to display altered patterns of oscillatory activity during WM processing, with the most common finding being altered modulation of upper alpha power during the maintenance phase of WM processing (Bailey et al., 2014; Murphy et al., 2019a; Segrave et al., 2010). Given evidence that tES can modulate oscillatory activity within the theta, upper alpha, and gamma frequency ranges (Boonstra, Nikolin, Meisener, Martin, & Loo, 2016; Hoy, Bailey, Arnold, & Fitzgerald, 2015; Miller et al., 2015), examination of EEG-derived measures of oscillatory activity may provide valuable

insights into the neurophysiological mechanisms underlying the cognitive effects of tES in MDD.

The current study aimed to directly compare the neuromodulatory effects of anodal tDCS and tRNS + DC-offset on WM performance and WM-related oscillatory activity in individuals with MDD. We hypothesised that both tDCS and tRNS would enhance WM performance when compared to sham stimulation, and that tRNS will be superior to tDCS in improving WM. We also examined potential effects of tES on theta, upper alpha, and gamma power during WM encoding and maintenance. Given evidence that MDD is associated with reductions in upper alpha power during WM maintenance (Bailey et al., 2014; Murphy et al., 2019a), combined with evidence that tES can modulate alpha activity in healthy individuals (Boonstra et al., 2016; Hsu et al., 2014), we hypothesised that both tDCS and tRNS would increase upper alpha power during WM maintenance when compared to sham stimulation, and that these enhancements would be more pronounced following tRNS as compared to tDCS. We also performed exploratory analyses to examine potential effects of tES on theta and gamma activity during WM encoding and maintenance, however we did not construct specific hypotheses for these analyses due to the paucity of previous evidence regarding MDD-related changes in theta and gamma activity during WM processing.

7.4. Methods

7.4.1. Participants

Forty-nine adults with MDD were recruited into the study. All participants were aged between 18 and 65 years, right-handed, fluent in English, and had normal or corrected-to-normal vision. Prior to inclusion, participants completed a clinical interview to confirm the presence of a current DSM-IV defined Major Depressive Episode and screen for other Axis 1

psychiatric disorders. A tES safety screen was used to identify and exclude participants with contraindicators to non-invasive brain stimulation, including epilepsy, stroke, traumatic brain injury, neurological illness, frequent or severe headaches, pregnancy, medical infusion devices, or metal implants in the brain or skull. Participants were also excluded if they reported recreational drug use within one month prior to testing, a history of substance abuse or dependence, or were currently taking medications which have been shown to interfere with the effects of non-invasive brain stimulation (i.e. benzodiazepines, antipsychotics, or mood stabilisers) (Brunoni, Ferrucci, et al., 2013; Stagg & Nitsche, 2011). At the time of testing, 26 participants were taking antidepressant medication and 23 were medication-free (Table 7.1). Written informed consent was obtained from all participants prior to engaging in the study. The experimental protocol was approved by the Alfred Human Research Ethics Committee and the Monash University Human Ethics Committee and was registered on the Australian and New Zealand Clinical Trials Registry (ACTRN12612001061820).

7.4.2. Design and procedure

The study utilised a sham-controlled, single-session, parallel-groups design. Each participant completed a single experimental session conducted at the Monash Alfred Psychiatry Research Centre, Melbourne. The session began with a clinical interview to collect demographic data and assess clinical characteristics and WM ability. Stratified sampling based on age, gender, and WM ability was then used to allocate participants to receive either sham stimulation, tDCS, or tRNS. The Sternberg WM task with concurrent EEG recording was administered at BASELINE, as well as approximately 5 minutes (POST-1) and 25 minutes (POST-2) after the end of stimulation (see Figure 7.1 for illustration of experimental design and procedure). While not reported in the current study, effects of tES were also assessed using combined transcranial magnetic stimulation and EEG (TMS-EEG),

recorded at BASELINE and approximately 15 minutes (POST-1) and 35 minutes (POST-2) following the end of stimulation.

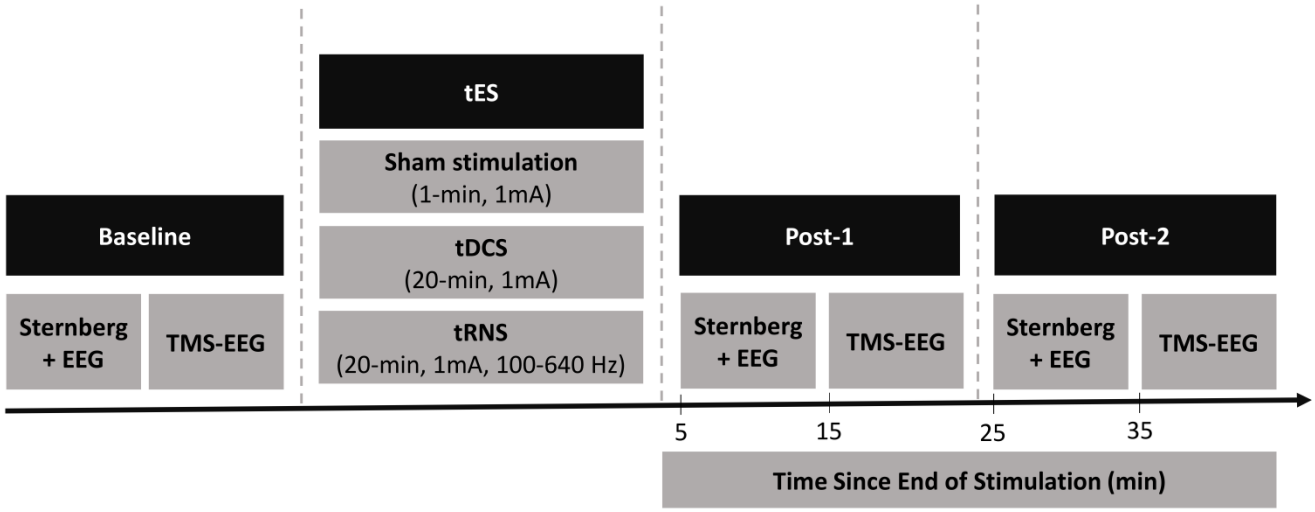

Figure 7.1. Overview of experimental design and procedure.

7.4.3. Clinical interview

All clinical interviews and cognitive tasks were administered by a single researcher trained in standardised administration. The Mini International Neuropsychiatric Interview (Sheehan et al., 1998) was used to confirm the presence of a current DSM-IV defined Major Depressive Episode and screen for other Axis 1 psychiatric disorders. Depression severity was assessed using the Hamilton Depression Rating Scale, 17-item ($HAM\text{-}D_{17}$) (Hamilton, 1960) and the Quick Inventory of Depressive Symptomology – Clinician Rated, 16-item (QIDS-C) (Rush et al., 2003; Trivedi et al., 2004). State and trait anxiety levels were assessed using the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 2010). Baseline WM ability was assessed using the Working Memory Index from the Wechsler Adult Intelligence

Scale, Fourth Edition (WAIS-IV) (Wechsler, 2008). Participants were confirmed as right-handed using the Edinburgh Handedness Inventory (Oldfield, 1971).

7.4.4. Transcranial electric stimulation

All stimulation conditions were delivered using the same Eldith Stimulator Plus machine (NeuroConn, Germany) and a pair of rectangular 5x7 cm electrodes (35cm^2) attached to the scalp using Ten20 conductive paste (Weaver and Co., Colorado, USA). Given evidence that engaging in concurrent cognitive activity whilst receiving tDCS can produce more pronounced after-effects (Andrews et al., 2011), participants completed the Paced Auditory Serial Addition Task (PASAT) whilst receiving tES (described below). For all stimulation conditions, the anodal electrode was placed over the left DLPFC (F3 using the 10-20 system of electrode placement) and the cathodal electrode was placed over the right supraorbital area.

Sham stimulation involved delivery of active tDCS for a total of 2.5 minutes (60s ramp-up, held constant for 30s, 60s ramp-down). This sham procedure has been shown to result in successful participant blinding (Boggio et al., 2008; Ferrucci, Bortolomasi, Brunoni, et al., 2009). Active tDCS was delivered at 1 mA (current density = 0.029 mA/cm^2) for a duration of 22 minutes (60 s ramp-up, 60 s ramp-down). High-frequency tRNS (100-640 Hz) was delivered with an intensity of 1 mA and a 1 mA DC-offset for a duration of 22 minutes (60 s ramp-up, 60 s ramp-down). A high-frequency range was chosen given evidence that the neuromodulatory effects of tRNS are primarily driven by oscillations in the upper end of the frequency range (100-640 Hz) (Fertonani et al., 2011). Delivering tRNS + DC-offset with these parameters produces a unidirectional current flow from the positively charged anode (over the left DLPFC, current intensity fluctuates between +0.5 mA and +1.5 mA) to the negatively charged cathode (over the right supraorbital area, current intensity fluctuates between -0.5 mA and -1.5 mA). Importantly, the stimulation parameters chosen for tDCS and

tRNS + DC-offset ensures that both techniques deliver an approximately equivalent net charge over the course of the stimulation session (mean charge of +1 mA at anode and -1 mA at cathode) and is therefore appropriate for directly comparing effects of tES techniques. Immediately following the end of stimulation, participants completed a questionnaire to evaluate whether tES caused any discomfort or adverse effects. The integrity of stimulation blinding was also assessed at this time by asking participants to report whether they believed they had received active or sham stimulation.

7.4.5. Working memory tasks

7.4.5.1. Paced Auditory Serial Addition Task

Participants completed three 5-minute blocks of the PASAT whilst receiving tES, with a one-minute break between the blocks. The PASAT is a challenging mental arithmetic task which has been shown to engage fronto-parietal regions involved in WM processing, including the DLPFC (Lazeron et al., 2003; Lockwood et al., 2004). In this task, single-digit numbers between one and nine are presented (auditory presentation via computer and surround sound speakers) to participants who are required to calculate the sum of the two most recently presented numbers. Potential responses (digits ranging from 1 to 18) were presented on a computer monitor and participants were instructed to indicate their response via mouse click prior to the presentation of the next digit. We used an adaptive version of the PASAT in which the interstimulus interval (ISI) between the presentation of numbers adjusts based on participants performance (Siegle, Ghinassi, et al., 2007). The ISI was initially set at 3000 ms and decreased by 100 ms following four consecutive correct responses or increased by 100 ms following four consecutive incorrect responses. Systematic adjustment of the ISI ensures that the task remains challenging but achievable for all participants. Participants began the PASAT after the 60 s ramping-up period for tES had ended.

