Community-based tDCS treatment for depression: Acceptability and Neuropsychological correlates.

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“If you can’t fly then run, if you can’t run then walk, if you can’t walk then crawl, but whatever you do, you have to keep moving forward.”

Martin Luther King, Jr

I chose a second quote for the dedication of this thesis as I feel this conveys the sentiment in the absence of the right words. I hope the benefit of conducting this research transcends the confines of this thesis, either directly or indirectly through the passing of knowledge and skills.

“And the story belongs not to any tribe but to all of humanity—to any sentient creature with the power of reason and the urge to persist in its being. For it requires only the convictions that life is better than death, health is better than sickness, abundance is better than want, freedom is better than coercion, happiness is better than suffering and knowledge is better than superstition and ignorance.”

Steven Pinker

Executive Summary

This thesis brings together 3 novel projects about major depressive disorder (MDD) and transcranial direct current stimulation (tDCS). The first project addresses acceptability and efficacy of tDCS in late-life depression (LLD) using a meta-analysis of individual-level patient data from randomised sham-controlled trials. Bayesian techniques answer two questions; Is active tDCS over dorsolateral prefrontal cortex (DLPFC) efficacious and considered acceptable in LLD compared to sham. It is hypothesised active tDCS over DLPFC will improve symptoms associated with LLD compared to sham and will be considered acceptable in LLD. Results show there is an 82% probability of a small effect and no statistical difference between dropout rates for acceptability. Project 2 addresses a qualitative analysis of acceptability using a new paradigm to investigate the feasibility and acceptability of at-home tDCS. The aim is to investigate the acceptability of at-home tDCS in MDD using qualitative methods by answering *How do patients with depression describe the acceptability of using a novel treatment, at-home tDCS?* Data collected via semi-structured interviewing conducted at 2 timepoints: post 21st session (final) and at 6 months follow up. Thematic analysis identified 4 main themes were classified: Side effects, Effectiveness, Time commitment, Support. Project 3 uses Auditory Verbal Learning Task to assess verbal learning with the research question was "Does verbal learning improve over time following tDCS treatment for MDD?". Treatment was hypothesised to be associated with improved verbal learning skills, as measured by total learning, and learning over trials, in line with McClintock et al (2020) findings. Assessments occurred at 3 timepoints after a tDCS sessions on: 1st session, the 10th session (after 2 weeks) and the 21st session (final). Contrary to the hypothesis, no statistically significant results were elicited. This was not expected but are in line with some reports. The final chapter takes the opportunity to discuss further the results of each project in more detail and the impact that COVID-19 may have on MDD research in the future.

Originality statement

'I hereby declare that this submission is my own work and to the best of my knowledge it contains no materials previously published or written by another person, or substantial proportions of material which have been accepted for the award of any other degree or diploma at UEL or any other educational institution, except where due acknowledgement is made in this thesis. Any contribution made to the research by others, with whom I have worked at UEL or elsewhere, is explicitly acknowledged in the thesis. I also declare that the intellectual content of this thesis is the product of my own work, except to the extent that assistance from others in the project's design and conception or in style, presentation and linguistic expression is acknowledged.'

Signed…R Rimmer……

Date…13/07/2022……

Declaration Of Prior Publication

This thesis includes material, findings and discussions that have been published in conferences, journal papers or are in preparation as manuscripts.

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In compliance with the University of East London Manual of General Regulations, Part 9, section 19, clause 19.8, copies of already published work (Woodham, Rimmer et al., 2021; Woodham et al., 2022; Rimmer et al., 2022) are included within the appendices of this thesis.

Acknowledgements

The research included in this thesis culminates three long years of hard work, with a 6 month pause on recruitment due to the COVID-19 pandemic lockdown. The extensive corpora of research have been combined across the chapters of this thesis. These include neuromodulation in major depression (combining cognitive neuroscience and clinical psychology), acceptability (social psychology) and neuropsychology (cognitive psychology). This work has been a deeply personal achievement and a journey at points I was not certain I would finish so I am pleased to complete and submit this thesis in partial fulfilment of the requirements for Degree of Doctor of Philosophy.

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Appendix 8. *Ethics Approvals*

Chapter 1: Introduction

Chapter Overview

This chapter will begin with a review of the historical aspects of depression and how the nosology of depression was developed. Then, the chapter will cover diagnosis, epidemiology, and aetiology of depression. Next, the current available treatment options and clinical issues with treatments will be discussed. The chapter will go through an overview of transcranial direct current stimulation (tDCS), the modalities, and mechanisms of action. The chapter discusses meta-analysis as an analytical technique in late-life depression (LLD), acceptability, and neurocognitive aspects of transcranial direct current stimulation as a brief review of each project of the thesis. The research aims, objectives, questions and hypothesis will conclude this chapter.

1. History of depression

Vulnerability within experiences is not unique to a certain subset, group or time. It is universal and constant as to be seen as inherent in the human condition (Fineman, 2008). So, it is likely mood disturbance and the vulnerabilities that predispose humans to such mood disturbance also predates written historical records. Anecdotal reports are documented across the Asian continent from as early as 10000 BC (Gautam, 1999) that are suggestive of mental distress. In fact, many documented historical reports from the Asian continent are littered with examples that suggest of an understanding of, but at the very least an expression of mental illness and more specifically, mood disorders. For example, in ancient India during 10000 BC–1000 BC, anecdotal mentions of melancholia and depressive disorders can be found. Taking a closer look during the Era of Lord Rama between 5000-4000 BC, emotional responses of Rama were documented as an initial nosology of mental illness. The presence of nosological approaches indicate some form of understanding around potential cause and effect and potential symptomology. Different from current nosological practices, this nosology was based around endogenous ("*Nijmanas rog*") and exogenous ("*Agantujmanas rog*")

mental illness, with a further divide between psychological and physical causes. It was eventually classified by aetiology during the Ayurvedic era (1500 BC-1400 BC; Gautam, 1999).

The record of mood disturbance continues through Mesopotamia and the Babylonian region (current day Iraq and Syria) circa 2000 BC (Reynolds & Wilson, 2013). During Babylonian times, the specific term 'depression' would have been unfamiliar. Though, there may have been a cultural understanding of depression, the cluster of symptoms presently used for diagnosis in the West might not have been implemented in the same way. Nonetheless, there is evidence of the concept of "being depressed" and even the knowledge of the now established "Western" symptoms, aetiology, and various forms of historical classifications (Reynolds & Wilson, 2013). Understanding of cause, effect and symptomology during this time will have impacted how depression was treated.

The collection of accounts can be found in Sumerian texts, with one example portraying the description of a clinical picture (Reynolds & Wilson, 2013) revealing an understanding of behavioural disorder that has an astonishing similarity to an agitated depressive state (Köcher, 1964, in Reynolds & Wilson, 2013). This text describes a 'head of the household', an '*awīlum'*, with biological features of depression including insomnia, anorexia, weakness, impaired concentration, and memory. At the time, a widely held belief suggested the '*awīlum'* had upset the Gods in some manner and the Gods had in turn caused these symptoms. The cure: a ritual practice called 'anti-*māmītu',* involving creating and burying figurines*,* with an incantation to the Sun God and God of Justice, 'Shamash', to counter any hold the 'God' may have on the '*awīlum'* (Ritter & Wilson, 1980, in Reynolds & Wilson, 2013).

Both vague and clear terminology are used to suggest mood disturbance. The word '*ašuštu'* might be understood to mean 'distress', with an associated verb, '*ašašu'* meaning 'a cutting off (or shortening) of life'. Also taken from the Sumerian language, 'z*ikurrudû*,' refers to suicide, suicidal thoughts or tendencies. Whereas '*hīp libbi'* could have several references such as a nervous breakdown, panic attacks or in the literal sense, 'a breaking of the mind'. These terms raise the possibility that their

description of the '*awīlum'* does in fact relate to what we understand as depression (Ritter & Wilson, 1980).

Whilst historic world accounts cannot be discounted, the current Western understanding and historical roots lie within Greco-Roman literature. Greek philosophers Hippocrates (460 BC- 360 BC) and Aristotle (384 BC- 322 BC) classified a term to describe depression 'melancholia'. The word melancholia, or melancholy derives from Greek 'μέλαινα χολή' or 'melaina chole' meaning black bile. Taken from the theoretical framework, 'humoral theory of disease', disease in its' entirety was understood to involve 4 humours key to bodily function (black bile, yellow bile, phlegm and blood). An example demonstrated by the belief held by Hippocrates, "*if a fright or despondency last for a long time, it is a melancholic affection*" (Hippocrates, Aphorismi 6.23; Darwin Adams, 1868). Melancholic disposition referred to those who are typically creative but can also become focused on a negative outlook towards the world (Ahonen, 2019). Aristotle and Hippocrates agreed that melancholy originates from a dysfunction in bile but differed on the source of melancholia. Aristotle locating the heart and Hippocrates the brain, though both identified this as a physical illness related to black bile (Reynolds & Wilson, 2013). Melancholia evolved to be an interchangeable term for the mood disorder, depression in the 20th century (Ahonen, 2019).

In Greco-Roman medicine, the 'humoral theory of disease' was revived under Galen (131–201 AD). Galen describes 3 types of melancholy dependant on where the ailment manifested, which relate to where the patient may be symptomatic: brain, blood, and stomach (Calabritto, 2012). One form, for example, for those with an inflamed stomach, Galen may suggest the blood is thicker and more atrabilious than normal; the stomach vapours believed to travel to the brain and thus cause melancholic presentations (Calabritto, 2012). Additionally, it may be an early form of nosology, or classification, of depressive-like illness and to an extent, this theory persisted in Europe until the 1800's.

During the Islamic Golden Age (900 -1400 AD) across the Persian Empire, constructs of mental illness were principally religiously based. Galen's patient might be explained as a possession by the Jinn or another form of demonology. In a dismissal of these forms of portrayals, Ibn Sina described the culmination of Indian renaissance in a collection of books known as 'Al Qanun fi al Tibb' or The Canon. The Canon combined Greek philosophy of Galen's 'humoral theory of disease' with the Islamic school of thought (Amr & Tbakhi, 2007; Dols, 1987). The treatment that followed addressed balancing black bile with procedures such as bloodletting, baths and medicines such as emetics, purgatives, and opiates (Dols, 1987; Daly, 2007). These practices were influential right through the Middle Ages and were the standard treatment practices for melancholia. The religious ideology around mental illness persisted and was explained as being due to sin. Allowing the body to 'purge' or release the so-called sin from the body was the recognised way to resolve these ailments. The term 'acedia' was used to describe this form of distress, defining what was known melancholia within the Greco-Roman world as a spiritual disease. This understanding of mental illness became ubiquitous across the Western world and likely contributed to stigma that has been pervasive until recent times (Daly, 2007).

Galen's seminal work on the humeral aetiology of melancholia was widely influential from the works of Avicenna (937-1037AD) to Timothy Bright's (1586) *Treatise of Melancholia*. Nosological classifications of melancholia also remained rooted in Galen's work, noted in works from Paul of Aegina (625-700AD), Jean Fernel (1497-1558), and Robert Burton (1621) who developed the 'anatomy of melancholia' (Jansson, 2011). The beginning of a wider division of melancholia transpired into head, body and hypochondriacal melancholia (Jansson, 2011).

German physician Johann Heinroth (1818) began to question the conceptualisation of melancholia. His description was of the 'exaltation or depression' of one or another's 'faculty of the mind' such as emotion, intellect, or volition. It was Heinroth's reconceptualization of melancholia to 'partial insanity' or the use of the term 'depression [of emotion]' that conceived depression to its

understanding today. Heinroth's model was apparent in the first documented reference in the 19th century of melancholia as depressive states by another German psychiatrist, Emil Kraepelin (Ban, 2014). Kraepelin proposed a brain pathology of 4 different types of melancholia. It can be defined as a cluster of symptoms rather than having one defining characteristic. Kraepelin's idea of being able to identify a cluster of symptoms paved the way for Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Diseases and Related Health Problems (ICD) nosology (American Psychological Association [APA], 2013; Ebert & Bär, 2010; World Health Organisation [WHO], 2020). These are the currently used classification of diagnosis today.