7.4.5.2. Sternberg working memory task

Cognitive effects of tES were examined using a modified verbal Sternberg WM task presented with Neuroscan Stim2 software (Compumedics, Melbourne, Australia). The Sternberg WM task was selected as it temporally separates the encoding, maintenance, and retrieval aspects of WM processing and thereby allows examination of oscillatory activity associated with each WM phase (Jensen et al., 2002; Jensen & Tesche, 2002; Segrave et al., 2010). The task involves presentation of a memory set containing eight letters, followed by a maintenance period in which the letters are removed. Participants are then presented with a probe letter and indicate using a button press whether the probe was present or absent in the memory set (see Figure 7.2 for Sternberg WM task design and stimuli timing). Letters in the memory set were pseudo-randomised so that no letter appeared in the same location consecutively or was presented as the probe twice in succession. Probe letters had a 50% probability of being present in the memory set. The trial sequence and task instructions were identical for all participants. Participants were instructed to keep their eyes open during the maintenance period of the task, given the strong modulatory effect that closing the eyes can have on alpha power (e.g. Barry, Clarke, Johnstone, Magee, & Rushby, 2007). Participants completed several practice trials prior to beginning the task. Participants completed a total of 52 trials presented in two blocks with a short break between them. Accuracy and response times were recorded for each participant. Any responses made outside of the 2000ms response period were considered incorrect.

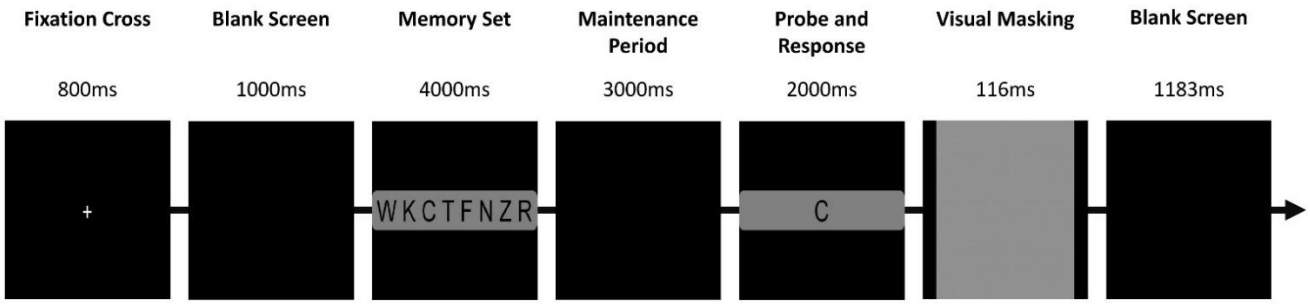

Figure 7.2. Sequence and timing of stimuli for the Sternberg WM task.

7.4.6. Electrophysiological recording and pre-processing

EEG recording was conducted in an electrically shielded, darkened, and sound-attenuated room using Neuroscan Acquire software and a Synamps 2 amplifier (Compumedics, Melbourne Australia). Thirty-four single Ag/AgCl scalp electrodes were positioned according to the 10-20 system (AF3, AF4, F5, F3, F1, FZ, F2, F4, F6, FC5, FC1, FCZ, FC2, FC6, C3, C1, CZ, C2, C4, P7, P5, P3, P1, PZ, P2, P4, P6, P8, PO3, POZ, PO4, O1, OZ, O2), while eye movement was measured using four electrodes placed above and below the left orbit and adjacent to the outer canthus of each eye. Electrodes were grounded to AFz and referenced online to an electrode between Cz and CPz. Impedances were kept below 5 kΩ prior to recording. EEG was sampled at 1000 Hz with a bandpass of 0.1-100 Hz.

Data was analysed offline in MATLAB (The Mathworks, Natick, MA) using EEGLAB for pre-processing (sccn.ucsd.edu/eeglab) (Delorme & Makeig, 2004) and fieldtrip for frequency analysis (http://www.ru.nl/donders/fieldtrip) (Oostenveld et al., 2011). A second-order Butterworth filter with a bandpass of 1-80 Hz and a band-stop filter of 45-55 Hz (12 dB/octave roll-off) was applied to the data. Data was epoched into 11500ms segments extending from the onset of the fixation cross to the middle of the blank screen for each trial. Incorrect trials were excluded from further analysis. Single electrodes were rejected if they displayed artifacts in more than 5% of trials, indicated by values exceeding -100 or 30 dB in

the 25-45 Hz range or voltages larger than 250μv. Individual epochs were rejected if they displayed kurtosis values > 5 for all electrodes or more than -100 to 30 dB in the 25-45Hz range. Artifact rejections were then manually checked by a trained researcher (OWM). Remaining artifacts related to eye movements and muscle activity were then manually identified and removed with fast independent component analysis (FastICA) using 'symmetric approach' and the 'tanh' contrast function. Visual identification of artifacts was conducted using criteria outlined in previous research (e.g. Chaumon, Bishop, & Busch, 2015; Delorme & Makeig, 2004) and is consistent with previous studies examining WM-related oscillatory activity in healthy and depressed individuals (Bailey et al., 2018). Missing channels were then interpolated using the 'spherical' function and recordings were re-referenced offline to an average reference. Following cleaning of EEG data and removal of epochs with excessive artifacts, all remaining participants had a minimum of 20 noise-free epochs available for analysis and the average number of epochs accepted for final analysis did not significant differ between the stimulation groups ($p > .05$).

7.4.7. Spectral analysis

EEG data was converted into the frequency domain using Morlet Wavelet Transform (3.5 oscillation cycles with steps of 1 Hz). Neural oscillatory power was calculated within the theta (4 - 7 Hz), upper alpha (10 - 12.5 Hz), and gamma (35 - 45 Hz) frequency bands. These frequency ranges were selected to correspond with previous research examining oscillatory activity during WM processing and the Sternberg task (Bailey et al., 2014; Hill et al., 2017; Howard, 2003; Hsieh et al., 2011; Roberts et al., 2013; Segrave et al., 2010). Oscillatory power during WM processing was calculated as event-related synchronisation / desynchronisation (ERS/ERD%) using the formula: [(Active - Reference) / Reference) x 100)], which provides positive values when oscillatory power increases in the active period relative to the reference period (i.e. neural synchronisation). The reference period used for

baseline correction was defined as the middle 600ms of the blank screen between the fixation cross and memory set. ERS/ERD% for each frequency band was calculated across the encoding (1800-5800 ms) and maintenance (5800-8800 ms) periods separately and then the encoding and maintenance values were separately averaged over trials for each participant.

7.4.8. Statistical analysis

All statistical analyses were performed using either MATLAB or IBM SPSS Statistics, version 25 (IBM Corp, Armonk, NY). Chi-square tests were used to assess the effectiveness of stimulation blinding between groups.

7.4.8.1. Cognitive data

Accuracy and response time on the Sternberg WM task were used as the primary WM outcome measures. One-way ANOVAs were used to confirm that stimulation conditions did not significantly differ in accuracy or response time at BASELINE (*p's* > .822). Effects of tES on accuracy and response time were first assessed using separate 3x3 mixed ANOVAs with CONDITION (sham, tDCS, and tRNS) as the between subjects factor and TIME (BASELINE, POST-1, and POST-2) as the within-subjects factor. Significant interaction effects were further explored via separate repeated measures ANOVAs for each stimulation condition to examine changes over TIME (BASELINE, POST-1, POST-2). Additionally, one-way ANOVAs were used to compare change-from-baseline (i.e., POST-1 - BASELINE, POST-2 - BASELINE) scores (Δ-scores) between stimulation conditions at each time-point (Δ-POST-1, Δ-POST-2). Analysis of Δ-scores allows for a direct comparison of whether changes in WM performance significantly differed between stimulation conditions, and is consistent with previous research examining tES-induced changes in WM performance (Hill et al., 2018; Zaehle et al., 2011). Bonferroni-corrected pairwise comparisons were used to

explore any significant main effects. Mauchly's test was used to evaluate the assumption of sphericity, with Greenhouse-Geisser corrections applied where appropriate.

7.4.8.2. EEG data

Effects of tES on task-related oscillatory activity were examined via non-parametric cluster-based permutation analyses using the Fieldtrip toolbox (Oostenveld et al., 2011). This technique examines changes in oscillatory activity across all EEG electrodes whilst controlling for multiple comparisons (Maris & Oostenveld, 2007) and has previously been used to examine effects of tES on WM-related oscillatory activity (Hill et al., 2017, 2018). Clusters were defined as two or more neighbouring electrodes with a t-statistic < .05. Two-tailed Monte Carlo *p*-values were subsequently calculated using 2000 permutations. Balancing of stimulation groups on oscillatory activity at BASELINE was confirmed using one-way ANOVAs which were non-significant for theta, upper alpha, and gamma power during WM encoding and maintenance (all $p > .05$). Effects of tES on oscillatory activity were first examined using separate repeated measures ANOVAs for each stimulation group to compare changes in oscillatory activity over time from BASELINE to POST-1 or POST-2. When any significant changes in oscillatory activity were observed over time, further comparisons were conducted using Δ-scores to examine whether effects on oscillatory activity significantly differed between stimulation conditions.

7.5. Results

7.5.1. Demographic and clinical measures

The stimulation groups did not significantly differ in age, years of formal education, WM ability, state or trait anxiety, or depression severity (see Table 7.1 for demographic and clinical characteristics of the participants).

Table 7.1.

Participant demographic characteristics (mean ± SD).

	Sham	tDCS	tRNS	F-statistic	*p*-value
Sample (*n*)	17	16	16		
Gender (F/M)	10 / 7	9 / 7	10 / 6		
Age (years)	28.34 ± 10.56	28.58 ± 7.24	28.47 ± 10.56	0.003	.997
Years of education	14.00 ± 1.84	14.19 ± 1.60	13.69 ± 1.54	0.368	.694
WAIS-IV WMI	106.00 ± 12.63	106.69 ± 13.82	107.94 ± 11.80	0.097	.908
HAM-D	17.35 ± 2.26	16.69 ± 2.33	17.00 ± 2.94	0.287	.752
QIDS	13.94 ± 2.25	13.19 ± 1.87	14.13 ± 2.66	0.763	.472
STAI - State	41.47 ± 13.07	43.06 ± 9.40	41.81 ± 9.03	0.100	.905
STAI - Trait	51.35 ± 12.07	57.50 ± 6.42	58.94 ± 10.78	2.646	.082
Medications					
None	10	6	7		
SSRI	6	3	6		
SNRI	1	3	1		
Tricyclic	0	1	1		
Atypical	0	3	1		

Degrees of freedom = 48 for all comparisons. $^{*}p = .05$; $^{**}p = .01$

Note: WAIS-IV WMI = Wechsler Adult Intelligence Scale, Fourth Edition – Working Memory Index; STAI = State-Trait Anxiety Inventory; HAM-D = Hamilton Depression

Rating Scale; QIDS = Quick Inventory of Depressive Symptomology; SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor; Tricyclic = Tricyclic Antidepressant; Atypical = Atypical Antidepressant.

7.5.2. Effects of tES on Sternberg WM task performance

7.5.2.1. Accuracy

Within-group comparisons

A significant time by stimulation interaction was observed for Sternberg WM task accuracy ($F(4,92) = 2.705$, $p = .035$, $\eta_p^2 = .105$). Examination of stimulation groups separately indicated that WM accuracy significantly increased from BASELINE to POST-1 for the sham (mean difference = 5.54, $p = .009$), tDCS (mean difference = 5.77, $p = .035$), and tRNS groups (mean difference = 5.41, $p = .019$) (Figure 7.3). When compared to BASELINE performance, WM accuracy remained significantly higher at POST-2 for sham (mean difference = 5.66, $p = .034$) and tDCS groups (mean difference = 6.85, $p = .018$), whereas the tRNS group did not display significant differences in WM accuracy from BASELINE to POST-2 (mean difference = 0.60, $p = .999$) (Figure 7.3).

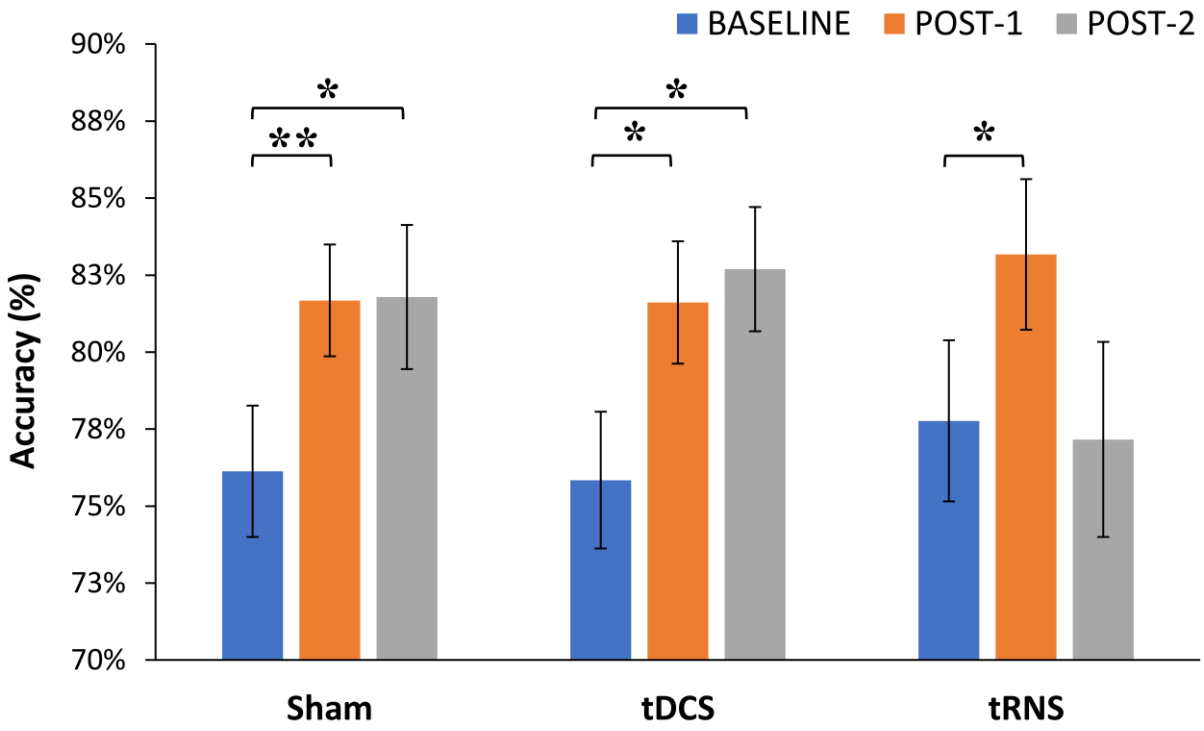

Figure 7.3. Accuracy on the Sternberg WM task across the three time points (BASELINE, POST-1, POST-2). Error bars denote standard error of the mean. * $p < .05$. ** $p < .01$.

Between-group comparisons

Between-group comparisons indicated that stimulation conditions did not significantly differ in their effects on accuracy from BASELINE to POST-1 ($F(2,48) = 0.010$, $p = .990$, $\eta_p^2 < .001$) (Figure 7.4A), whereas significant differences were observed in the effects of stimulation condition from BASELINE to POST-2 ($F(2,48) = 3.743$, $p = .031$, $\eta_p^2 = .140$) (Figure 7.4B). Specifically, the tDCS group displayed significantly greater improvements in accuracy from BASELINE to POST-2 when compared to the tRNS group (mean difference = 7.452, $p = .044$), whereas no differences were observed between the tDCS and sham group (mean difference = 1.195, $p > .999$), or the tRNS and sham group (mean difference = 6.257, $p = .107$) (Figure 7.4B).

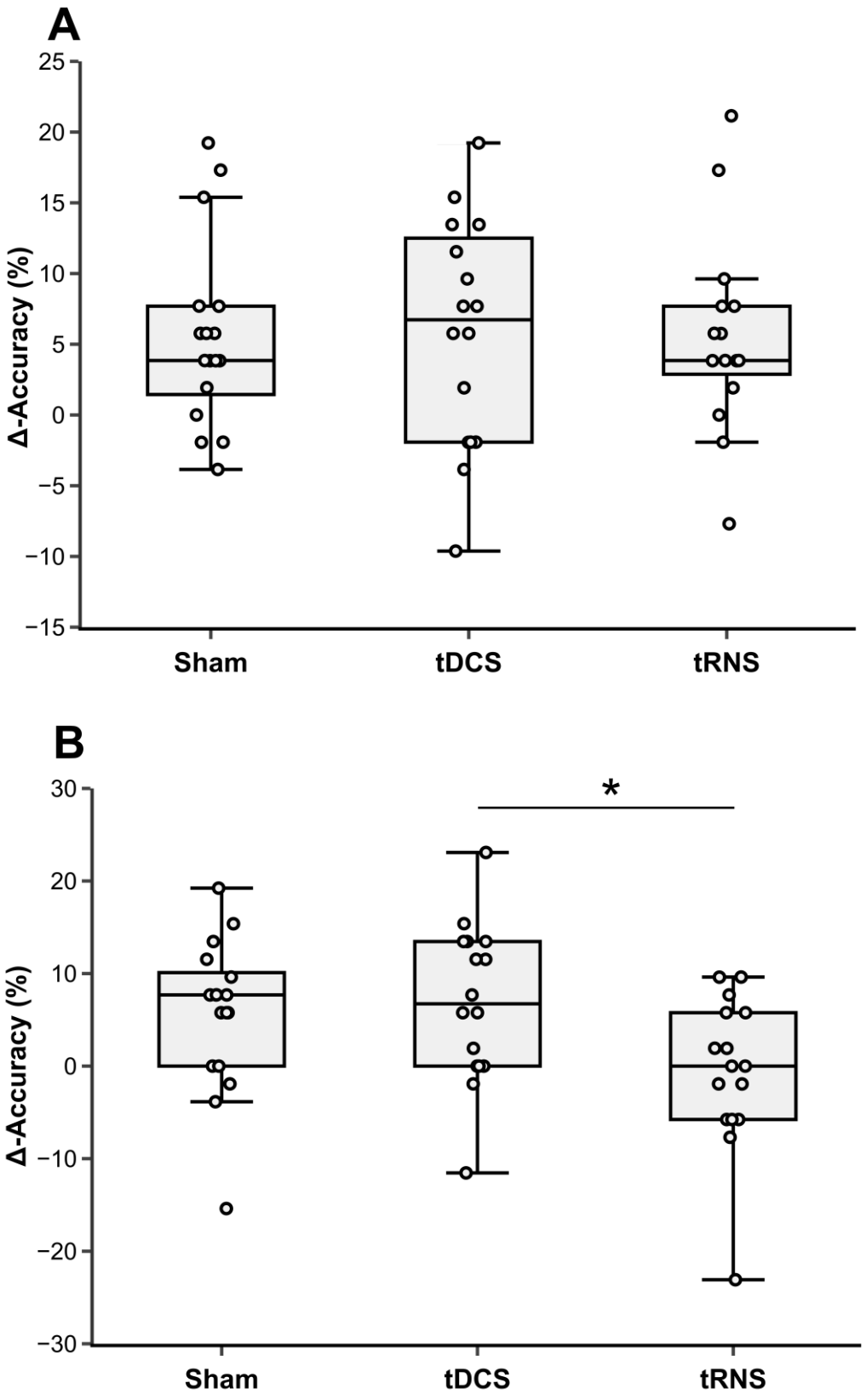

Figure 7.4. Box-and-whisker plots showing change-from-baseline scores (Δ-scores) for Sternberg WM task accuracy at POST-1 (A) and POST-2 (B). Individual participant data

points are overlaid (hollow circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Significant differences between groups are highlighted with an asterisk (* $p < .05$).

7.5.3. Response time

Response time significantly improved over time for all stimulation conditions (sham: $F(2,32) = 7.727$, $p = .002$, $\eta_p^2 = .326$; tDCS: $F(2,30) = 13.872$, $p < .001$, $\eta_p^2 = .480$; tRNS: $F(2,30) = 7.747$, $p = .002$, $\eta_p^2 = .341$), however, no significant differences were observed between stimulation conditions ($F(2,46) = 0.172$, $p = .843$, $\eta_p^2 = .007$), and no time by stimulation interaction was observed ($F(4,92) = 1.901$, $p = .117$, $\eta_p^2 = .076$) (Table 7.2).

Table 7.2.

Response time on the Sternberg WM task for sham, tDCS, and tRNS groups (mean ± SD).

	BASELINE	POST-1	POST-2
Sham	1125.66 ± 153.55	1025.49 ± 143.55	1057.02 ± 115.78
tDCS	1103.95 ± 139.2	1040.39 ± 156.56	982.03 ± 145.38
tRNS	1105.38 ± 168.32	1034.83 ± 135.81	1027.91 ± 139.51

7.5.4. Effects of tES on oscillatory activity during working memory processing

7.5.4.1. Within-group comparisons

Sham

No significant effects of sham stimulation were observed at either timepoint for theta, upper alpha, or gamma ERS/ERD% (all *p's* > .05).

tDCS

At POST-1 (immediately following tDCS), a significant increase in upper alpha ERS/ERD% during WM maintenance was observed bilaterally over parieto-occipital regions (p = .005) (Figure 7.5). Increased upper alpha ERS/ERD% during WM maintenance was also observed at POST-2 (on EEG recorded 25-minutes following tDCS), which was present over left frontal regions (p = .026) and bilaterally over parieto-occipital regions (p < .001) (Figure 7.6). The tDCS group did not display any significant changes in encoding period upper alpha ERS/ERD% from BASELINE to POST-1 or POST-2, nor were any significant changes observed in encoding or maintenance period theta or gamma ERS/ERD% from BASELINE to POST-1 or POST-2 (all p's > .05).