Overview:

This section will define major depressive disorder as a diagnosis using nosological approaches. A selective review of the epidemiology and aetiology of major depression will be discussed. Then, the biological dysfunction of MDD and theoretical understanding of depression will be presented. First line treatments that are currently available on the national health service (NHS) and clinical issues with treating major depression will be reviewed.

1.1 Major depressive disorder

Diagnosis

Major depressive disorder (MDD) is the clinical presentation of a cluster of symptoms lasting for 2 weeks or more. There are 2 major classification systems: ICD, 11th revision (WHO, 2020) and DSM, 5th edition (APA, 2013) used to diagnose MDD. These provide the definitions of a depressive episode and account for the heterogeneity of MDD as it is currently understood, with the comparison diagnostic criteria demonstrated in Table 1. *MDD Symptoms: ICD vs DSM*. There is a threshold of severity for clinical significance which is based on number and intensity of symptoms as well as the impact on functional ability. The criteria delineate subtype (atypical, melancholic), duration, severity, and course of disorder (DSM-5; APA, 2013; ICD-11; WHO, 2020). Ultimately, the diagnosis of MDD is somewhat subject to the report of those experiencing (i.e., subjective) and the clinical documentation of symptoms impairing functioning (Nestler et al., 2002).

Epidemiology

MDD presents a significant socio-economic challenge. Globally, MDD is now the leading cause of disability, affecting over 322 million people worldwide (Friedrich, 2017). Between 2005-2015, the years lived with disability for people experiencing MDD increased by approximately 18% and MDD

has been ranked as the single largest contributor to non-fatal health loss (Vos et al., 2015). In addition, nearly 800,000 people died following suicide in the year 2015, with many more making attempts of suicide (WHO, 2018).

Table 1. MDD Symptoms: ICD-11 vs DSM-5

Diagnosis for Major Depressive Disorder

	ICD–11	**DSM–5**
Core Symptoms, *persistent for 2 weeks or more*	Depressed mood Loss of interest Reduction in energy	Depressed mood by self-report or observation made by others. Loss of interest or pleasure
Other symptoms that may be present	• Difficulty concentrating • Feelings of worthlessness or excessive or inappropriate guilt, • Hopelessness • Recurrent thoughts of death or suicide changes in appetite or sleep • Psycho motor agitation or retardation • Reduced energy or fatigue	• Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day. • A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down). • Fatigue or loss of energy nearly every day. • Feelings of worthlessness or excessive or inappropriate guilt nearly every day. • Diminished ability to think or concentrate, or indecisiveness, nearly every day. • Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
Number of symptoms required for moderate - severe dx	At least one 'core' symptoms with a total of 5 or more assessed, which are occurring most of the day, nearly every day for 2 weeks or more; *(mild depression can be diagnosed with 4 symptoms)* Severity is assessed by the intensity of the presenting symptoms, as more severe forms may have more or less symptoms and/or manifest in a more marked degree forms.	At least one 'core' symptoms with a total of 5 or more assessed along with severity and function (cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not due to the direct physiological effects of a substance (e.g., drug abuse, a prescribed medication's side effects) or a medical condition (e.g., hypothyroidism)), duration and course of the depression to determine its severity

In the United Kingdom (UK), the prevalence of MDD is higher than average. A probable first episode MDD reaches 6.7% and recurrent MDD episodes range between 7.2%-12.2% compared to the global average of around 4.7% (Smith et al., 2013; Ferrari et al., 2013). This may be due, in part, to the reliance of self-report measures over objective, standardised tools (Smith et al., 2013). There is some variation in prevalence when looking specifically across age, gender, ethnicity, educational and relationship status, ability to work, current depressive symptoms and neuroticism (Smith et al., 2013). The age of onset is typically early to mid-20's across both high income and low to middle income countries (range is from 18-29 years), women are twice as likely to develop MDD than men (Smith et al., 2013; Kessler & Bromet, 2013). Ethnic minority groups and migrants also have a slightly higher risk of developing MDD (Tarricone et al., 2012) and being separated or divorced is consistently associated with development of MDD (Smith et al., 2013; Kessler & Bromet, 2013). More severe rates of MDD report the highest inability to work due to sickness and neuroticism was highest in this group (Smith et al., 2013).

Aetiology

Complex theories that both converge and diverge across biological, psychological, and social spheres are termed and defined. They are explained in the context that these aspects can predispose, precipitate, or perpetuate the presence and course of a depressive illness. In this section, a biological understanding of dysfunctions found in MDD are explained. Then, some of the key biological and psychological theories underpinning these dysfunctions are discussed, as well as a description of the roles of stress and genetics.

Neurobiology

Neurobiological theories posit MDD is characterised by emotion dysregulation (Mennin et al., 2007). Emotion regulation has been located within a complex interconnected network of brain regions

including various regions of prefrontal cortex, anterior cingulate cortex (ACC), basal ganglia as well as multiple brainstem nuclei, the hypothalamus and amygdala (Kober et al., 2008). Each brain region acts and facilitates different aspects of emotion regulation (Park et al., 2019). The biological dysregulation seen in MDD leads to reduced functional activity or hyperactivity across the cortex, such as in the connections between the frontal-limbic system. These connections are bidirectional between prefrontal cortex and the hippocampus and amygdala, through modulation of hypothalamus, basal ganglia, and midbrain (Park et al., 2019). Following increased activation of the hypothalamic-pituitary-adrenal (HPA) axis, amygdala activity increases in response to negative stimuli, and increased connectivity to temporal poles from the amygdala occurs. Activity increases in the anterior cingulate cortex (ACC) while inhibiting negative stimuli and activity increases in right dorsolateral prefrontal cortex (DLPFC) when anticipating negative stimuli (Park et al., 2019). Also, an increase in insular cortex (IC) activity occurs with depressive rumination and decreased connection of IC with limbic structures; there is lower resting state activity, lower functional connectivity, and reduced responsivity to emotional stimuli in left DLPFC, as well as reduced or impaired activity in ventrolateral (vlPFC), ventromedial (vmPFC), and dorsomedial (dmPFC) prefrontal cortexes (Park et al., 2019).

A comprehensive multimodal assessment using coordinate meta-analysis found convergent effects in co-localised brain regions (Gray et al., 2020). The subgenual cingulate cortex was identified from pooled structural (task activation, voxel-based morphometry (VBM)) and physiological-functional findings (resting state, voxel-based pathophysiology (VBP)) in MDD (Gray et al., 2020). In addition to the left hippocampus, the right amygdala/putamen, the left retrosplenial cortex, and the right middle occipital/inferior temporal gyri, though, failed to find grey matter atrophy or increased/decreased functions when compared to controls (Gray et al., 2020). The regions of structure-function that were significant have been associated with pathology and treatment approaches, with clinical subtypes improving convergence (Gray et al., 2020). This suggests specific

regions that may support further research in MDD and with a large proportion of the included studies (60%) being drug naïve may suggest these findings are limited to first-episode presentations (Gray et al., 2020). Further, that there are separate structure-function findings in those with frequent recurrence of episodes or treatment resistance.

Monoamine Theory

Theories to explain MDD were initially characterised by the "Monoamine Theory of Depression", which identified the important role of norepinephrine and serotonin as downstream mechanisms of action. The proposal that MDD occurs when the availability of monoamines have centrally decreased, either catecholamine (e.g., norepinephrine) or indolamine (i.e., serotonin), defined the monoaminergic neurotransmitter hypothesis (Krishnan & Nestler, 2010). This occurs through an affected pre and post synapsis.

Both norepinephrine and serotonin are released into the synaptic cleft. Altered regulatory auto-receptors may lead to alterations in the reuptake and feedback release. This may be due to a depletion of enzymes i.e., tryptophan or tyrosine hydroxylase, increased specific binding or catabolizing enzymes such as monoamine oxidise-A (MAOA) or cathechol-o-methyltransferase (CoMT), malfunction or sub-sensitive receptors (Belmaker & Agam 2008; Mulinari, 2012) which is characterised as the monoamine receptor hypothesis. First generation medication, MOAI and tricyclics were established from this basis, though these were found to have high side effect profiles. There was an ongoing shift in the evidence as to which neurotransmitter may be more influential in this hypothesis, norepinephrine, or serotonin. The tip of balance appeared with the arrival of selective serotonin reuptake inhibitors (SSRIs) as a second generation of antidepressant treatment. SSRIs have a reduced side effect profile, though, does not seem to be as efficacious (Mulinari, 2012).

As mentioned, the understanding of monoaminergic neurotransmission was as downstream modification. However, these mechanisms of action did not explain the therapeutic effect and thus this theory does not fully account for the delayed response of antidepressants or the 20% of patients that have a refractory form of MDD in which symptoms persist despite multiple treatment trials or the occurrence of neural compensation or sub sensitivity (Boku et al.,2018). One explanation of delayed time to therapeutic effect is the time required to sensitize and normalise serotonergic tone of the 5-HT1A serotonin auto receptor at the synapse (Wainwright & Galea, 2013). However, ablating or disrupting serotonin does not create a depressive phenotype which suggests this system is not the only underlying system in MDD. Returning to monoamine receptor hypothesis, second generation antidepressant medications included noradrenaline based (noradrenaline reuptake inhibitors (NARIs)), or combined treatments such as serotonin and noradrenaline reuptake inhibitors (SNRIs) or noradrenergic and specific serotonergic antidepressants (NaSSAs) (Racagni & Popoli, 2008).

Chronic antidepressant usage was found to induce adaptive changes in post-receptor signalling cascades, and gene expression such as activation of signalling cascades or transcription factors or the activation/repression of specific genes (Racagni & Popoli, 2008; Sharp, 2012). This gave rise to the signalling adaptation hypothesis. As this shift focused downstream of the postsynaptic receptors, identification of gene expression changes in genes linked to neuroplasticity were identified (Racagni & Popoli, 2008; Sharp, 2012). Furthermore, neuroplastic changes were established such as synaptogenesis and remodelling, alteration of dendrite function, long-term potentiation (LTP) and long-term depression (LTD) (Racagni & Popoli, 2008; Sharp, 2012).

Psycho-neuroendocrinology Theory

The HPA axis is a complex stress response system in the body, triggering the response arginine vasopressin (AVP) and corticotropin releasing hormone (CRH) secretion from the hypothalamus via the paraventricular nuclei (Turnbull & Rivier, 1999). The synthesis of adrenocorticotrophic hormone (ACTH) is initiated (Nicolaides et al., 2015). ACTH travels via the blood stream to release glucocorticoid cortisol, reduce neural morphology and neurogenesis in the hippocampus (Boku et al., 2018). This occurs until a negative feedback loop stops the cascade which cortisol passes the blood-brain barrier and suppresses the release (Boku et al., 2018). Along with stress responsiveness, it is central to homeostatic metabolism and neuropsychiatric functioning. Expression of these hormones (CRH, ATCH) can excite and modulate the serotonergic and noradrenergic neurons respectively (De Kloet, Joëls, & Holsboer, 2005; Joëls & Baram, 2009) which in turn also regulate the HPA axis: serotonin inhibits the secretion of CRH in hypothalamus, and ACTH in pituitary glands and noradrenaline promotes secretion of CRH in the hypothalamus (Jeon & Kim, 2016). Experiencing external stress, such as childhood stressors, can markedly increase ACTH and when actively depressed, a further increase is seen in ATCH secretion (Stetler & Miller, 2011). This suggests that hyperactivity of HPA axis may precede a depressive episode and represent a manifestation of neurobiological abnormality persistence (Pariante & Lightman, 2008).

Further, there are distinct biological correlations involving the HPA axis, for instance melancholic depression is characterised by HPA-axis hyperactivity, whereas there are larger levels of inflammation and metabolic disturbance in atypical depression (Lamers et al., 2013). Though, HPA markers (AVP, CRH, ACTH) show no significant difference between responders and non-responders in predictive treatment response (Fischer, Macare & Cleare, 2017). This may suggest a generic stress response is seen in MDD or this response remains even after the immediate response to treatment. Equally, other endocrine stress response systems such as hypothalamic-pituitary-thyroid (HPT) or

hypothalamic-pituitary-gonadial (HPG) systems may also play a role within MDD pathology (Musselman & Nemeroff, 1996).

Inflammation-neurotrophic Theory

Cytokines are inflammation modulators and are involved in both acute and chronic inflammation (Turner et al., 2014). Cytokines can be classed as interleukins (i.e., IL-1, IL-6), interferons (i.e., IFN-α, IFN-β) and tumour necrosis factors (i.e., TNF-α) (Turner et al., 2014).

Cytokines are the primary expression is within the central nervous system (CNS) but can also be identified peripherally (Turnball & River, 1999). The presence of peripheral cytokines was extensively researched. Cytokines found to be expressed as metabolic changes in peripheral blood samples of MDD patients were identified as inflammation markers and potential biomarkers for investigation (Raison, Capuron, & Miller, 2006; Miller, Maletic & Raison, 2009; Köhler et al., 2017; Pu et al., 2020). Bi-directional communication between immune and endocrine centres are mediated by HPA axis activity. Pleiotropic properties of cytokines influence secretion from HPA axis, and the central activity of cytokines might account for the hyperactivity seen in HPA axis via a disturbance of the feedback loop (Schiepers, Wichers & Maes, 2005).

Cytokines interact with nervous and neuroendocrine systems via neurotransmitters, as well as interacting with neurogenesis-degeneration and antidepressant action (Jeon & Kim, 2016). Cytokines have been correlated with MDD via the relationship between stress, antidepressant treatment and up or down regulation of brain derived neurotrophin factor (BDNF). The mechanisms of actions are understood as the neurotrophin hypothesis of depression (Duman & Monteggia, 2006).

Neurotrophins (i.e., BDNF) are involved in the survival and differentiation of neurons and a major regulator of synaptic transmission and plasticity (Bramham & Messaoudi, 2005). BDNF as a growth factor binds to tyrosine kinase receptor B (TrkB) receptors to promote growth, proliferation, neuroplasticity, and has a powerful neuroprotective role such as in caspase-regulated apoptosis (Groves, 2007). The reduction in BDNF along with inflammation, can cause oxidative and nitrative stress both acute and chronic. This triggers an autoimmune response, reducing neurogenesis and increasing neurodegeneration, particularly in limbic regions ultimately leading to depressive symptoms. Whereas chronic antidepressant treatment upregulates the mRNA expression of BDNF in the hippocampus and serotonin and noradrenaline (Jeon & Kim, 2016; Duman & Li, 2012).

Novel Theories of Depression

More recent advances in these theories have identified N-methyl-D-aspartate (NMDA), a glutamate receptor antagonist, demonstrating fast acting antidepressant like properties (Pittenger & Duman, 2008). The role of glutamate has been highlighted as part of the brain network disruption seen in MDD (Ramirez-Mahaluf et al., 2017). Simulated glutamate decay was slowed in ventral ACC (vACC), which produced a sustained activation of vACC. The concurrent activation of DLPFC did not suppress the vACC hyperactivity and caused interference in DLPFC. Particularly with cognitive signals, which created an expected disruption mimicking depressive like cognitive disturbance. When the simulation was treated with SSRIs or brain stimulation, the vACC hyperactivity was counteracted (Ramirez-Mahaluf et al., 2017). This is suggestive of an abnormal glutamate metabolism within vACC for MDD.

Both the use of a single dose of ketamine or non-ketamine NMDA receptor antagonists have rapid efficacy on alleviating symptoms in MDD (Kishimoto et al., 2016). It is suggestive there are differences in synaptic and extra synaptic neuroplasticity, given NMDA activation typically produce neuroplastic results. With a preference on extra synaptic NMDA receptors or possible preferential

NMDA blockages in GABA causing paradoxical increasing in glutamate tone, offers counterbalance explanation to what might be an expected intuitive cellular worsening from a blockage (Pittenger & Duman, 2008).

Glutamate and its' composite glutamate/glutamine are found more localised to the ACC, whereas a widespread reduction of gamma-aminobutyric acid (GABA) was observed, when compared to healthy controls (Godfrey et al., 2018). GABA reduction was statistically significant across depressed groups, though the inclusion of remitted patients removed any statistical difference between depressed patients and healthy controls, suggesting treatments that elicit remission, may also normalise GABA levels (Godfrey et al., 2018).

Psychological Theory

Early theories of MDD present a psychoanalytical approach to depression. In his seminal work, Mourning and Melancholia, Freud (1917, 1986) reviewed a connection between grief and depression which explored loss as a precursor to the development of MDD. An observation of loss of a central source of love or emotional security can stimulate the same negative emotions seen in MDD such as anxiety, fear, and anger and Freud proposed an exaggerated feeling of guilt and irrational self-criticism as a proponent to MDD driven by buried or hurt feelings of childhood loss or trauma (Freud, 1917; Taylor, 2008). Further, MDD may develop when inwardly directing hostile ambivalent feelings from a loss to the self (Pysczynski & Greenberg, 1987).

Under a behavioural theory, MDD symptoms can been hypothesised as reduced reward and decreased associative positive reinforced behaviours which strengthens depressed or passive behaviour and punishment of healthy behaviours (Ferster, 1973, Lewinsohn, 1974). Precursors to reductions in reward functions can occur as cognitions and overt avoidant behaviour predispose the development of MDD (Ferster, 1973). Response-contingent positive reinforcement, abbreviated as

"resconposre" in the literature or RCPR, elicits depressed behaviours such as dysphoria, fatigue and somatic symptoms, when the rate of RCPR is low and can also provide an explanation for other behaviour such as lower rates of activity (Lewinsohn, 1974). The number and availability of potentially reinforcing events and an individual's response to environmental stimuli to develop a positive reinforcement determines the total amount of RCPR (Lewinsohn, 1974). The theory stipulates MDD is accompanied with the reduction of RCPR. The total amount of RCPR will be lower for both at group level and individually i.e., lower RCPR across depressed groups compared to non-depressed groups, but also individually, the total amount of RCPR is less when depressed compared to when the individual is not depressed. The intensity of depression covaries with a rate of RCPR and improvement or recovery is associated with an increase of RCPR (Lewinsohn, 1974). This theory, in essence, suggests a combination of environmental changes and avoidant type behaviours inhibit those experiencing MDD from experiencing reward and the following reinforcement is reduced for healthy RCPR, punishment of healthy behaviours and reinforcement of depressed or passive behaviour (Ferster, 1973, Lewinsohn, 1974).

The use of proxy measures of positive reinforcement (daily activity diaries and a self-report index of environmental reward) found a mediating role between avoidance and depression, with increased avoidance both behaviourally and cognitively (Carvalho & Hopko 2011). This means an increased risk of the development of MDD with the reduction of positive reinforcement (Carvalho & Hopko 2011). Positive reinforcement can be developed as a therapeutic treatment called behavioural activation (BA) and is designed to support the access of positive reinforcement events (Jacobson, Martell, & Dimidjian, 2001). However, a measurement of contact with the reinforcer confounds the measurement of the hypothesised behaviour change. Further, using a standardised measure of reinforcement such as Pleasant Event Scale (PES; MacPhillamy & Lewinsohn, 1974; MacPhillamy & Lewinsohn, 1982) confounds any measurements of reinforcement with a measurement of mood.

Nevertheless, it is generally accepted that contact with certain events can improve the mood (Manos, Kanter & Busch, 2010).

Cognitive theories root from a proposal by Aaron Beck (1967). An information-processing model, characterised as a thinking disorder, describes MDD as a prolonged and pronounced negative bias in a "cognitive triad": negative views on the self, the future, and others. Cognitive distortions were identified as selective abstraction, magnification, minimisation or overgeneralisation, and negative self-attributions (Beck, 1967).

A further proposed cognitive theory is based on Seligman's (1975, 1979) learned helplessness and attribution styles and has undergone several revisions and adaptations. The control perspective purports the notions that following an uncontrolled loss, there is a low expectation for control over future outcomes and this subsequently produces symptoms under motivational, cognitive, and affective types (Pysczynski & Greenberg, 1987). Abramson et al., (1978) present an alternative helplessness acting as a mediator between the loss of control and emerging helplessness attributes, creating a three-dimensional taxonomy of attributions, defining specific aspects of learned helplessness: "*(a) the greater the internality of the attribution, the greater the loss of self-esteem; (b) the greater the stability of the attribution, the greater the chronicity of the helplessness deficits; and (c) the greater the globality of the attribution, the wider the range of behavioural domains to which the helplessness effects generalize"* (Pysczynski & Greenberg, 1987, p. 123).

Alloy et al (1988) developed the hopelessness theory of MDD suggesting a vulnerability develops during a depressive episode for those who experience negative inferential thinking as a response to a negative event. The inference of negative consequences will follow an active negative event and feelings of worthlessness or being fundamentally flawed is a rationale for the occurrence of a negative event (Alloy et al, 1988).

Combining both behavioural and cognitive approaches developed the most popular model of cognitive-behavioural therapy (CBT). As a treatment, it combines the thought, behaviour, and emotions (Beck, 1995; Blenkiron, 1999). Under this model, psychological dysfunction is understood as information processing and learning mechanisms (Haslett-Stevens & Craske, 2008). The cognitive-behaviour approach uses human behaviour orientated by experimental process, so any given behaviour is a function to the environmental and internal spaces it surrounds (Goldfried & Davison, 1994). Therefore, CBT is designed to target specific symptoms and behaviours. The third assumption relates to learning to adopt the change desired over maladaptive information processing and learning. CBT is considered a scientific approach, through the therapist's evaluation of change at the level of the patient (Haslett-Stevens & Craske, 2008).

Both cognitive and psychodynamic approaches propose self-criticism and dependency as personality traits may predispose for a specific vulnerability. As such if one has high levels of self-criticism and perceive not meeting such standards, this could trigger a depressive event or in those with high dependency, a focus on interpersonal relations, and an interpersonal loss, abandonment or rejection may result in a depressive episode (Blatt & Zuroff, 1992).

The onset of MDD can be predicted by some psychological factors derived from cognitive and personality-based approaches i.e., dysfunctional attitudes, cognitive styles, cognitive reactivity, and negative emotionality were related to the first onset of a depressive episode (Fu et al., 2021). Due to low number of studies using a cognitive theory, Fu et al., (2021) were not able to review moderators. For personality-based studies investigating negative and positive emotionality, negative emotionality (most studied was neuroticism) was related to the first onset of MDD (pooled OR: 2.43, 95% CI: 1.41 to 4.19) and positive emotionality did not decrease the onset of MDD (pooled OR: 0.93, 95% CI: 0.84 to 1.03). There were not enough data to examine behavioural and diathesis-stress theory models

and no prospective psychodynamic studies to allow any examination of this theory. Whilst there is some evidence that psychological theories (cognitive and personality-based theories) predicted the onset of MDD, there is still much research to conduct to definitively conclude this (Fu et al., 2021).

Though, personality traits are known to have an impact on the development of MDD. Neuroticism is characterised as "*the tendency to experience frequent, intense negative emotions associated with the sense of uncontrollability (the perception of inadequate coping) in response to stress*" but is also expressed as anxiety, worry, emotional anger or avoidance (Barlow et al., 2014a; Barlow et al 2014b). Typically, the personality trait of neuroticism has been known as stable and genetically based but is now understood to integrate genetic, neurobiological, and environmental factors in the presentation of neuroticism (Barlow et al., 2014a). Results from polygenic scoring on the Big Five genome-wide associations were predictive for MDD (de Moor et al., 2015) but not for extraversion/reward dependence. One explanation for this is the gene for extraversion is more complex (i.e., more polygenic and rare variants), when compared to neuroticism (Van Den Berg & de Moor, 2020). Stress across the lifetime can have a direct impact on MDD, their symptoms and is moderated by levels of neuroticism present. In other words, the impact of stressful situations is greater for those vulnerable to or with higher levels of neuroticism (Vinkers et al., 2014).