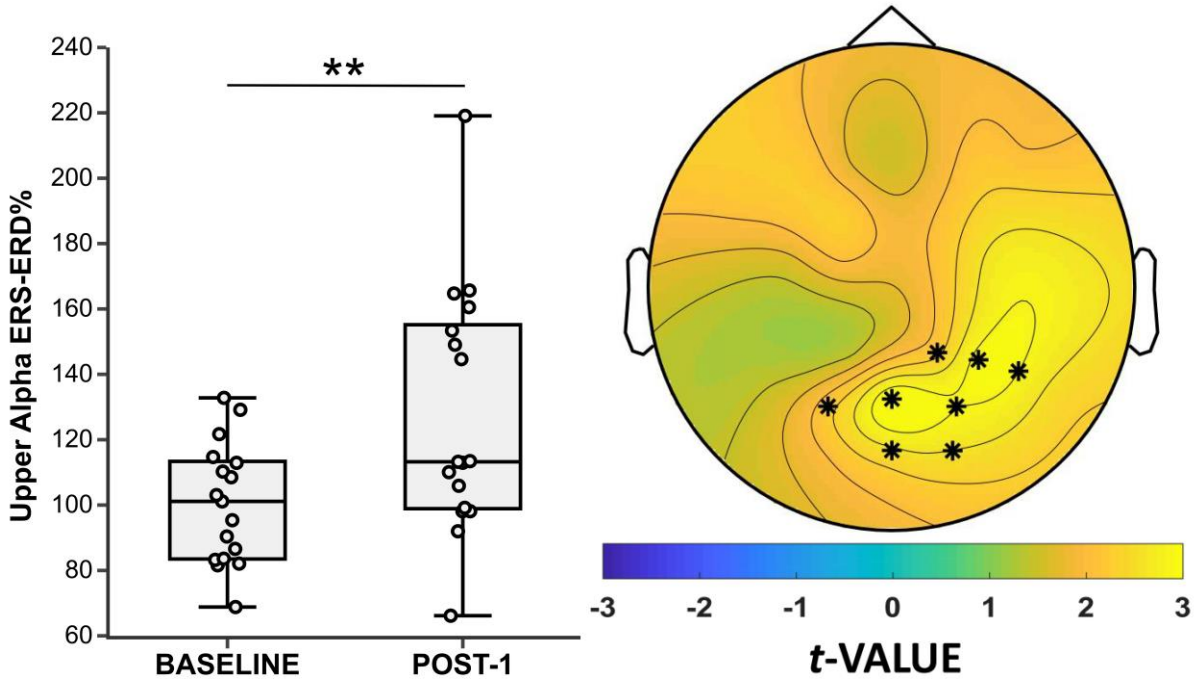

Figure 7.5. Difference in maintenance period upper alpha ERS/ERD% from BASELINE to POST-1 for the tDCS group. Box-and-whisker plot displays upper alpha ERS/ERD% at

BASELINE and POST-1 averaged across electrodes from the significant parieto-occipital cluster (**p < .01), with individual participant data points overlaid (hollow circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Topographical map displays differences in oscillatory ERS/ERD% (POST-1 - BASELINE), with EEG electrodes forming significant clusters marked by stars (p < .01).

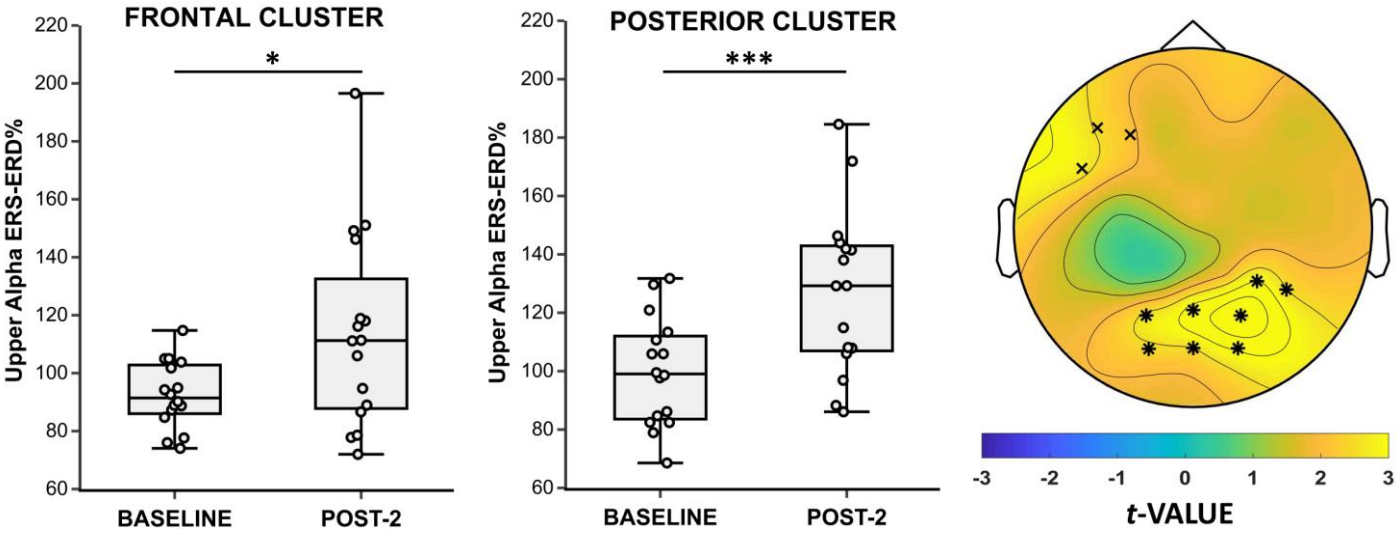

Figure 7.6. Difference in maintenance period upper alpha ERS/ERD% from BASELINE to POST-2 for the tDCS group. Box-and-whisker plot displays upper alpha ERS/ERD% at BASELINE and POST-2 averaged across electrodes from the significant clusters (*p < .05, **p < .01, ***p < .001), with individual participant data points overlaid (hollow circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Topographical map displays differences in oscillatory ERS/ERD% (POST-2 - BASELINE), with EEG electrodes forming significant clusters marked by black crosses (p < .05) and stars (p < .01).

tRNS

Following tRNS, increased WM maintenance period upper alpha ERS/ERD% was observed over right frontal regions on EEG recorded 25-minutes post-stimulation (POST-2) (p = .029) (Figure 7.7). The tRNS group did not display any significant changes in encoding period upper alpha ERS/ERD% from BASELINE to POST-1 or POST-2, nor were any significant changes in encoding or maintenance period theta or gamma ERS/ERD% observed from BASELINE to POST-1 or POST-2 (all p > .05).

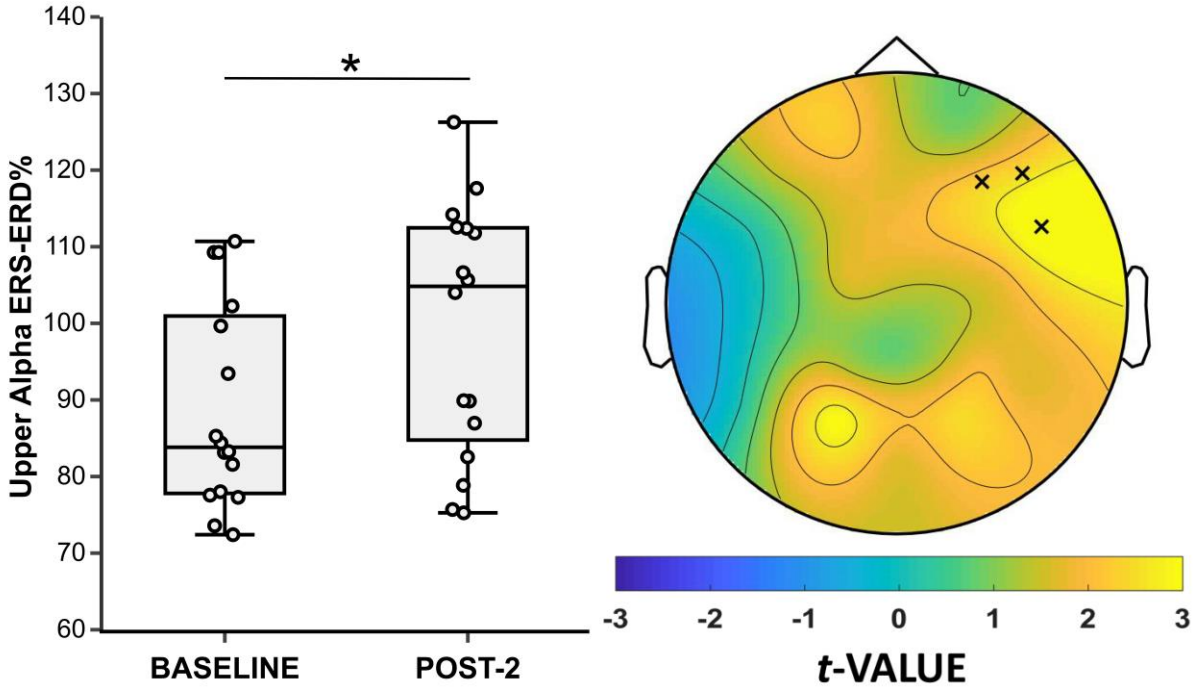

Figure 7.7. Difference in maintenance period upper alpha power from BASELINE to POST-2 for the tRNS group. Box-and-whisker plot displays upper alpha ERS/ERD% averaged across electrodes from the significant frontal cluster at BASELINE and POST-2 (*p < .05), with individual participant data points overlaid (hollow circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Topographical map displays differences in oscillatory ERS/ERD% (POST-2 - BASELINE), with EEG electrodes forming significant clusters marked by black crosses (p < .05).

7.5.4.2. Between-group comparisons

When compared to sham stimulation, tDCS was associated with significantly larger increases in maintenance period parieto-occipital upper alpha power from BASELINE to POST-1 (p = .018) (Figure 7.8A), and from BASELINE to POST-2 (p = .030) (Figure 7.8B). In contrast, changes in maintenance period upper alpha power did not significantly differ between the tRNS and sham groups at POST-1 or POST-2 (all $p > .05$). Exploratory correlations did not reveal any significant relationships between Δ-scores for WM accuracy and oscillatory activity (all p*'s* > .05).