Stressful Life Events and Genetics

Heritability of MDD is around 37% (Sullivan, Neale, & Kendler, 2000). Stressful life events (SLEs) have been consistently reported as an acute strong precursor to a depressive episode (Kessler, 1997; Almeida & Kessler, 1998). There are 5 domains which are identified as SLEs: health, housing, relationships, employment, and finance (Caspi et al., 2003; Haberstick et al., 2016). Vulnerability to developing a depressive episode following an SLE is largely driven by genetic predisposition (Sullivan, Neale, & Kendler, 2000) or early life stress (Pechtel & Pizzagalli, 2011).

SLEs were believed to interact with the serotonin transporter polymorphism gene (*5-HTTLPR*) in the serotonin transporter gene (SLC6A4). Gene-environment interaction (GxE) studies suggested there was a specific endophenotype 5-HTTLPR gene (S-carriers) that present a vulnerability to stress in which these carriers of the S-allele have a latent personality trait known as neuroticism or negative affectivity (Uher & McGuffin, 2010; Caspi et al., 2010). The theory is known as "diathesis-stress model" (Monroe & Simons, 1991). Genetic disposition does not end here, though, as out of 26 target genes that have been reviewed, 6 other genes were identified to have significant result for MDD: APOE, DRD4, GNB3, HTR1A, MTHFR, and SLC6A3, along with 5-HTTLPR/ SLC6A4. However, the results were not replicated (Bosker et al., 2011). The lack of replication was also supported by genome-wide association studies (GWAS; Wray et al., 2012). Some challenges that have been identified are moderate heritability and high prevalence of MDD. The heterogeneity of both genetic and non-genetic factors combined with limited understanding of genotype-phenotype relationship (Levinson et al., 2014). Addressing some of these challenges within the study design has led to 80 genomic loci with associations with MDD (Direk et al., 2017; Howard et al., 2018; Wray et al., 2018).

Early life stress has been defined as a single or multiple life event in that the experience exceeds the child's coping ability and leads to a prolonged activation of stress (Pechtel & Pizzagalli, 2011). Identified subtypes of early life stress associated with the development of MDD include physical abuse, sexual abuse and unspecified neglect (Carr et al., 2013) but can also extend to household dysfunction, disaster and social deprivation (Brown et al., 2009). When faced with prolonged HPA axis activation, brain regions that have longer maturation courses such as prefrontal cortex (PFC) development are vulnerable to the development of dysfunction (i.e., prefrontal dysfunction). Executive dysfunction can lead directly to emotional dysregulation and rumination contributing to incidences of MDD (Pechtel & Pizzagalli, 2011).

Neuroplastic Theory

Neuroplastic theories of MDD bring together neurobiological (i.e., neuroimaging), cognitive (i.e., memory impairment) and information processing deficits (i.e., attention or memory negative biases), and psychological constructs (i.e., patient reported symptoms) (Price and Duman, 2020). With a focus on PFC, HPA axis, dopamine system in ventral tegmental area-nucleus accumbens (VTA-NAc), amygdala and hippocampus, and the role these regions play in neuroplasticity through direct or indirect action at molecular and cellular signalling levels. A disruption of neurotrophin factors such as BDNF and synaptic connectivity is what is proposed to lead to the development of MDD (Duman et al., 2016).

1.2 Current Treatment Options

In the UK, National Institute for Health and Care Excellence (NICE) guidelines provide evidenced based preferential options for the treatment and management of MDD. The first line treatments are antidepressants and psychological therapies. The first line treatments are influenced by the duration and severity of the episode, any historical course and response to treatment, as well as personal preference and priorities (point 1.5.1.3; NICE, 2022). More complex presentations are managed under secondary mental health care establishments but a large proportion, the majority of those who receive a diagnosis, treatment and management will do so under primary care by a general practitioner (GP, Kessler et al., 2003; Wilson et al., 2003).

Prior to starting treatments, evidence suggests a triad of good practices can support prevention and or recovery of those with MDD. These include healthy eating, physical exercise, and sleep hygiene (Briguglio et al., 2020) and are also supported within the NICE guidance.

Antidepressant Treatments

There has been significant development in antidepressant treatment over the last few decades offering increased choice for patients and clinicians such as SSRIs and SNRIs. A recent network meta-analysis shows overall random-effect summary standardised mean difference (SMD) is 0.3, (95% Credible interval (CrI) 0.26 -0.34; p= > 0.0001) suggesting small or modest effects (Cipriani et al., 2018). When looking at individual antidepressants, all of those included in the meta-analysis were statistically more effective than placebo with odds ratio (ORs) ranging between 2.13 (95% credible interval [CrI] 1.89–2.41) for amitriptyline, and 1.37 (1.16–1.63) for reboxetine (Cipriani et al., 2018).

Following a re-analysis of Cipriani et al., (2018) network meta-analysis, it was found the efficacy of antidepressants for MDD over placebo was unclear (Munkholm, Paludan-Müller & Boesen, 2019).

The overall design used in Cipriani et al., (2018) led to bias and there were several specific biases identified which were not considered in Cipriani et al (2018) analysis. A 'placebo run in' usually entails participants having placebo prior to the commencement of the study, though this was not clearly defined by Cipriani et al., (2018) (Munkholm, Paludan-Müller & Boesen, 2019). There was a deviation from Cochrane's overall risk of bias, in which Cipriani used a 'moderate' scaling to measure risk of bias, instead of low, unclear or high. Further, overall dropout and dropout due to adverse events were combined to measure acceptability and tolerability but did not assess any harms, or adverse events from any data relating to dropout due to adverse events, which led to further biases. In addition, 'placebo run in' trials and participants with established antidepressant doses were combined leading to a bias towards the active drug (Munkholm, Paludan-Müller & Boesen, 2019). Using the study design 'placebo run in' as a measure of comparison, inflates the effect size and effects the benefit/harm balance of placebo-controlled studies (Munkholm, Paludan-Müller & Boesen, 2019).

Currently, recommendations for MDD are to consider an SSRI as the first line option in antidepressant treatment and if there has been no or minimal response after 3-4 weeks, first increase support and consider alternatives or augmentation after this (NICE, 2022). Effective dose ranges are thought to be towards the lower end of the prescribing spectrum. For SSRIs, equivalent dose to fluoxetine 20-40mg, venlafaxine optimises between 75-150mg and maximum efficacy for mirtazapine is reached at 30mg (Furukawa et al., 2019). This contrasts with APA, which suggests titrating to maximum doses (APA, 2010). Limited efficacy is frequently seen after an initial course of treatment with less than 50% responding to drug treatment and the rate of relapse can be as great as 80% within one year of remission (Rush et al., 2006). There are emerging concerns relating to the lack of efficacy for long term use of antidepressant and contribution to worsening outcomes to a subset of patients experiencing MDD (Fornano et al., 2019).

Side-effects and acceptability can often be rationales for discontinuation of treatment in clinical practice, both professionals and patients are faced with the potential trade-off decision between both. Typical unwanted side effects such as neurological (i.e., tremor), sexual dysfunction and anticholinergic effects (i.e., dry mouth) are attributed to reasons for discontinuation and low adherence to treatment (Sinyor et al., 2020). Furthermore, these interventions are associated with an uncertain onset of effect being up to four weeks until early response is seen (Machado-Vieira et al., 2008).

Acceptability is often defined as attrition or dropout rates. In the case of Cipriani's (2019) network meta-analysis, only two forms of medication; agomelatine (OR 0.84, 95% CrI 0.72–0.97) and fluoxetine (0.88, 0.80–0.96) were associated with fewer dropouts than placebo (Cipriani et al., 2018). There was some tolerability for other medications with the ORs ranging between 0·43 and 0·77; the more tolerable medications were agomelatine, fluoxetine, escitalopram, citalopram, vortioxetine and sertraline (Cipriani et al., 2018). However, given that only two medications were higher in acceptability when measured against placebo might suggest medication overall is not as an acceptable choice of treatment.

A new wave of research has brought rapid-acting and effective antidepressant treatments such as the glutamatergic modulator, ketamine. Further, promising and evolving research being conducted into serotonergic psychedelics such as psilocybin and lysergic acid diethylamide (LSD) as other alternative treatments for MDD (Kraus et al., 2019).

Ketamine has shown to have a large significant impact on the symptoms of MDD, when given intravenously which lasts from 1-7 days post infusion (Lee et al., 2015). It has demonstrated a good safety profile with minimal side effects of a psychotomimetic symptoms or transient elevations in blood pressure and heart rate (Lee et al., 2015). However, chronic use increases the risk of abdominal cramps, ulcerative cystitis, and short-term memory impairment (Shahani et al., 2007).

Psilocybin has been found to have a moderate to large effect that could last from 1 week up to 6 months post a single or two dose administration and a higher dose (or two dose) showed greater symptom improvements. Overall, psilocybin shows a good level of acceptability, and tolerability, though there appears to be a risk of self-limiting increases in blood pressure which means it may not be suitable for all, while further research is conducted (Yu et al., 2022).

In relation to conventional medications, so far across the efficacy of pharmacology and psychotherapy, there is no significant difference found between the conventional options (Cuijpers et al., 2013). Lower drop-out rates in therapy groups suggest a higher acceptability for therapy of any form versus pharmacotherapy alone (*n* =30; ORs = 0.66; 95% CI 0.47 – 0.92) or as an adjunct to medication (Cuijpers, et al., 2010a). However, using dropouts only as a measure of acceptability may not capture the complex factors attributed to acceptability, when transferring to real-world comparative settings.

Psychological Treatments

For patients who seek treatment for MDD with their GP, preference for psychological therapies over pharmacology is around 70% in favour of psychotherapy (McHugh et al., 2013). As a first line treatment, cognitive behaviour therapy (CBT) is the most offered form of therapy. Overall, in terms of efficacy, CBT is often found to be most efficacious form of psychotherapy (Wampold et al., 2002; Nieuwsma et al., 2012). CBT, in real terms, continues to demonstrate mixed results. No significant difference in the efficacy between psychotherapies has been found and interpersonal therapy performing best (most efficacious; Cuijpers et al., 2008).

CBT shows significantly higher drop-out rates in a comparative analysis across psychotherapies (Cuijpers et al., 2008). The drop out data was either not given or limited to an overall dropout rate

with some including participant data for any session not attended within the dropout data and reasons for high dropout rates specifically for CBT were not established (Cuijpers et al., 2008).

An abbreviated version of CBT would be most practicable within a primary care setting (Haslett-Stevens & Craske, 2008). Specific to MDD treatment, without specified core features for example where a depressive episode may be less circumscribed, a brief version of CBT is likely to be ineffective (Haslett-Stevens & Craske, 2008). Though, meta-analyses have shown to favour brief CBT in primary care for MDD, when compared to usual GP care (Cape et al., 2010). The effect size was low (*d* -0.33, 95% confidence interval (CI) -0.60 to -0.06, *k* = 4, *n* = 450) in comparison to longer treatments and brief CBT had greater outcomes for anxiety than those with MDD or mixed group (a presentation with anxiety and depression; Cape et al., 2010).

The risk difference of patients no longer meeting criteria for MDD, and absolute rates of response and remission were significant (p=0.002) between all participants who received psychotherapy (62%), and control conditions (43%) did not meet MDD criteria after (Cuijpers et al., 2014). The absolute presence of MDD found no significant difference between type of psychotherapy (p=0.25). Different types of control conditions show large differences, from waiting lists as a control (17%), care as usual (48%) and 'other' controls (52%), and there was high to very high heterogeneity in most subgroups. Significant response rates were found after psychotherapy when compared to control conditions (p<0.001), defined as a 50% reduction on the Hamilton Rating Scale for Depression (HAMD). Remission rates for studies that defined as a score of 7 or lower on the HAMD were not significant when compared to control conditions but did represent a trend (p=0.07) (Cuijpers et al., 2014). Whereas studies that defined a score of 6 or lower on the HAMD, remission rates (41%) were significantly higher compared to control conditions (21%). Overall, the number of studies including CBT was higher than any other psychotherapy, those included in the remission score of 6 or lower (n=12) had a higher rate of CBT studies included in them in comparison to those

studies with a remission rate of 7 or lower (n=14; Cuijpers et al., 2014). This may mean that any results may require caution as it is not clear if the differing response ratings, therapy type and loading of the therapy in each remission group have differences that are significantly affecting the results.

Age is a considerable factor in the efficacy of psychotherapy. The effect size for adults is larger than adolescents and children. Across the adult age group effect sizes ranged from 0.66 (0.51-0.82 for older adults) to 0.98 (0.79-1.16 for younger adults), the effect size appears to decline until oldest old, when it reaches the highest efficacy again at 0.97, though there are less studies including oldest old age group (Cuijpers et al., 2020).

Psychotherapy has efficacy that lasts beyond the acute treatment phase, that is after the end of treatment. From 6 months or longer post randomisation shows psychotherapy significantly outperforms 'treatment as usual' in all outcomes (recovery, remission, partial remission, response, and reduction in depression severity) and across quality of life (QoL) measures (Karyotaki et al., 2016). It may be patients notice a perceived improvement in QoL following psychotherapy treatment and this is impacting on the lasting effects of treatment which is not felt with treatment as usual. As an independent construct, QoL independently improved unrelated to improved symptomology of MDD and it is unclear if there is any causal or temporal relationship between these two factors (Kolovos, Kleiboer & Cuijpers, 2016).

A major criticism of the research base for psychotherapy is many studies included in meta-analyses have been found to be of low quality. Conducted by rating against the different domains in Cochrane Risk of Bias tool and quality assessment using Chi Square to produce an average quality score, the effect size of psychotherapies may be overstated (Cuijpers et al., 2010; Chen et al., 2014). Despite there is ongoing discussion around the quality of the studies performed to robustly examine the

effects of psychotherapy as a treatment, recent meta-analyses have found ongoing low-quality studies affected overall effect sizes with high level of heterogeneity (Cuijpers et al., 2020).

Repetitive TMS interventions for MDD

Transcranial magnetic stimulation (TMS) is a form of non-invasive neuromodulation using a magnetic coil to create brief high-current pulses that can temporarily excite or inhibit specific areas (Hallett, 2000). Repetitive TMS (rTMS) is applied across the prefrontal region of the scalp and induces a magnetic field that causes depolarisation of the underlying neurons. This in turn modulates the neuron circuits that are involved with emotion regulation and symptoms of MDD (McClintock et al., 2018). rTMS has been approved by NICE (2015) with guidelines to indicate its' use for MDD. NICE guidelines suggest daily sessions of 30 mins for a course which is typically 2- 6 weeks long (NICE, 2015). There is approved safety (McClintock et al., 2018) and efficacy (Mutz et al., 2019) for the use of rTMS in MDD. In clinical practice, rTMS that can be high frequency or low frequency is most common, while theta-burst TMS (TBS) is also demonstrating potential efficacy (Mutz et al., 2019). Further, rTMS can be used across MDD treatment groups (Kiebs, Hurlemann, and Mutz, 2019). There is some suggestions TMS is more effective for those within hard-to-treat groups, i.e., treatment resistant, or intolerant may benefit most (Perera et al., 2016). However, a key critique for rTMS is the requirement to attend a clinic to receive treatment. The equipment is very bulky, whereas alternatives such as tDCS have greater portability.

Important clinical issues with treating MDD

The clinical course of MDD can be complex. For some, increased relapse rates can lead to the development of a chronic presentation, despite common treatments such as antidepressant medications and talking therapies being available (Gopinath et al., 2007; Nierenberg et al., 2003).

A challenge is presented at all aspects in accessing treatments through healthcare settings including clinical recognition, initiation, the adequacy of currently available treatments and in treatment response seen in patients (Pence, O'Donnell & Gayne, 2012). Within the National Health Service (NHS), there are often priority targets set, for example the current focus for NHS mental health service provision is dementia care, child, and adolescent mental health care (CAMHS) and meeting targets for Improving Access to Psychological Therapy (IAPT), which may cause a challenge with optimising primary care for MDD (Rasmussen & Young, 2022). Certainly, access to correct and timely treatment is compounded by rate of unassisted detection of depression such as not using a screening tool like Patient Health Questionnaire-9 (PHQ-9), is around 50%, and can lead to professional misinterpretation of the presenting symptoms (Kroenke, Spitzer & Williams, 2001; Mitchell, Vaze & Rao, 2009).

Poor adherence to the treatment plan and poor tolerability to the treatment offered such as side effects from medication or the ability to attend clinics for therapy sessions act as contributory aspects to the development of treatment resistance (Nemeroff, 2007). Moreover, symptom severity, chronicity, co-morbidities, and older age are significant contributable factors (Thase, 2011). These significant contributable factors act as a challenge for professionals in identification and have a negative impact on the rate of recovery for patients (Rasmussen & Young, 2022). When identified, and adequately treated, there is a clear positive clinical response to treatment of MDD in older age and there is no significant difference between psychological or pharmacological interventions (Cuijpers et al., 2006; Nelson et al., 2008). Particularly with therapy being designed to be reviewed by the therapist outcomes (Haslett-Stevens & Craske, 2008), the effect of treatment and perception of recovery is to some degree predicated on the therapist rather than being patient-led.

Following treatment remission, the presence of residual fatigue and sleep symptoms are common and can cause difficulties even in achieving the simplest of tasks (Zajecka, 2013). Although, symptoms can extend far beyond fatigue and sleep disturbance to include ongoing depression or

anxiety symptoms, low libido, and include a range of somatic symptoms such as back pain, aching joints, stomach pain. Further, residual cognitive symptoms can be present such as memory process impairment and increased cognitive reactivity (Israel, 2010). Those patients experiencing residual symptoms can be subclassified based on the presenting symptoms, the level of psychosocial functioning and this is currently adequately assessed by primary care GPs (Israel, 2010; Rasmussen & Young, 2022).

Another main clinical consideration is choice for the patient. Patient preference has an importance at policy and service delivery level. The former may relate to allocation of resources. The latter suggests that patients with their preferred treatment improves outcomes and have better treatment retention levels (Mergl et al., 2011; Swift, Callahan & Vollmer, 2011).

Summary

These sections have served to lay the foundations of the wider topic of depression. It began with the presentation of the history that led to the establishment of MDD as it is understood today across the Western world. A definition, epidemiology, and prevalence of MDD and a discussion on the current theories that may offer some explanation to the psychopathology of MDD. Current treatments along with the presenting clinical issues to treating MDD summarise this section. Antidepressants have limited efficacy and psychotherapy has limited provision and efficacy, other neuromodulations are not portable and therefore cannot be used in within the home environment.

Each of these can complicate the course of MDD if they are not addressed. One route can be to find an alternative to the current treatments. Novel, non-invasive neurostimulation modalities have been proposed for the treatment of MDD. Providing an alternative to current treatment options could offer another option for patients, might help alleviate the burden on psychotherapy services and

could be an option with a less distressing side effect profile. The next section will provide the context for the thesis projects with a discussion on tDCS as a novel treatment option for MDD.

1.3 Transcranial direct current stimulation

Overview

In this section, the reader will be provided with an overview of tDCS, what tDCS is, known modalities of tDCS. Next, the mechanisms of action of tDCS and aftereffects will be discussed. tDCS in the context of the efficacy as a treatment for MDD and the latest evidence for the side effect, safety, and acceptability of tDCS will be examined.

Transcranial direct current stimulation

Using electrical stimulation for a therapeutic effect can be traced as far back as the classical period of Plato and Aristotle (510 BC-323 BC) (Priori, 2003; Sarmiento et al., 2016). The electrical discharge of torpedo fish, when placed on the scalp, created a stupor-like state, and alleviated the patient of pain from a headache (Priori, 2003; Sarmiento et al., 2016). In the early 1800's, Galvani and Volta's work on galvanic currents progressed this field into clinical medicine and Galvani's nephew, Aldini tried the first form of electrical stimulation in patients with reported recovery from melancholia (Priori, 2003). In present day, there is an array of non-invasive brain stimulation techniques that are used to treat several ailments including MDD.

Non-invasive brain stimulation (NIBS) relates to a cluster of brain stimulation techniques, including tDCS, TMS, and transcranial alternating current stimulation (tACS). Non-invasive means that the stimulation can be given without the need of an incision, implant or procedure that breaks the skin (Woods et al., 2016). TDCS applies stimulation in the form weak electric current that is direct compared with tACS that applies a with a sinusodial-wave pattern to the scalp. TDCS and these forms of transcranial electrical stimulation (TES) have a range of benefits over standard treatment, in areas such as cost-effectiveness, portability, and a low side effect profile (Tortella et al., 2014), such

as changes in skin sensation (itching, tingling, burning sensation) during the procedure and headache (Matsumoto & Ugawa, 2017). TMS is also a form non-invasive neuromodulation (Hallett, 2000).

tDCS is applied to the scalp using a weak direct electrical current that induces spontaneous changes in cortical regions of the brain, with two or more electrodes placed on the scalp. The effect is polarity-specific, dependent on the direction of the current flows. Weak, constant polarisation of the neuronal resting membrane potential towards depolarisation is seen with positive (anodal) direct current stimulation and increased spontaneous modulation of cells. Negative (cathodal) stimulation produces opposite effects, hyperpolarization of the resting membrane potential (Nitsche et al., 2003).

Establishing the initial tDCS post stimulation effects were rooted in studies using TMS through combined animal and human research (Nitsche & Paulus, 2000), and expanded on as is the potential for tDCS use in MDD (Palm et al, 2016). Long lasting excitation in TMS, which increased approximately 150% above baseline, is evident for up to 90 minutes after the end of stimulation (Antal et al., 2004; Nitsche & Paulus, 2000, 2001; Nitsche et al., 2003). Depolarisation of the neuronal resting membrane potential was seen with positive (anodal) direct current stimulation, increased spontaneous firing of cells and dependent on the direction of the current flow. With the converse, towards hyperpolarisation following cathodal stimulation. A prime target to understand the physiological effects of tDCS and measure TMS-induced excitability changes using motor evoked potentials (MEP) in humans is the primary motor cortex. Induced changes outlast acute effects and long-lasting excitation is evident between minutes, and up to 24 hours after the end of stimulation (Antal et al., 2004; Nitsche and Paulus, 2000, 2001; Nitsche et al., 2003). The length of effect after tDCS is likely dependent on the form of modification (Liebetanz et al., 2002, Nitsche et al., 2003) and though, still purported to be representing acute-phase changes. This can be seen in the promotion of both LTP, or the strengthening of synaptic activity and lasting signal transmission between two

neurons and LTD, the selective reduction of synaptic efficacy but remain within early phase of plasticity. There are various forms of neuroplasticity, such as single cell synaptic and non-synaptic plasticity, in which LTP and LTD are involved. More widely, neuroplasticity can be involved in cortical remapping following brain injury (Wittenberg, 2010), where changes in interactions between brain regions can be seen. Further, activity-dependent neuroplasticity can be induced, such as found following changes in emotion, environment factors (Davidson & McEwen, 2012) and occur as part of healthy development across the life course.

Nitsche and Paulus (2000) demonstrated MEP with the use of TMS in healthy subjects as the basic neurophysiology of neuronal excitation, in relation to current polarity but also highlights the criticality of electrode position and duration of the stimulation session. This study further demonstrated mechanisms like short term potentiation for anodal stimulation. Long lasting excitation, which increased approximately 150% above baseline, is evident for up to 90 minutes after the end of stimulation (Nitsche & Paulus, 2001). In contrast to TMS, tDCS does not directly trigger action potential in neuronal cells, as it does not exceed the threshold for depolarisation while TMS does induce neuronal discharge. Rather, tDCS facilitates neuromodulation of the neuronal resting membrane potential at a subthreshold level, shifting towards depolarisation (Nitsche & Paulus, 2000, 2001; Palm et al., 2016).