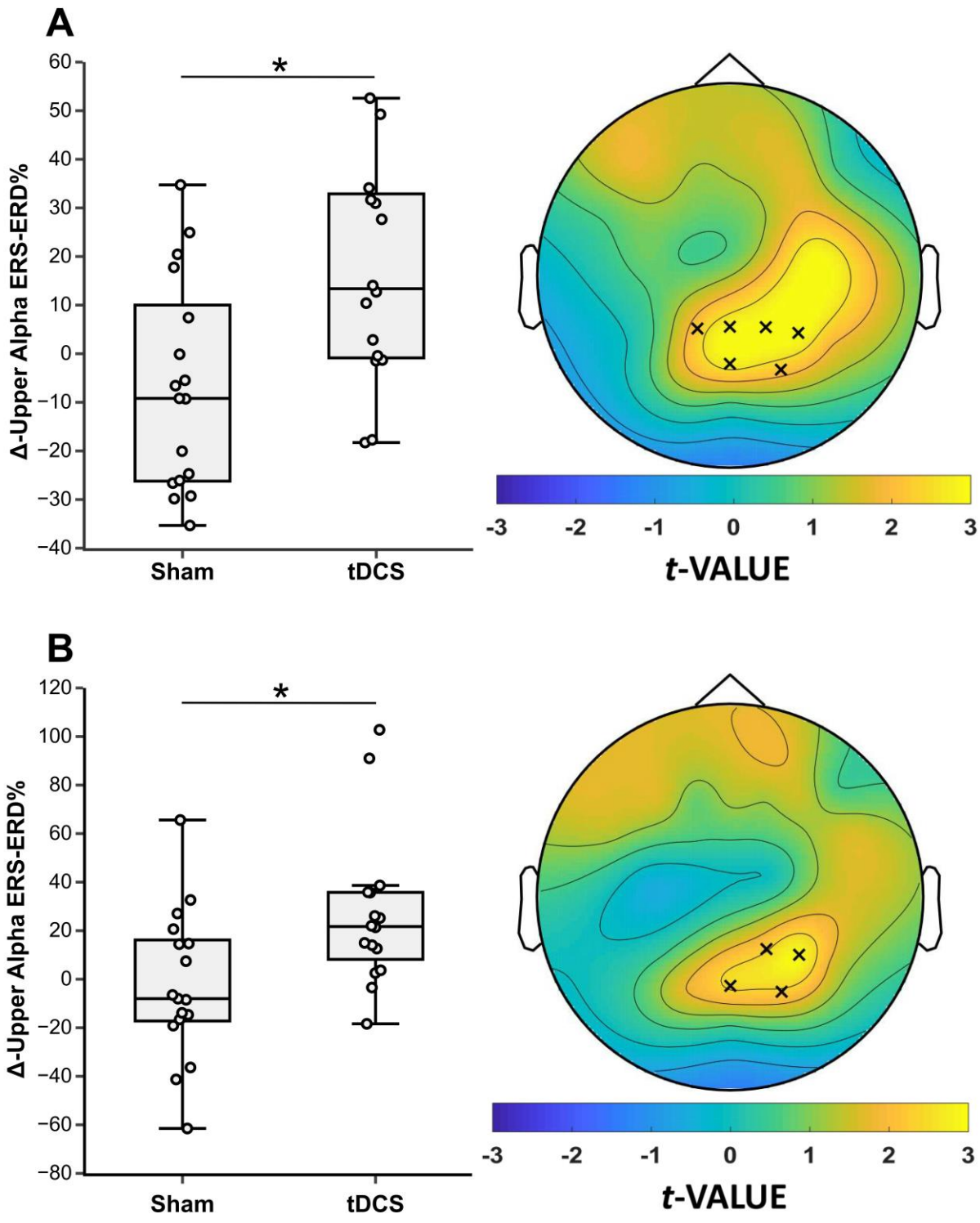

Figure 7.8. Comparison of maintenance period Δ-upper alpha power for the tDCS and sham conditions at POST-1 (A) and POST-2 (B). Box-and-whisker plot displays Δ-upper alpha ERS/ERD% averaged across electrodes from the significant cluster (*p < .05), with individual participant data points overlaid (hollow circles). Boxes extend from the 25th to 75th percentiles with the median represented by a horizontal line. Topographical map

displays differences in oscillatory power when comparing tDCS and sham at POST-1 (A) and POST-2 (B), with EEG electrodes forming significant clusters marked by black crosses ($p < .05$).

7.5.5. tES tolerability and blinding integrity

All stimulation conditions were well tolerated, and no significant, prominent, or persistent adverse effects were reported. Twenty-three of the 49 participants (46.94%) reported minor adverse effects whilst receiving tES, including: slight itching or discomfort under the electrode (15 participants), mild burning sensation (2 participants), or a mild headache (10 participants). The incidence of each minor adverse effect did not significantly differ between the three stimulation conditions (all $p > .05$). Participants were unable to guess at better than chance level whether they had received active or sham stimulation (χ^2 (1, N = 49), = 1.289, $p = .525$), indicating that adequate blinding of stimulation conditions was maintained.

7.6. Discussion

The aim of the present study was to directly compare the effects of tDCS and tRNS + DC-offset on cognitive and neurophysiological measures of WM in MDD. Contrary to our hypotheses, neither tDCS nor tRNS improved WM performance to a significantly greater degree than sham stimulation. However, the tDCS condition did show greater improvements in accuracy than the tRNS condition 25 minutes following stimulation. When examining the effects of each stimulation condition separately, both tDCS and tRNS significantly increased upper alpha ERS/ERD% during the WM maintenance period, whereas no significant changes in oscillatory activity were observed following sham stimulation. When comparing these oscillatory changes between stimulation conditions, increases in upper alpha remained

significant for the tDCS group but not for the tRNS group. These findings demonstrate the capacity of tDCS to induce alterations in WM-related neurophysiological activity which persist beyond the end of stimulation, however the absence of significant improvements in or relationships to WM performance indicated that these neurobiological effects were not sufficient to reliably enhance cognitive function in MDD.

7.6.1. Effects of tES on working memory performance

Examination of cognitive performance indicated subtle yet significant improvements in WM accuracy and response time for all stimulation conditions, however, neither tDCS nor tRNS improved WM performance to a significantly greater degree than sham stimulation, suggesting the improvements may reflect practice effects rather than an effect of the stimulation. When considering each stimulation condition separately, both sham and tDCS groups displayed significant improvements in WM accuracy on immediate and delayed cognitive testing, whereas WM accuracy for the tRNS group increased immediately following stimulation but then returned to pre-stimulation levels on delayed testing. Contrary to our hypothesis, direct comparison of active stimulation conditions on delayed testing revealed that tDCS improved WM accuracy to a significantly greater degree than tRNS.

The absence of cognitive modulation compared to sham following a single session of tDCS in the current study contrasts with several previous studies in MDD which observed increases in WM performance following single session stimulation (Boggio et al., 2007; Loo et al., 2012; Moreno et al., 2015; Oliveira et al., 2013; Wolkenstein & Plewnia, 2013). The cognitive effects of tDCS are known to be highly variable between studies and individuals (Jacobson, Koslowsky, et al., 2012), and this variability is influenced by a complex interaction between stimulation parameters and individual characteristics (e.g. age, skull thickness, presence of psychiatric illness, etc.) (Chew, Ho, & Loo, 2015; Li et al., 2015). Stimulation parameters, in particular the variation in current density (i.e. the ratio of injected

current divided by the surface area of stimulation electrodes; mA/cm^2), may have influenced the discrepant results of the current study. The current study delivered tDCS with a low current density (0.029 mA/cm^2), which has been shown to enhance WM performance in healthy individuals (e.g. Andrews et al., 2011; Fregni et al., 2005; Jeon & Han, 2012; Ohn et al., 2008), and in MDD (Fregni, Boggio, Nitsche, Rigonatti, et al., 2006). However, a recent meta-analysis indicated that higher current densities may be more effective for enhancing WM performance in clinical populations such as MDD (Hill et al., 2016), raising the possibility that the current density delivered in the present study was insufficient to induce reliable WM improvements. Still, large variability exists in studies of the cognitive effects of tDCS even when delivering a higher current density. For instance, several studies have reported enhanced WM performance in MDD when delivering tDCS with higher current densities (0.057 - 0.080 mA/cm^2) (Boggio et al., 2007; Loo et al., 2012; Moreno et al., 2015; Oliveira et al., 2013), whereas others have failed to replicate these findings (Brunoni, Moffa, et al., 2016; Loo et al., 2010; Martin et al., 2018; Wolkenstein & Plewnia, 2013). The current findings are therefore consistent with the presence of broad variability in the cognitive effects of tDCS and suggest that delivery of tDCS using the current parameters is insufficient to induce reliable enhancements of WM performance in MDD. Importantly, however, while the current study balanced stimulation groups on demographic and clinical variables which have been shown to influence the outcome of tES, the use of a parallel groups design inevitably contributed to variability in the outcomes due to heterogeneity in individual characteristics between groups. Future large-scale research studies using a within-groups design sizes will allow for greater consideration of individual characteristics which influence the outcome of tES, and thereby better inform the factors contributing to variability in the cognitive and neurophysiological response to stimulation.

The results showed that a single session of tRNS + DC-offset to the left DLPFC did not induce any significant changes in WM performance when compared to sham stimulation. We are not aware of any previous sham-controlled studies applying tRNS in MDD, either with or without a DC-offset, and evidence regarding the cognitive effects of tRNS in healthy individuals is mixed. The current findings are broadly consistent with research in healthy individuals by Mulquiney, Hoy, Daskalakis, and Fitzgerald (2011), who reported that a single session of anodal tDCS improved WM performance whereas no significant improvements were observed following tRNS. However, while Mulquiney et al. examined effects of tRNS without a DC-offset, the current study delivered tRNS with a 1 mA DC-offset which maintains a consistent polarity at stimulation electrodes and thereby combines the characteristics of tDCS (i.e. net polarisation of neuronal membrane potentials) and tRNS (i.e. introducing noise into the neural system) (Ho et al., 2015). Interestingly, we previously found that delivering tRNS + DC-offset in healthy individuals increased WM performance to a significantly greater degree than both anodal tDCS and sham stimulation (Murphy et al., in submission). These contrasting findings may relate to state-dependent effects of tRNS - stimulation protocols which demonstrate efficacy in healthy populations may induce different cognitive and neurophysiological effects when delivered in MDD (Gögler et al., 2017; Moreno et al., 2015). Hence, while the current study did not observe significant WM improvements following a single session of tRNS + DC-offset, further research is warranted to investigate whether tRNS may induce more pronounced effects if delivered using different stimulation parameters.

7.6.2. Effects of tES on oscillatory activity during working memory processing

We found that tDCS significantly increased upper alpha ERS/ERD% over parieto-occipital regions during the WM maintenance period. Upper alpha oscillations have been functionally linked to inhibitory processes which facilitate efficient cognitive processing via

suppression of non-task relevant neural regions during cognitive activity (Klimesch, 2012; Klimesch et al., 2007; Zanto, Rubens, Thangavel, & Gazzaley, 2011). Within this framework, increased posterior upper alpha power during the maintenance phase of the Sternberg WM task following tDCS would indicate greater functional inhibition of visual processing regions which may interfere with the active maintenance of WM stimuli (Klimesch, 2012; Klimesch et al., 2007). Interestingly, several previous studies have reported that individuals with MDD display abnormal modulation of upper alpha activity during the maintenance phase of the Sternberg WM task, which has been interpreted as indicating dysfunctional inhibitory processes in MDD (Bailey et al., 2014; Segrave et al., 2010). Moreover, we previously observed that the current cohort of participants with MDD displayed significantly less posterior upper alpha ERS/ERD% during WM maintenance when compared to a sample of healthy controls balanced on age, gender, and WM ability (Murphy et al., 2019a). Given this, increases in maintenance period upper alpha power following tDCS may indicate a shift towards normalisation of altered WM-related oscillatory activity in MDD. However, the absence of improvements in WM performance or relationship between neurophysiological changes and WM performance indicate that these neurobiological changes are insufficient to produce observable enhancements in WM performance in a sample of individuals with MDD.