When investigating TMS in MDD, functional and structural changes were observed in several cortical regions, especially the left dorsolateral and ventromedial cortex, the amygdala and the hippocampus following a successful positive course of TMS (Campbell et al., 2004; Hamilton, Siemer, & Gotlib, 2008; Koenigs, & Grafman, 2009). Combine this with a hypoactivity and hyperactivity across left and right DLPFC brain regions respectively (Grimm et al., 2008) gave the initial basis for the rationale of tDCS in these regions. With excitatory stimulation of the left DLPFC and the inhibitory stimulation over the right DLPFC, there is suggestion tDCS normalizes cortical activity. Though it is possible subcortical influences from amygdala, hippocampus seen in neuroimaging studies or even other

psychopathology, or comorbidities may have an impact on tDCS (Palm et al., 2016). Further, it is unclear if single polarity tDCS stimulation is responsible for improvements in MDD symptoms or whether it is a combination of both polarizations (Palm et al., 2016).

Modalities of tDCS

A key proposed mechanism of action of tDCS is located at calcium-dependent glutamate synaptic receptors, in which the aftereffects are proposed to be related to the induction of neuroplasticity. By pharmacologically blocking NMDA receptors, diminished effects of tDCS were seen (Liebetanz et al., 2002, Nitsche et al., 2004). Liebetanz et al (2002) used carbamazepine (CBZ), dextromethorphan (DMO) and a placebo tablet to investigate the possible mechanism of direct current induced after effect excitability changes. CBZ was chosen for its' ability to stabilises membrane potential in voltage dependent manner and suggest 600mg CBZ should selectively interfere with anodal stimulation. DMO is an NMDA receptor blocker which mediates neuroplastic changes of the motor cortex such as LTP or LTD. Results showed CBZ caused a selective prevention of MEP increase after anodal stimulation and DMO suppressed the tDCS induced affect effects, irrespective stimulation polarity. The affect-effects of tDCS are dependent on its action at the membrane potential. Anodal stimulation, post CBZ dosage, lowered the resting membrane potential toward depolarisation and highlight the potential importance to lasting after-effects. Another impact on glutamate-associated plasticity is tDCS-induced reduction of local GABA neurotransmission, due to the glutamate relationship to GABA as regardless of stimulation polarity (Stagg et al., 2009). This study used magnetic resonance spectroscopy (MRS), which detect changes of glutamate and GABA, after a tDCS session.

Longer term effects are often characterised as NMDA receptor-dependant and are presumed to reflect changes in synaptic efficacy and plasticity. Human studies within the primary motor cortex reveal glutamatergic receptors, in which the after-effects are proposed to be related to the

induction of neuroplasticity. NMDA receptor agonists/antagonists show the ability to selectively block, or indeed prolong, the MEP post-effects of anodal stimulation (Nitsche et al., 2003; Nitsche et al., 2004). With the activation of NMDA receptors, follows an influx of calcium ions, which is essential to plasticity (Stagg, Antal & Nitsche, 2018).

It is worth noting when tDCS is delivered to specific areas, it is not only cellular-level changes that have been reported and as such as tDCS stimulation to regions such as primary motor cortex (M1) (Polanía et al., 2011a,b, 2012) and the prefrontal cortex (Keeser et al., 2011) may interfere with functional connectivity in various networks, both cortical and subcortical. This is probably due to the propagation of larger and more distal compartments being homogenously polarised.

Further, there is suggestion of cumulative after-effects of repeated sessions with MEP sustaining even after 24 hours, an effect also blocked through NMDA antagonists which is initially reduced and then increased excitability (Monte-Silva et al., 2013). Evidence provided through MRS, which detect changes of glutamate and GABA after a tDCS session, found reductions of GABA locally after anodal tDCS while reduced glutamatergic neuronal activity followed cathodal stimulation with a highly correlated reduction in GABA (Stagg et al., 2009). Taken together, this suggests neuroplasticity following tDCS is both calcium and NMDA dependent and comparable to LTP and LTD likely at glutamatergic synapses and probably accessed through the reduction of GABA (Stagg, Antal & Nitsche, 2018).

In addition, the modulation of serotonergic and dopaminergic systems implicated in MDD may be influenced by tDCS. A significant improvement of the serotonin transporter (SLC6A4) was seen in long/long homozygotes than short allele carriers after tDCS (Brunoni et al., 2013a). The genetic polymorphism enzyme involved in the catabolism of dopamine, CoMT, appear to influence anodal stimulation effects on prefrontal functioning (Plewnia et al., 2013). This neuronal process

modulation is being used as an advantage in the development of tDCS protocols that require LTP or LTD, such as learning and memory.

Practical application of tDCS has established parameters to optimise the effectiveness of tDCS. The current in tDCS is typically in the range of 0.5 – 2 mA and is applied through 2 electrodes placed on the scalp with a conductive substance such as a saline solution or gel (Dedoncker et al., 2016; Turi et al., 2014). The MDD treatment protocol has current flowing from the anode electrode to the cathode electrode (and electrons flow from the cathode to the anode). The surface area of the sponge-electrode used in studies in MDD are typically large for comfort, approximately 25 – 35 cm^2, and sponge-electrode size can range from 3.5 – 100 cm^2 (Dedoncker et al., 2016; Turi et al., 2014). This means the stimulation is non-focal. The current passes with high impedance, through the skin, subcutaneous tissue, and skull. It is estimated that 25 – 50 % of the given current reaches through the cerebrospinal fluid (CSF) to grey matter (Rush & Driscoll 1968; Vöröslakos et al., 2018). Factors such as area of stimulation, electrode size, conductive fluid, distance between electrodes, as well as individual differences contribute to the final current intensity (Dedoncker et al., 2016; Rush & Driscoll 1968; Turi et al., 2014; Woods et al., 2015). A course of treatment ranged from 5-20 sessions. An optimal 'course' would be the equivalent of 12 or more sessions (Chase et al, 2020).

The efficacy for treating MDD with tDCS

Meta-analyses of tDCS studies have provided evidence for clinical efficacy both for improvement in depression rating scores, and in response and remission rates. This section will discuss the current evidence for efficacy in MDD.

Meron et al., (2015) meta-analysis provided a detailed overview of the research to date, narrative analysis, and insights into previous meta-analysis approaches on efficacy. They found significant

efficacy with a small effect (k = 11, g = 0.30, 95% CI = [0.04, 0.57], p = 0.027), defined as outcome measures and outcomes (Including rating scale score changes and response/remission rates). Though, initially, did not find categorical significant results which were in line with prior meta-analyses (Kalu et al., 2012 and Berlim et al., 2013, respectively). Meron et al (2015) present detailed information on previous meta-analyses and found Shiowaza et al., (2014) had used continuous and categorical measures with significant results for active tDCS over sham tDCS. This means both rating scale scores (continuous measures) have reduced and there has been an effect from tDCS on response and remission rates. There are benefits to using both continuous measures to offer superior sensitivity to those left with symptoms and categorical measures have superior specificity for those without symptoms or disease (Meron et al., 2015).

Meron et al., (2015) identified how each meta-analysis handled and analysed the largest included study (Brunoni et al., 2013b). Both continuous (rating scale scores) and categorical outcomes (response and remission rates) had been analysed at different timepoints (week 2 vs. week 6, the primary outcome). This led to repeat analysis with this change using the primary outcome (week 6) and revealed a statistical significance for both response and remission (response: LOR = 0.81, [0.28, 1.34], p = 0.003, remission: LOR = 0.73, [0.13, 1.33], p = 0.017), as well as a slight increase in treatment scores effect (g = 0.37, [0.09, 0.65], p = 0.008) (Meron et al., 2015).

Using individual-level participant data (IPD) of active versus sham tDCS treatment to increase accuracy of effect size, Brunoni et al., (2016a) found significant improvement in depression scores (b = 0.347, 95% CI 0.12–0.57, P= 0.002), when compared to sham tDCS. They found active tDCS was superior to sham for response (34% v. 19% respectively; OR= 2.44, 95% CI 1.38–4.32, P= 0.002), and remission (23.1% v. 12.7% respectively, OR= 2.38, 95% CI 1.22–4.64, P = 0.002) and demonstrated they were comparable to both repetitive TMS, and antidepressant treatment provided by primary care. Further, the results identified 2 areas of optimisation for future trials which were

'refractoriness' (the level of treatment resistance) and 'dose', with significance towards higher doses (Brunoni et al., 2016a).

Mutz et al (2018) addressed a broad antidepressant efficacy across various non-invasive brain stimulations depression (tDCS, TMS and theta-burst stimulation) of treating a current depressive episode in unipolar and bipolar disorder. In relation to tDCS, significant response (k=9, OR=4.17, 95% CI [2.25; 7.74]) and remission rates (k =8, OR=2.88, 95% CI [1.65; 5.04]) were observed in a comparison of active to sham tDCS. This meta-analysis was the largest to date and unique in its analyses of efficacy data. As it was not confounded by co-initiation of treatment and had randomised allocation of sham tDCS to account for placebo effects.

Comparing to sham treatment, Mutz et al (2019) network meta-analysis of randomised sham-controlled trials revealed that a course of tDCS treatment is associated with a fourfold increased rate of clinical response (OR = 4.32, 95% CI [2.02; 9.29]) and a threefold increased rate of clinical remission (OR = 3.07, 95% CI [1.58; 5.99]). As presentations that are routinely managed within primary care settings, tDCS appears to be better suited in those who respond to treatment with first episode or recurrent type depressive episodes (Meron et al., 2015; Brunoni et al., 2016a; Mutz et al., 2018).

Safety, side effects and acceptability of tDCS

In relation to safety, tDCS has a good safety and acceptability profile with no significant differences in the drop-out rates between those who received active and those who received sham conditions (Meron et al., 2015; Moffa et al., 2020; Mutz et al., 2018).

Brunoni et al (2011) completed a comprehensive review of adverse effects following tDCS. The results support a mild profile of side effects. However, a degree of selection bias in reporting,

assessing, and publishing adverse events (AEs) across studies was noted. As such, proposed a standardised questionnaire to aid in reporting AEs (Brunoni et al., 2011) and which might help to mitigate inconsistent reporting with AEs (Kessler et al., 2012; Nitsche et al., 2003; Poreisz et al., 2007).

The most common side effects were itching (n=46, 39.3%), tingling (n=26, 22.2%), headache (n=17, 14.8%), burning sensation (n=10, 8.7%) and discomfort (n=12, 10.4%; Brunoni et al., 2011).
Rare side effects include skin lesions and blurred vision. Skin lesions have been produced following poor electrode skin contact; this could be related to design or preparation of the electrode (Palm et al., 2014; Rodríguez et al., 2014). This is corrected by diminishing electrode density (by increasing the size of the electrode) and electrical resistance (using rubber electrodes covered with sponge and conductive substance i.e., saline) at the site (Woods et al., 2015). While skin lesions on the dermis are unpleasant, this electrochemical reaction is not expected to diffuse into the brain so not attributable to any form of brain injury (Bikson, Datta & Elwassif, 2009), as no oedema or injury of the blood-brain barrier or cerebral tissue following tDCS has been observed using MRI (Nitsche et al., 2004).

An instance of blurred vision has been reported in 2 occasions out of 83 reported occasions of side effects during the randomised control trial (RCT) (Loo et al., 2010) and a continuation study (Martin et al., 2013). In Martin et al (2013), tDCS was being given weekly or bi-weekly to investigate prevention of relapse and they found instances of blurred vision in 7% of patients and 11% respectively (Martin et al., 2013). Both studies had the anode place at pF3 on international 10/20 EEG system.

Treatment-emergent (hypo)mania (TEM) has presented in tDCS showing a small but significant risk following the commencement of tDCS (Berlow et al., 2019). There were 13 cases of mania or hypomania to date among patients with a diagnosis of a mood disorder receiving tDCS out of 411

patients (Berlow et al., 2019) of which 8 were taking a concurrent or co-initiation of SSRIs. One case met diagnostic criteria for a manic episode with psychotic features (Brunoni et al., 2011). There are likely multiple factors involved in these cases. Most were taking SSRIs and having adjunctive tDCS. It would be difficult to disentangle which or both treatments resulted in a (hypo)manic response. Stimulation montage which involves larger stimulation of deep central brain areas may pose a greater risk of mania presentation than those of montages that use frontal positions such as in major depression (Gálvez et al., 2011). Some of the participants were diagnosed with bipolar depression and antidepressants are well established to potentially cause a manic switch within this clinical group (Post et al., 2003).

Ethical considerations raise some vital questions. Currently, tDCS is not available as a mainstream treatment for MDD on the NHS. However, there is an ever-expanding private market of devices for purchase, with Europe approving its first at-home device classified as a medical device for the treatment of depression in 2019. The first question is whom should deliver tDCS in clinical environment (i.e., medical staff, specialised staff, or the patient) and how it should be regulated, if at all (Brunoni et al., 2012). The other ethical concern is around the tolerable risk of inducing maladaptive long-term neuroplastic changes (Brunoni et al., 2012). These uncertainties may present as limitations to future clinical research. As use widens, maladaptive long-term neuroplastic change is a valid possibility. Short term changes have been induced by tDCS in moral judgement, deception, decision making and in utilitarian behaviour, with polarity effects on selfish vs selfless behaviours in women (Edgcumbe et al., 2019; Fumagalli et al., 2010; Luber et al., 2009). Considering the wider effect of structural, functional brain activity, and psychopathology and personality, it is possible induced, undocumented changes have occurred across these realms.

All-cause discontinuation rate or dropout rate is often the standard objective measure for acceptability. If the dropout limit is not met, an intervention can be considered accepted as a potential novel treatment. Dropout rates for tDCS are around 6% (Alonzo et al., 2019; Aparício et al.,

2016) between active and sham groups and not statistically different (Aparício et al., 2016; Brunoni et al., 2016a; Moffa et al., 2017). Dropout ratings assists with providing a limited understanding of tolerability for the treatment but fails to address the rationales for any dropout nor address improvements in acceptability. If the treatment is found to efficacious, acceptability can offer a bridge to translating a treatment from research across to real-world implantation and concordance of treatment.

Summary

This section has provided an understanding of the background knowledge of tDCS with research background in TMS research. There has been a discussion around the modalities of tDCS and efficacy, safety, adverse events, and acceptability of tDCS. The next section will provide a brief overview on how tDCS is used as a methodology for 3 separate projects. The first will be a meta-analysis focused on the efficacy of tDCS in LLD, the next will be a qualitative project on acceptability and the final project will be tDCS and neurocognitive effects.

1.4 A Brief Introduction to the Thesis Projects

Overview

The next section will give a brief overview and rationale for the thesis in LLD, acceptability, and neurocognitive aspects of tDCS use. These 3 areas will be discussed in greater detail in the respective chapter introductions. A description of the feasibility clinical trial that was conducted alongside the projects follow the thesis project overviews. The section will lead directly into the research scope, aims and objectives, the research questions, and hypotheses.

Project 1: A systematic review and meta-analysis of randomised controlled trials of tDCS in late-life depression

LLD affects between 3.3% and 6% of those aged 65 or older (Volkert et al., 2013; Byers et al., 2010; Andreas et al., 2017). Presentation can be more somatic in symptoms compared to those of younger ages experiencing a depressive episode which leads to lower diagnosis and treatment (Reynolds III, Alexopoulos & Katz, 2002), along with increased distress, higher comorbid disease burden and functional decline (Sutin et al., 2013). Primary care options are preferred for this age group (Unützer et al., 2003). Available treatments, antidepressants, and psychotherapy (NICE, 2022) showed no significant difference between treatment options with a large effect size (0.72) (Cuijpers et al., 2006). Pharmacological options can be problematic as medication can produce sides effects (Alexopoulos, 2011), higher nonadherence (Holvast et al., 2019) and have lower efficacy (Tedeschini et al., 2011). Further, though psychotherapy is preferable for those experiencing LLD (Unützer et al., 2003; Huang et al., 2015) with an apparent efficacy for resolving depressive symptoms (Frost, Bauernfreund & Walters, 2019; Kishita, Takei & Stewart, 2017; Thomas et al., 2018), the quality of research is low (Cuijpers et al., 2006; Holvast et al., 2017) and include over estimations of their effects (Cuijpers et al., 2010b). tDCS could be a potential novel treatment offered as an alternative first line treatment within the primary care setting. However, knowledge about the efficacy and

acceptability is not known and there has not yet been a meta-analysis of the available evidence to date. The first project will address this gap in the literature.

Project 2: A qualitative account of acceptability using a new paradigm to investigate the feasibility and acceptability of at-home tDCS

A feasibility experiment is used to see if an intervention can be shaped to be relevant and sustainable. One of the appropriate areas of interest may focus on acceptability (Bowen et al., 2009). The main questions asked in a feasibility study are: can it work, will it work, and does it work? (Bowen et al., 2009). An additional benefit of conducting a feasibility study is cost-effectiveness, though it does not save on time (Morgan et al., 2018). Maximising the information gained from a study question such as one around acceptability is an important offset to the time cost. Acceptability in healthcare interventions should reflect an understanding in design, implementation, and evaluation and this is a process that should occur prior to the intervention and post intervention (Sekhon, Cartwright & Francis, 2018).

Social validity has been termed to describe the acceptability of healthcare treatment and the change in behaviour that follows (Kazdin, 1977; Wolf, 1978). Principle research around treatment acceptability began with the understanding of potential service users in child behaviour management services, evaluating positive and reductive behaviour procedures (Miltenberger, 1990). There have been multiple scales developed for assessing acceptability, with most of them being variation of Kazdin's (1980a) Treatment Evaluation Inventory (TEI) which measures treatment acceptability using a 15-item 7-point Likert questionnaire, or Witt and Martens (1983) Intervention Rating Profile (IRP), comprised of 20 items, on a 6-point Likert-type scale which also measures treatment acceptability (Kazdin, 1980; Witt & Martens, 1983). It is unclear if the currently available tools are suitable for measuring treatment in adults, given the modelling on child outcomes.

Acceptability can be affected by many different factors such as the setting of treatment (Burgio et al., 1995) or how intrusive the treatment (Reimers et al., 1992; Spreat & Walsh, 1994). The type of treatment can raise both differences and similarities across acceptability (Miller & Keeley, 1992). A treatment which describes a medical intervention, such as describing what tDCS is or its function, did not seem to impact acceptability levels (Miller et al., 1998) but there are differences with professionals in making recommendations on a treatment (Carter, 2007).

Following a critical review of 9 standardised forms measuring acceptability, Finn and Sladeczek (2001) reveal eight areas of treatment acceptability placing no more importance on one topic area than another: (a) definition of treatment acceptability; (b) content and purpose; (c) test reliability; (d) test validity; (e) statistical analysis; (f) sample characteristics; (g) scoring procedures; and h) uses of the measure in research and practice (Finn & Sladeczek, 2001). There is minimal guidance on conducting an acceptability assessment within complex interventions research (Sekhon, Cartwright & Francis, 2018). Some examples might be using a quantitative (structured questionnaire) or qualitative (probing questions) approach but how this should be defined or operationalised is not clear (Sekhon, Cartwright & Francis, 2018). To gain a valid measure of patient preference, Sidani et al. (2009) propose a 3-step approach is required to assess treatment acceptability. Presenting information to enhance participant understanding of the option, assessing perception of the treatment intervention, and then inquiring on what their choices are (Sidani et al., 2009).

Sekhon et al. (2018) proposes a new theoretical framework of acceptability (TFA) to address this using inductive and deductive methods to identify 7 constructs of acceptability: affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness, and self-efficacy. The TFA offer a potential method of guiding clinicians to address barriers to treatment (Hudson et al., 2019) and is being included in study protocols as a primary method of assessing acceptability and feasibility using semi-structured interviewing across a wide range of research

topics (for example, Bell et al., 2020; Saracutu et al., 2019; Linnemayr et al., 2018; Griever et al., 2019).

tDCS is a relatively new form of treatment for MDD and there is established efficacy for tDCS as a treatment. However, there is a very limited understanding on how participants feel about the treatment and whether they would deem it as an acceptable treatment beyond drop out data. This project would aid in understanding the level of acceptability of the treatment. To address the gap in the literature, a qualitative assessment of acceptability of tDCS within a MDD population will be conducted.

Project 3: The neurocognitive assessment of depression following tDCS treatment using auditory verbal learning test

Verbal learning and memory are understood in terms of how humans retain and use information classed as symbolically representable objects. This can include numbers, word lists, and letter combinations. The auditory verbal learning test (AVLT) assesses verbal learning and memory, as well as the perceived spatial-temporal relation between those symbolically representable objects, i.e., the verbal item (word) to be remembered occurs before or after another unrelated discreet aspect (Tulving & Madigan, 1970). Within the research sphere, verbal learning students may refer to recalling or acquisition a word is described as 'attachment of response to stimuli' and forgetting the word refers to 'loss of response availability' versus a memory student who would use terms relating to storage and retrieval (Tulving & Madigan, 1970).

Neurocognitive disturbances have been found in MDD, which have significant moderate effect and remediation of neurocognitive symptoms improves the outcome for depressed patients (Rock et al., 2014). A large international multi-site study using tDCS has been conducted with MDD participants. In this study, participants were diagnosed with either MDD or bipolar depression, given a high or low

dose tDCS and assessed at baseline, after 4 and 8 weeks. Results demonstrated significant neurocognitive improvement with high dose tDCS as measured using a verbal learning task (McClintock et al., 2020). It is possible effects are dose dependent as well as dependent on the length of sessions, early studies had not optimised the treatment parameters and this to further investigate this, we will be looking at verbal learning and memory within this thesis.

TDCS appears to have some effect on neurocognitive changes within the clinical population. A recent meta-analysis of IPD looking at global cognitive effects with executive function, memory and attention found no overall significant effects but did find active tDCS was favoured over sham in delayed AVLT, author and year category fluency, Stroop interference and letter number sequencing (Martin et al., 2018).

The AVLT was developed by Andre Rey (1964) as a measure of learning and memory (Rey, 1964). The English translation was completed by Taylor (1959) and Lezak (Lezak et al., 2004) and developed to add in free recall of 5 trials of words, and a recognition test to assess verbal learning and memory. AVLT consists of 15 words spoken by the rater on 5 successive trials; after each trials the participant is asked to free-recall as many words as they can. Measures on the AVLT might include (a) recall on individual AVLT trials, (b) total words recalled in five trials, (c) difference between recall on Trial I and Trial V (or maximum recall), (d) subjective organization, and (e) type of error (Weins, McMinn & Crossen, 1988).

There are well established normative data available for AVLT (Boller-Wilson & Bleeker, 1986; Geffen et al., 1990; Ivnik et al., 1992; Van Der Elst, et al., 2005). When conducting tests repeatedly over a period using the same form shows improved performance and thus having alternative forms would be useful with a repeated measure methodology. There has been development of alternative forms that show no significant different to the original form (Geffen, Butterworth & Geffen, 1994), thus suitable to use different forms over different time points.

Historically, AVLT has not been sensitive to change in psychiatric illness such as MDD or anxiety when used within a clinical population (Davidoff et al., 1990; Schmidt, 1996). In that, scores did not differ significant from healthy controls. Though verbal learning and memory are implicated in MDD (Austin et al., 1992). The current evidence base for the effect of neurocognitive effects shows mixed results (Martin et al., 2018; McClintock et al., 2020) and a large proportion of these assessments have been conducted within a clinical setting. This study will look to add to the knowledge base by assessing AVLT (Rey, 1964) following a treatment course of home-based tDCS.

1.5 **Description of Feasibility and Acceptability Clinical Trial**

The clinical trial was designed as a pilot, open-label, single arm, single site study to investigate the feasibility and acceptability of home-based tDCS. Home-based tDCS is conducted in the same way as tDCS in a clinic but the portability of the device allows for tDCS to be completed within a participant home. Research ethics committee approval by the London Fulham Research Ethics Committee, and local University Research Ethics Sub-Committee approval were provided. All the participants were provided with a written informed consent form, as a standardised informed consent form and completed at screening for the study (ClinicalTrials.gov ID: NCT03632434).