When examining the electrophysiological effects of tRNS over time we observed changes consistent with our hypothesis, reflected by increases in upper alpha during WM maintenance on EEG recorded 25-miuntes post-stimulation. However, these changes did not significantly differ from sham stimulation, indicating that delivery of tRNS + DC-offset with the current parameters is not sufficient to induce substantial or persistent changes in WM-related oscillatory activity in MDD. We previously demonstrated the potential of tRNS + DC-offset to modulate WM-related oscillatory activity in healthy individuals, whereby a single session of tRNS + DC-offset using the same stimulation parameters was found to

significantly increase WM encoding period theta and gamma power when compared to both anodal tDCS and sham stimulation (Murphy et al., submitted for publication). While the cognitive and neurophysiological outcomes of tES are known to be highly variable in healthy individuals, delivering these techniques in clinical conditions such as MDD raises further challenges due to the limited understanding of how tES interacts with MDD-related neural activity to produce observable cognitive improvements. Indeed, there is extremely limited information regarding the optimal tRNS stimulation parameters for modulating cognitive and neurophysiological outcomes in healthy individuals, and this evidence is entirely absent in MDD. Improving the effectiveness and reliability of tRNS as a therapeutic tool will therefore require further research examining the optimal stimulation parameters for modulating cognitive performance in MDD, as well as a greater understanding of the neurophysiological changes underlying these cognitive improvements.

7.7. Concluding remarks

In conclusion, we provide evidence that a single session of anodal tDCS to the left DLPFC induced sustained effects on WM-related oscillatory activity, reflected by increases in upper alpha ERS/ERD% during the WM maintenance phase. The neurophysiological effects of tDCS remained significant when compared to sham stimulation and were consistent across immediate and delayed EEG recordings. Despite this, tDCS did not enhance WM performance to a significantly greater degree than sham stimulation, indicating that these neurobiological effects were insufficient to translate into observable cognitive improvements in a sample of individuals with MDD. We also found that delivery of tRNS using the current stimulation parameters did not induce significant changes in cognitive or neurophysiological measures of WM when compared to sham stimulation. The current study supports the potential of tDCS to modulate WM-related neural activity in MDD and highlights the utility

of EEG for assessing the underlying neurophysiological effects of tES. Research investigating whether delivery of tDCS or tRNS techniques with alternative stimulation parameters or repeated sessions may produce more pronounced neurophysiological alterations and observable improvements in WM performance in MDD.

7.8. Disclosures and conflicts of interest

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CHAPTER EIGHT

General Discussion

8.1. General Overview and Summary of Findings

Major Depressive Disorder (MDD) is a highly prevalent psychiatric illness associated with significant rates of morbidity and mortality (Kessler et al., 2009, 2005a). Individuals with MDD commonly display impairments in working memory (WM), a cognitive system which encompasses the encoding, short-term maintenance, and manipulation of information related to goal-oriented behaviour (Baddeley, 2002). Current psychopharmaceutical and counselling treatments are relatively ineffective for remediating the cognitive symptoms of MDD (Herrera-Guzmán et al., 2010; Raskin et al., 2007), and impairments in cognitive function often persist following remission of affective symptoms (Conradi et al., 2011; Snyder, 2013). Established treatments for MDD also possess a number of practical limitations which limit treatment compliance and accessibility. These limitations highlight the need to develop alternative interventions which are more effective, reliable, and accessible for improving WM functioning in MDD. To do so requires a greater understanding of how the neurobiological processes underlying WM processing are altered in MDD, and how these neurobiological changes relate to cognitive functioning, as well as identification of interventions that can modulate them.

Non-invasive transcranial electrical stimulation (tES) techniques have shown promise as a means to enhance WM performance in healthy individuals and those with MDD when delivered to the dorsolateral prefrontal cortex (DLPFC) (Andrews et al., 2011; Boggio et al., 2007; Fregni et al., 2005; Moreno et al., 2015). Early studies provided promising proof-of-principle evidence of improved WM performance following a single session of transcranial direct current stimulation (tDCS) in healthy individuals and MDD (Boggio et al., 2007; Fregni et al., 2005). However, more recent studies and meta-analyses have shown that when the patterns of results across large numbers of tDCS studies are considered, it is apparent that effects on WM performance are often modest in size and highly variable between individuals

(Hill et al., 2016; Martin et al., 2018; Nikolin et al., 2018). Transcranial random noise stimulation (tRNS) is another form of tES which has been shown to enhance WM performance in healthy and clinical populations (Popescu et al., 2016; Snowball et al., 2013). Importantly, the neuromodulatory effects of tRNS are believed to rely upon different underlying neurobiological mechanisms to tDCS, raising the possibility that tRNS may overcome some of the factors contributing to high variability in tDCS outcomes (Fertonani & Miniussi, 2017; Ho et al., 2015; Moliadze et al., 2014; Prichard et al., 2014; Terney et al., 2008). Consistent with this, several studies have demonstrated that tRNS and may induce more pronounced neurophysiological and behavioural effects than anodal tDCS (Fertonani et al., 2011; Inukai et al., 2016). However, there is very little research investigating the cognitive effects of tRNS in healthy individuals, only a single case study has applied this technique in MDD (Chan et al., 2012). The neurophysiological mechanisms underlying the effects of tRNS are largely unknown. For both tDCS and tRNS, a greater understanding of how stimulation influences underlying neurobiological activity and how these effects facilitate cognitive processing could help improve the reliability of cognitive outcomes. One method to investigate the neurobiological effects of tES and how they relate to cognitive modulation is through recording of task-related electroencephalography (EEG) to examine changes in WM-related oscillatory activity.

Therefore, the aim of the current thesis was to compare the cognitive and neurophysiological effects of tDCS and tRNS in healthy individuals and in MDD, and to better characterise the pattern of neural oscillatory activity associated with WM encoding and online maintenance in MDD. To achieve these aims, three studies were conducted:

- Study One used task-related EEG to investigate the presence of alterations in oscillatory activity during WM encoding and online maintenance in MDD, as

compared to a sample of healthy individuals closely balanced on potentially confounding demographic and cognitive variables.

- Study Two compared the effects of a single session of tDCS vs tRNS vs sham stimulation on cognitive and neurophysiological measures of WM in healthy individuals, using task-related EEG to examine effects of tES on oscillatory activity during WM encoding and online information maintenance.
- Study Three compared the effects of a single session of tDCS vs tRNS vs sham stimulation on cognitive and neurophysiological measures of WM in individuals with MDD, using task-related EEG to examine effects of tES on oscillatory activity during WM encoding and online information maintenance.

Collectively, this series of studies demonstrated that individuals with MDD display prominent alterations in oscillatory activity during WM processing, which were present even when achieving the same level of WM performance as healthy controls. We also demonstrated that both tDCS and tRNS can modulate aspects of altered WM-related oscillatory activity in MDD. Finally, the findings also specifically supported tRNS as a means to enhance WM performance and modulate underlying task-related neurophysiological activity in healthy individuals. The following provides a more detailed summary of the main findings from each study.

8.1.1. Study One: Individuals with Depression Display Abnormal Modulation of Neural Oscillatory Activity during Working Memory Encoding and Maintenance

Modulation of oscillatory activity within the theta, upper alpha, and gamma frequency ranges is believed to play a crucial role in supporting WM encoding and maintenance, however there have previously only been three studies examining potential alterations in

WM-related oscillatory activity in MDD and existing evidence is conflicting. The first study in this thesis aimed to improve characterisation of the neurophysiological processes underlying WM processing in MDD using EEG recording. Participants included 46 individuals with MDD and 41 healthy controls, thereby making this the largest study to date to examine MDD-related alterations in oscillatory activity during WM processing. Importantly, this study overcomes potentially confounding factors inherent in previous research and was the first to balance the healthy and depressed cohorts on WM ability, thereby separating performance driven group differences from WM processing driven differences in WM-related oscillatory activity.

Participants completed the Sternberg WM task to assess WM performance, whilst concurrent EEG was recorded and event-related synchronisation / desynchronisation was calculated for theta, upper alpha, and gamma activity during the encoding and maintenance phases of WM. The findings demonstrated that individuals with MDD display prominent alterations in WM-related oscillatory activity when compared to healthy controls, including less frontal-midline theta power during WM encoding and maintenance, more upper alpha power over occipital regions during WM encoding, as well as less gamma and upper alpha power over occipital regions during WM maintenance. These alterations in WM-related oscillatory activity were related to depressive symptom severity, whereby higher depression severity was associated with greater reductions in upper alpha and gamma power during WM maintenance. Importantly, no correlations were observed between WM performance and oscillatory activity, and the MDD group achieved intact WM performance despite displaying alterations in theta, upper alpha, and gamma power during WM processing. These findings demonstrate that the neural processes associated with WM processing are altered in MDD even when individuals do not display behavioural evidence of WM impairments, thereby suggesting that WM processing in MDD may rely upon different neurophysiological

mechanisms to healthy individuals and challenging the accepted norm that robust modulation of oscillatory activity plays a crucial causal role in supporting WM processing in MDD.

8.1.2. Study Two: Transcranial Random Noise Stimulation is More Effective than Transcranial Direct Current Stimulation for Enhancing Working Memory in Healthy Individuals: Behavioural and Electrophysiological Evidence

Given the limited understanding of the neurobiological effects of tDCS on WM in healthy individuals, and the absence of previous research examining the effects of tRNS on the neurobiological activity underlying WM processing, we aimed to both compare the efficacy of these techniques as a means to enhance WM performance in healthy individuals and to better characterise the neurophysiological changes underlying potential cognitive improvements. To achieve this aim, we allocated 49 healthy individuals to receive either anodal tDCS (N = 16), high frequency tRNS + DC-offset (N = 16), or sham stimulation (N = 17) to the left DLPFC for 20-minutes. The stimulation parameters selected for tDCS and tRNS + DC-offset ensured that both active stimulation conditions delivered an equivalent net change over the course of stimulation, thereby controlling for potentially confounding effects of variance in electrical charge on cognitive and electrophysiological outcomes. Participants completed the Sternberg WM task with concurrent EEG recording before and at 5- and 25-minutes post-stimulation. Event-related synchronisation / desynchronisation was calculated for theta, upper alpha, and gamma activity during the encoding and maintenance phases of WM. It was found that tRNS + DC-offset induced more pronounced and consistent enhancements in WM performance when compared to both tDCS and sham stimulation. tRNS-induced enhancements in WM performance were accompanied by increases in task-related theta and gamma activity during WM encoding, which remained significant when compared to both tDCS and sham stimulation. tDCS did not significantly improve WM

performance or alter any measures of WM-related oscillatory activity when compared to sham stimulation. These findings demonstrate the potential of tRNS + DC-offset to modulate cognitive and electrophysiological measures of WM and indicate that this technique may be more effective and reliable than tDCS for enhancing WM in healthy individuals.

8.1.3. Study Three: Effects of Transcranial Direct Current Stimulation and Transcranial Random Noise Stimulation on Working Memory Performance in Major Depressive Disorder: Behavioural and Electrophysiological Evidence

Study One demonstrated that MDD involves widespread changes in WM-related oscillatory activity when compared to healthy controls, and Study Two indicated that tRNS is more effective than tDCS for enhancing WM performance and modulating WM-related oscillatory activity in healthy individuals. Hence in Study Three we aimed to directly compare the effects of tDCS and tRNS on WM performance and WM-related oscillatory activity in MDD. Forty-nine participants with a previous diagnosis of MDD who were in the midst of a depressive episode were allocated to receive either anodal tDCS (N=16), high-frequency tRNS + DC-offset (N = 16), or sham stimulation (N = 17) over the left DLPFC for a duration of 20-minutes. WM performance and oscillatory activity were examined using the same procedures as Study Two. When compared to sham stimulation, tDCS was associated with significant increases in WM maintenance period upper alpha power on EEG recorded 5- and 25-minutes post-stimulation. We also observed increases in WM maintenance period upper alpha power following tRNS, however these changes did not remain significant when compared to sham stimulation. Despite these neurobiological effects, neither tDCS nor tRNS enhanced WM performance to a significantly greater degree than sham stimulation. Direct comparison of active stimulation conditions indicated that tDCS increased WM task accuracy to a significant greater degree than tRNS. The absence of significant cognitive improvements

when compared to sham stimulation indicates that the neurophysiological alterations induced by these techniques did not translate into observable cognitive improvements in a sample of individuals with MDD. These findings support the potential of tDCS to induce effects on WM-related oscillatory activity which persist beyond the end of stimulation and highlights the utility of EEG as a means to investigate the neurophysiological effects of tES. However, these findings do not support the efficacy of tDCS or tRNS as effective neuromodulatory tools to induce robust improvements in WM performance in MDD.

8.2. Theoretical and Clinical Implications

Taken together, the findings from these studies have significant implications for understanding the neurobiological changes associated with WM processing in MDD, as well as for the capacity of tDCS and tRNS to improve WM performance in healthy individuals and those with MDD. The findings from this thesis also highlight clear differences in the neurophysiological and cognitive outcomes of delivering tES in healthy versus depressed individuals. The primary implications of these findings are discussed in greater detail below.

8.2.1. Understanding the nature of altered WM processing in MDD

Despite considerable academic research, the pathophysiological changes which contribute to WM dysfunction remain poorly understood. EEG-derived measures of oscillatory activity provide a temporally precise means to examine neurophysiological activity during individual phases of WM processing and may therefore inform the nature of altered WM processing in MDD. Previous research had described abnormal modulation of upper alpha power during WM maintenance in acutely depressed individuals, however the direction of changes in alpha modulation, and whether they were detected at all, differs greatly between studies (Bailey et al., 2018, 2014; Segrave et al., 2010). Alterations in upper

alpha power are thought to index dysfunction in top-down driven inhibitory processes, and it was thought that maladaptive patterns of alpha may causally contribute to WM dysfunction in MDD (Bailey et al., 2014; Segrave et al., 2010). However, these studies compared individuals with MDD with WM dysfunction to healthy individuals with intact WM function, and upper alpha power is known to differ based on WM performance alone (Palva et al., 2010). Given this, it was not clear whether the observed group differences in upper alpha power reported in previous studies reflected neurobiological changes related to MDD or were simply an electrophysiological signature resulting from comparison of two groups of individuals with significant differences in WM performance. By comparing oscillatory activity between healthy and depressed individuals with comparable WM performance (both on the experimental task and in WAIS WM index), Study One overcome this methodological limitation and demonstrated that MDD is associated with alterations in upper alpha activity during WM processing even in the absence of observable cognitive impairment. Moreover, the findings of Study One provided the first evidence that individuals with MDD display alterations in theta and upper alpha activity during the initial encoding of WM stimuli, as well as reductions in gamma power during WM maintenance. Collectively, these findings highlight that MDD is associated with widespread alterations in the oscillatory activity which supports WM processing, and that these neurobiological changes can be observed even in the absence of cognitive deficits. These findings raise several important implications for understanding the neurophysiological changes associated with WM processing in MDD.

The overwhelming majority of research characterising the functional significance of theta, upper alpha, and gamma activity for WM processing has been conducted in healthy individuals (e.g. Klimesch, Sauseng, & Hanslmayr, 2007; Roux & Uhlhaas, 2014; Roux, Wibral, Mohr, Singer, & Uhlhaas, 2012) and it is unclear whether oscillations within these frequency bands play a similarly crucial role in supporting WM processing in clinical

conditions such as MDD. While it has been proposed that oscillations within the theta band enable encoding of multiple items in WM (Sauseng et al., 2010), the findings of Study One demonstrate that prominent reductions in frontal theta power during WM encoding and maintenance in MDD did not significantly impair WM performance. Similarly, individuals with MDD achieved intact WM performance despite displaying significantly less upper alpha power WM maintenance, a finding which contrasts with the wide-held view that robust modulation of upper alpha activity is required to protect WM maintenance from interference (Jensen et al., 2002; Klimesch et al., 2007; Roux & Uhlhaas, 2014). Finally, while some researchers have proposed gamma oscillations as a neural substrate responsible for the online maintenance of WM information (e.g. Herrmann, Munk, & Engel, 2004; Roux & Uhlhaas, 2014; Roux, Wibral, Mohr, Singer, & Uhlhaas, 2012), reduced gamma power during WM maintenance in MDD was not associated with any impairments in WM performance. If oscillatory activity within the theta, upper alpha, and gamma frequency ranges is indeed crucial for efficient WM processing, then the presence of widespread alterations in these oscillatory dynamics would be expected to result in notable deficits in cognitive measures of WM performance. The findings of Study One would therefore challenge the assumption that robust modulation of theta, upper alpha, and gamma oscillations are crucial for effective WM performance, at least in MDD.

The dissociation between intact WM performance and intact patterns of oscillatory activity highlights the need for further research investigating the functional significance of oscillatory activity in supporting cognitive processing. Previous research examining the putative role of neural oscillations has primarily utilised correlational designs to characterise the pattern of theta, alpha, and gamma activity associated with high and low cognitive performance or WM load (Howard, 2003; Jensen et al., 2002; Jensen & Tesche, 2002). A reliance on correlational studies limits the ability to determine a causal role of oscillations, as

while it is widely accepted that neural oscillations are causally related to intact cognitive processing the current findings raise the possibility that they are merely associated with it. Determining the potential functional significance, if any, of altered oscillatory activity in MDD will require a deeper understanding of the precise role of oscillatory activity in cognitive processing. Non-invasive stimulation methods may prove useful in elucidating the functional significance of neural oscillations as they can be used to externally entrain or interrupt ongoing oscillatory activity in cortical regions and examine resulting effects on cognitive processing. This has been demonstrated in healthy individuals, whereby delivery of repetitive transcranial magnetic stimulation (rTMS) in the alpha frequency range can enhance alpha power and thereby increase short-term memory capacity (Sauseng et al., 2009). The related brain stimulation technique of transcranial alternating current stimulation (tACS) may also prove useful in this regard. Future research using these techniques to systematically modulate oscillatory activity may therefore elucidate the role of oscillatory activity during WM processing and improve understanding of the functional significance of altered oscillatory activity in MDD. Moreover, the role of oscillatory activity in MDD will be informed by research investigating whether alterations in neural oscillations are more pronounced for depressed individuals with WM dysfunction as compared to those with intact WM function, and whether the magnitude of these oscillatory changes predicts the severity of WM impairments.

8.2.2. tDCS and tRNS to improve cognition in healthy individuals

The past decade has seen significant academic and public interest in the use of tES to enhance cognitive performance in healthy and clinical populations. Early evidence for the therapeutic and cognitive enhancing effects of tDCS led to an exponential increase in academic research, while enthusiastic and often misleading media coverage of this research led to private companies marketing tDCS devices as a simple do-it-yourself gadget for

cognitive enhancement and the treatment of various clinical conditions (Dubljevic, Saigle, et al., 2014). Interest in the application of tES was further bolstered due to their relatively high safety profile, portability, and low cost, making them particularly attractive candidates for widespread application. Despite significant public interest, the enthusiastic adoption of these techniques has preceded robust evidence regarding their efficacy as a means to induce reliable and meaningful cognitive enhancements in healthy individuals. While important questions remain regarding the mechanisms through which tDCS alters cognition, even less is known about tES techniques beyond tDCS, such as tRNS. Study Two aimed to address these gaps in understanding using a sham-controlled design to compare the cognitive and electrophysiological effects of tDCS and tRNS in healthy individuals.

Study Two did not find evidence for the superiority of tDCS over sham stimulation for modulating WM performance or task-related oscillatory activity in healthy individuals. These findings contrast with previous research in healthy individuals which observed significant enhancements and WM performance and modulation of task-related oscillatory activity when delivering a single session of anodal tDCS to the DLPFC with similar stimulation parameters (i.e. 0.029 mA/cm^2 for 10-20 minutes) (Andrews et al., 2011; Hoy et al., 2013; Jeon & Han, 2012; Mulquiney et al., 2011; Zaehle et al., 2011). The cognitive effects of tDCS are known to be highly variable both between individuals, and thus studies, with the outcome of stimulation being dependent on a complex interplay between stimulation parameters and the anatomical, demographic, and psychological characteristics of the individual receiving stimulation (Ammann, Lindquist, & Celnik, 2017; Chew et al., 2015; Li et al., 2015). Whilst differences in participant characteristics may partially explain the contrasting findings between Study Two and past research, the results provide further evidence that the outcome of tDCS are highly variable. A key challenge facing the research

field is whether tDCS can be delivered in a manner which produces more consistent and pronounced outcomes.

Study Two also provided the first evidence that delivery of tRNS + DC-offset in healthy individuals can induce significantly larger improvements in WM performance when compared to both tDCS and sham stimulation. Arguably more important, however, was the finding that improvements in WM performance following tRNS were significantly more consistent than those observed following tDCS. This finding has significant implications for the application of tES in healthy individuals and suggests that tRNS + DC-offset may induce more pronounced and reliable enhancements in cognitive function. While it is likely that many of the same anatomical, demographic, and psychological characteristics which influence the outcome of tDCS also apply to tRNS, the findings of Study Two indicate that effects of tRNS on WM performance are more robust and consistent across healthy individuals when compared to tDCS.

Therefore, the current thesis provides initial evidence that tRNS + DC-offset may overcome some of the factors currently limiting the reliability of tDCS in healthy individuals. Several studies have observed non-linear effects of tDCS stimulation dosage on neurophysiological outcomes, whereby increasing current density or stimulation duration can result in less pronounced or even opposing effects on cortical excitability (Batsikadze et al., 2013; Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche, 2010) and cognitive performance (Benwell et al., 2015; Hoy et al., 2013). One explanation for the non-linear effects of tDCS relates to homeostatic neural mechanisms which are activated following stimulation with a constant direct current and serve to counter-regulate persistent changes in neuronal membrane potentials (Kurachi & Ishii, 2004; Ridding & Ziemann, 2010). In contrast, tRNS + DC-offset delivers a direct current with a randomly fluctuating intensity which may prevent activation of homeostatic mechanisms, thereby resulting in more consistent outcomes

(Fertonani & Miniussi, 2017; Fertonani et al., 2011). The findings of Study Two are consistent with this interpretation and warrant further studies to replicate and extend upon these findings by systematically investigating the consistency of neurophysiological and cognitive outcomes induced by tDCS and tRNS + DC- offset.

8.2.3. The therapeutic application of tDCS and tRNS in MDD

One particularly interesting finding of this thesis is that tDCS and tRNS induced differing neurobiological and cognitive effects in healthy and depressed individuals even when delivering the same stimulation parameters and experimental protocol. For instance, Study Two found that tRNS + DC-offset was superior to both tDCS and sham stimulation for enhancing WM performance and modulating oscillatory activity in healthy individuals, whereas Study Three demonstrated that neither tDCS nor tRNS was superior to sham stimulation for modulating WM performance in MDD. Given that the current sample of healthy and depressed participants were closely balanced on age, gender, and WM ability, these contrasting findings may relate to the state-dependence of tES effects. Namely, the weak electrical current delivered by tDCS and tRNS is of insufficient intensity to directly induce neuronal firing but rather provides subthreshold modulation of ongoing neural activity (Fertonani & Miniussi, 2017; Woods et al., 2016). Given evidence from Study One that WM processing in MDD is associated with widespread changes in oscillatory activity, combined with evidence that the effects of stimulation are crucially dependent on the neural state of the brain at the time of stimulation (Fertonani & Miniussi, 2017; Woods et al., 2016), it is therefore likely that delivery of tES during WM processing in MDD will induce differing neurophysiological and cognitive effects than in healthy individuals.

While it has been established that both tDCS and tRNS hold the potential to modulate neurophysiological activity and cognitive functions, the primary challenge facing tES research concerns how to deliver these techniques in a manner that induces meaningful and

reliable effects. Improving the reliability and efficacy of tES for enhancing cognitive function in MDD requires a greater understanding of the neurobiological processes underlying WM processing in MDD, how tES alters these neurobiological processes, and how these changes translate into cognitive improvement. The current thesis reflects an important initial step towards these goals, firstly by characterising the pattern of altered oscillatory activity associated with WM encoding and maintenance in MDD, and by providing valuable information regarding the effects of tDCS and tRNS on WM performance and WM-related oscillatory activity in MDD. Both tDCS and tRNS can be delivered using a wide variety of stimulation parameters and it is likely that other stimulation protocols would have differing effects on cognitive and neurophysiological outcomes in MDD. For instance, the neurobiological changes associated with MDD may mean that inducing reliable cognitive enhancements requires stimulation to be delivered with higher current densities, longer durations, or different electrode montages. A greater understanding is required of how pathophysiological alterations in brain structure and function influence the outcome of stimulation in psychiatric and neurological conditions, which will assist in developing tES stimulation protocols which are optimised for targeting aberrant neural functioning and thereby improving symptomology in clinical conditions. Continued use of combined cognitive and neurophysiological outcome measures will likely prove beneficial in developing tDCS and tRNS stimulation protocols which are optimised for modulating cognition in these populations.

8.3. Methodological Considerations and Future Directions

8.3.1. Sample size and use of parallel-groups design

As previously discussed, a range of demographic, cognitive, and clinical variables can influence the outcome of tES (e.g. Chew, Ho, & Loo, 2015; Li et al., 2015). Given high variability in the response to tES, research investigating cognitive and neurophysiological effects of stimulation would benefit from large-scale studies using a within-groups design to better control for potential confounding effects of individual characteristics. The current thesis balanced stimulation groups on key variables which have been shown to influence the outcome of tES, including age, gender, WM ability, and in the case of Study Three, depression severity. However, the use of a parallel groups design inevitably contributed to variability in the outcomes due to heterogeneity in individual characteristics between groups. Future large sample research studies using a within-groups design sizes will allow for greater consideration of individual characteristics which influence the outcome of tES, and thereby better inform the factors contributing to variability in the cognitive and neurophysiological response to stimulation. Computational modelling research has proved useful in identifying the role of anatomical characteristics in influencing the outcome of tES (i.e. skull thickness, bone density, etc.), and may therefore reflect a time- and cost-effective means to examine potential effects of other individual characteristics on tES current flow (e.g. Bikson, Rahman, & Datta, 2012; Miniussi, Harris, & Ruzzoli, 2013; Miranda, Lomarev, & Hallett, 2006). Given the broad parameters within which tES can be delivered (e.g. variation in current intensity, stimulation duration, electrode location, etc.), understanding the factors which influence the outcome of stimulation may lead to the development of personalised stimulation protocols which are customised to the specific characteristics of the individual receiving stimulation, and thereby improve reliability and effectiveness of therapeutic and cognitive stimulation.

8.3.2. Working memory assessment

The Sternberg WM task has been widely used in EEG research as it separates different phases of WM so they can be examined independently to each other, however, there are several limitations to this task that are worth considering. Firstly, while the Sternberg WM task demonstrated sufficient sensitivity to identify improvements in WM performance following tRNS in Study Two, it is less sensitive than other measures for identifying subtle improvements in WM performance following tES (Mulquiney et al., 2011; Teo et al., 2011). The temporal separation of WM phases in the Sternberg WM task results in a longer duration for each trial and thereby limits the number of trials which can be completed within an experimental session. In contrast, other measures of WM, such as the *n*-back task, have a faster trial time and therefore many more trials, giving more opportunity to detect change. While the Sternberg WM task is well suited for examining the effects neurophysiological effects of tES on specific WM phases, future studies will benefit from investigating a wider range of WM outcome measures to better identify highly subtle effects of stimulation. Secondly, while we used an eight letters WM span in the Sternberg WM task, future research may benefit from systematically varying the number of stimuli to examine effects of tES across higher versus lower WM loads. Thirdly, the Sternberg WM task used in the current study provides a robust measure of oscillatory activity related to the temporary encoding, short-term maintenance, and retrieval components of WM, however, this measure does not tap into the manipulation aspect of WM processing. Further research is therefore required to expand upon the current evidence of altered oscillatory activity during WM encoding and maintenance and examine whether MDD also involves alterations in WM-related oscillatory activity related to the manipulation component of WM processing.

8.3.3. EEG analyses

Analyses of EEG data in Study One focussed on oscillatory activity at single electrodes, thereby allowing us to clarify previous inconsistencies in the MDD-EEG literature regarding the presence and direction of alterations in WM-related oscillatory activity. In addition to oscillatory power changes, EEG data can be analysed to provide valuable information regarding aspects of neural connectivity which support WM processing. EEG-derived measures of neural connectivity include coherence in the phase of neural oscillations between brain regions, as well as phase synchronisation between oscillations of different frequencies (Sauseng & Klimesch, 2008). Neural connectivity is believed to play a crucial role in supporting WM processing, with some proposing that cross-frequency phase coupling of theta and gamma oscillations may reflect a neural substrate for the active maintenance of WM stimuli (Roux & Uhlhaas, 2014; Sauseng et al., 2009). Future research using EEG-derived measures of connectivity may therefore provide greater characterisation of the neurobiological changes underlying altered WM processing in MDD, particularly given neuroimaging evidence that MDD involves disruptions in connectivity between frontal and parieto-occipital regions during WM processing (Vasic et al., 2009). Moreover, given evidence that tDCS can alter resting and task-related functional connectivity (Daniel Keeser et al., 2011; Polanía, Paulus, & Nitsche, 2012), EEG-derived measures of connectivity may also inform the neurobiological processes underlying the cognitive effects of tES.

8.3.4. tES stimulation parameters

There is significant work to be done in order to determine the potential of alternative tES protocols for modulating neurophysiological and cognitive outcomes in healthy and clinical populations. The current thesis examined a single set of stimulation parameters for both techniques, and it is possible that other protocols may induce more pronounced or reliable effects in these populations. Determining the potential of these techniques will

require much greater investigation of how stimulation parameters interact with individual characteristics to determine the outcome of stimulation. This is particularly important when delivering tES in MDD, as the potential influence of depression severity, degree of cognitive impairment, and antidepressant medications on tES outcomes remains poorly understood. For instance, research in healthy individuals has shown that cognitive and neurophysiological effects of tDCS vary based on the pre-existing cognitive ability of the individual receiving stimulation (Benwell et al., 2015; Heinen et al., 2016; Hsu et al., 2014), hence it is likely that tES will also induce divergent effects when delivered in depressed individuals with and without cognitive impairment. For both tDCS and tRNS, stimulation parameters which may be optimised include stimulation intensity and duration, as well as electrode size and montage. For tRNS, initial evidence in healthy individuals suggests that including a DC-offset results in more pronounced neurophysiological effects than tRNS without an offset (Ho, Taylor, & Loo, 2015), however, further research is required to systematically compare the cognitive and neurophysiological effects of delivering tRNS with and without a DC-offset in both healthy and clinical populations such as MDD.

8.3.5. Inclusion of neurophysiological measures

It remains to be determined whether tES can be implemented as reliable and effective treatments for clinical conditions such as MDD. Addressing this will require researchers to first understand the effects that tES are inducing on brain activity and how these translate into behavioural and cognitive changes. To this end, future research studies applying tES in healthy and clinical populations should utilise both cognitive and neurophysiological outcome measures. An initial step towards understanding the underlying mechanisms of tES would involve the identification of reliable neural correlates of tES-induced cognitive improvement. Moreover, further research is required to investigate potential differences in the response to tES between healthy individuals and MDD. Improving understanding of

pathophysiological changes in oscillatory activity in MDD, and how these influence the outcome of tES, will greatly assist in interpreting potential factors which limit the efficacy of tDCS and tRNS and is an important first step in developing stimulation protocols which are optimised for treatment of MDD.

8.4. Concluding Statement

This thesis has presented an original series of studies which contribute to the understanding of neurobiological changes associated with WM processing in MDD, and the cognitive and neurophysiological effects of tDCS and tRNS in healthy and depressed individuals. The findings of the current thesis go beyond previous research in this area by demonstrating that WM processing in MDD involves alterations in theta, upper alpha, and gamma activity even when no observable cognitive deficits are present. Further, the current findings demonstrate that potential of tDCS to modulate aspects of WM-related oscillatory activity in MDD and provide the first evidence regarding the cognitive and neurophysiological effects of tRNS in this population. Importantly, this thesis provides the first evidence that tRNS + DC-offset may reflect a more reliable and effective means to enhance WM performance in healthy individuals when compared to anodal tDCS. These findings establish the utility of EEG as a means to examine the neurophysiological effects of tES in healthy and clinical populations. In conclusion, the research contained within this thesis provides valuable information regarding the cognitive and neurophysiological effects of delivering tDCS and tRNS in healthy and depressed individuals. Further, these findings serve as a foundation for future research investigating the neurobiological changes associated with WM processing MDD. It is hoped that this line of research will improve understanding of the neurophysiological processes underlying WM processing, and ultimately, lead to more

effective and reliable application of these techniques to enhance cognitive function and ameliorate cognitive impairment.

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