Participants

Participants were assessed using a structured Mini-International Neuropsychiatric Interview (MINI; Version 7.0.2) (Sheehan et al., 1998) to establish diagnosis of Major Depressive Disorder. Depressive severity was assessed by the 17-item HAMD (Hamilton, 1960). Eligibility criteria was as follows: Inclusion criteria were minimum age of 18 years, being in a current depressive episode as determined from the MINI interview, having at least a moderate severity of depressive symptoms as determined by a 17-item HAMD rating of ≥ 16. All participants were required to be engaging in psychological therapy, which could include online CBT, or to be taking antidepressant medication, and all participants were community-dwelling, none were an inpatient in a hospital admission or a resident in a care home. Exclusion criteria included treatment resistant depression as defined by poor clinical response to 2 or more antidepressant trials, any concurrent DSM-5 comorbid Axis I or II disorder within the previous 6 months, including bipolar disorder, obsessive compulsive disorder, or primary psychotic disorder, having significant risk of suicide or self-harm, pregnant women or women who were breastfeeding, history of ECT, TMS or VNS, any exclusion criteria for receiving tDCS, including having a scalp or skin condition (e.g. psoriasis or eczema), having metallic implants, including intracranial electrodes or a pacemaker.

The enrolment target was 30 participants, based on a 20% attrition rate to achieve a sample size of 24 participants with major depression. 26 participants were enrolled, 24 completed the study and 2 participants discontinued participation (n= 1 did not like tDCS sensation, session 3; n=1 did not disclose reason, session 12).

Once enrolled, the participants completed a clinical interview which provided information on their demographics, current mental state, support network, educational background, treatment, and history of treatment, GP information details. A risk assessment was conducted for all participants as part of the MINI assessment as significant risk of suicide or self-harm was an exclusion criterion.

Device

Two devices were used as the intervention in the main study. Neuroelectrics StarStim tDCS device (n=3) or Flow Neuroscience Flow device (n=23) with a bifrontal montage at DLPFC and cathode at right DLPFC (10/20 EEG positions F3 and F4, respectively). Stimulation is 2 mA, and electrode area is 35 cm^2 for 30 minutes per session. The rationale for 2 devices were related to COVID-19 lockdown. The Neuroelectrics device required in-person, researcher led application, where the Flow device could be managed remotely. For the studies within this thesis, data from Flow Neuroscience was used only.

Frequency

The intervention consists of a 6-week course of active tDCS over DLPFC, consisting of 5 sessions per week for the first 3 weeks followed by 2 sessions per week for 3 weeks, for a total of 21 tDCS sessions. The duration of each session is 30 minutes. Follow up sessions were offered to all enrolled participants at 3 months post intervention and 6 months post intervention. The tDCS parameters are based on meta-analyses (Meron et al., 2015; Brunoni et al., 2016a; Mutz et al., 2018) which demonstrate that treatment effects are most evident at 2 mA current of 30-minute stimulus duration for 21 sessions for participants with MDD.

Process

For Neuroelectrics StarStim tDCS device, a neoprene cap was fitted to the participants head by the researcher. Two electrodes were placed inside the cap and connected to a Bluetooth device. A pre-programmed software (NIC2) was used to deliver the stimulation with 10 second ramp up and down. The researcher was physically present in the participant home to observe the effect and to start (and stop as necessary) the stimulation. The stimulation was programmed to end after the 30 min stimulation and ramp down. The participant was instructed to sit quietly for each session and was directly supported by the researcher regarding electrode position, additional saline, side effect management, as well as any other concerns. During the stimulation session, the researcher did not speak with the participant. The participants were instructed to inform the researcher if there were any concerns re: side effects or other concerns (i.e., one occasion a participant's doorbell rang).

For Flow Neuroscience tDCS device, a headset was delivered to the participants home and the participant was directed to place the electrodes within the device using a Flow Neuroscience App instruction video. The researcher was on a live Microsoft Teams videoconferencing while this happened. The device was placed on the head by the participant and the participant was able to check the position using Flow Neuroscience App. The app was also used to start (and stop as necessary) the device. TThe participant was instructed to sit quietly for each session and directed by the researcher regarding electrode position, additional saline, side effect management, as well as any other concerns, remotely. The researcher remained present remotely via Microsoft Teams videoconferencing until the end of the session, so the participant could access the researcher for any questions at any time. During the stimulation session, the researcher did not speak with the participant unless there were any concerns re: side effects or any other concerns (i.e., one occasion a participant's phone rang, which stopped the stimulation/or doorbell rang).

All participants were in the same space for each stimulation session (i.e., in front room, using same chair) but there was variation with some participants preferring to be seated (n=20) and others lying

down (n=6). The researchers remained on the videoconference software, but again some participants preferred the researcher to turn their video off (n=4).

At each session, a brief catch up was conducted prior to the commencement of the session to review any changes to medications, any side effects or adverse events since the last visit and verbal consent taken to go ahead with the next session. Each week an adverse event form and a Young Mania Rating Scale (YMRS) (Young et al., 1978) were performed to monitor for any adverse events. Some participants continued with tDCS after the study was completed using their own purchased device or keeping the device from the study (n=5).

Assessments

Treatment acceptability was assessed using a standardised form which included a 7-point Likert scale which was completed at visit (V) 1 prior to the first stimulation session; V21, the end of the study and V23, classed as the 6 month follow up visit.

Mood scales were used to assess depressive symptoms using 17-item HAMD (Hamilton, 1960), anxiety symptoms using Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959) and a self-report form using PHQ-9 (Kroenke, Spitzer & Williams, 2001). Adverse effects were assessed using the tDCS Adverse Events Questionnaire (AEQ) (Brunoni, et al., 2011) and YMRS (Young et al., 1978). Functional ability was assessed using Sheehan Disability Scale (SDS) (Sheehan & Sheehan, 2008). All were completed at V1 prior to the stimulation, then every week during the 5 tDCS sessions per week at V5, V10, V15, during maintenance - at 2 tDCS sessions per week at V17, V19, V21, and at the open label/follow up sessions, V22, V23.

Neuropsychological assessments: 2 neuropsychological assessments were chosen to be completed remotely: Auditory Verbal Learning Test (AVLT) (Rey, 1964) and Symbol Digit Modalities Test (SDMT)

(Smith, 1991) were conducted at 4 times points pre and post V1, after 2 weeks of stimulation (V10) and the end of the study after the final stimulation session (V21).

Outcomes

To assess feasibility of the intervention for trial, measured by a minimum participant retention of 70% following enrolment. To assess acceptability of the intervention, responses were measured using a questionnaire for treatment acceptability. Secondary exploratory outcomes for mood scales (17-item HAMD, HAMA, PHQ-9) and functional ability (SDS).

Results

All participants responded and/or remitted; other assessments conducted including mood and functional ability were significantly improved (17-item HAMD, HAMA, SDS). Adverse events were reported and measured using AEQ (Brunoni et al.,2011). These reflect the current established mild side effects expected for tDCS use, results can be found in Woodham et al (2022).

1.6 **Research Scope**

This thesis brings together 3 projects with different aspects of research using the central thread of a tDCS clinical trial. The clinical trial was conducted to assess the acceptability and feasibility of at-home tDCS for MDD. The first project will address the research knowledge gap of efficacy and acceptability of tDCS for LLD. The second project will use a new paradigm to review the qualitative themes around acceptability of tDCS as a novel treatment for MDD. Project three will examine neurocognitive offline effects of tDCS (before and after the tDCS) in MDD participants to see if and how these change with treatment.

1.7 **Research Questions, Objectives & Methodologies**

This thesis will include the following projects:

<u>Project 1:</u> Meta-analysis of individual participant data in late-life depression on acceptability and efficacy, extracted from randomised sham-controlled trials in LLD.

Objective: Investigate the efficacy and acceptability of tDCS in LLD in an IPD meta-analysis

Question 1: Is active tDCS over DLPFC efficacious in LLD compared to sham, as measured by an improvement of depressive symptoms?

Hypothesis 1: Active tDCS over DLPFC will improve symptoms associated with LLD compared to sham conditions.

Question 2: Is active tDCS over DLPFC considered acceptable in LLD, in comparison to sham conditions?

Hypothesis 2: Active tDCS over DLPFC will be considered acceptable in LLD, when compared to sham conditions.

Methodology: Using Bayesian meta-analytic techniques, I will analyse the current research for the efficacy and acceptability of active tDCS over sham tDCS in LLD

<u>Project 2:</u> Qualitative analysis of acceptability using a new paradigm to investigate the feasibility and acceptability of at-home tDCS

Objective: Investigate the acceptability of home-based tDCS in major depression using qualitative methods

Question: *How do patients with depression describe the acceptability of using a novel treatment, at-home tDCS?*

Primary Statement: To understand the themes around the acceptability of using tDCS at home.

Methodology: tDCS will be employed both as a treatment and causal methodology. The data will be collected using semi-structured interview using an acceptability questionnaire that includes open-ended questions. Interviews will be conducted at 2 timepoints: post V21 (final tDCS session) and at V23, 6 month follow up. Using a thematic analysis will allow us to identify and understand the themes around acceptability of tDCS as a health-based intervention for depression.

<u>Project 3</u>: Neurocognitive effects of tDCS using a neuropsychological task (Auditory Verbal Learning Task, AVLT) to assess verbal learning.

Objective: Examine neurocognitive effects of home-based tDCS using the auditory verbal learning task, within MDD patient population.

Question: Does verbal learning improve over time following tDCS treatment for MDD?

Hypothesis: tDCS treatment will be associated with improved verbal learning skills (measured by total correct answers recalled and learning over trials, expressed as total correct over x5 trials with the AVLT), in line with McClintock et al (2020) findings.

Methodology: tDCS will used as a causal methodology with Auditory Verbal Learning Task (AVLT) (Rey, 1964), a neuropsychological testing of task-based activity, following the tDCS sessions at post 1st session, post 10th session (after 2 weeks) and post 21st session (final) to examine the neurocognitive correlates of tDCS.

Chapter 2: Systematic review and meta-analysis of randomised controlled trials of tDCS in late-life depression

Chapter Overview

This chapter will discuss what is LLD through defining the symptoms, epidemiology, and symptomatology of LLD. The clinical importance of LLD, along with the challenges with treating LLD will be presented and discussed. Understanding the aetiology and the main treatments provide the basis for the current evidence of the use of tDCS in LDD. The literature review gained limited evidence which required combining to establish the efficacy and this will be qualified within the chapter. The chapter then discuss what meta-analyses are and the principles of conducting a meta-analysis. The materials, methods, data analysis, results, and discussion of an individual participant data approach will end this chapter.

2.0 Introduction

What is late-life depression: definition, epidemiology, and symptomatology?

LLD is defined as a major depressive episode (MDE) occurring in those of older age, typically aged 65 years and older (Lebowitz et al., 1997). Persistent feelings of sadness and, or anhedonia (a lack of interest or enjoyment), for most of the day on most days persisting over a period of 2 weeks are the core symptoms. One or both core symptoms must be present in LLD. Along with these core symptoms, any combination of "specifiers" or symptoms include sleep disturbance (insomnia or hypersomnia); changes to loss of appetite or weight (increased or decreased) for no apparent reason; fatigue or loss of energy; psychomotor retardation or agitation; trouble with concentration or making decisions; worthlessness and excessive inappropriate guilt feelings; thoughts around death and suicidal ideation. According to the DSM, fifth edition (DSM-5), a combination of 5 or more symptoms including core symptoms with a significant impairment on their functioning is used to

identify and diagnose a current depressive episode (APA, 2013). In the United Kingdom (UK), ICD, version 11 (ICD-11), is used for diagnostic purposes (World Health Organisation, 2018). ICD-11 criteria for a current depressive episode consist of the same core symptoms: depressed mood or lack of interest, enjoyment most of the day for 2 weeks, with significant functional impairment and a requirement for 5 or more symptoms occurring to meet the threshold of diagnosis, with ICD-11 offering 'qualifiers' instead of 'specifiers'. Where these differ, are across additional symptoms. ICD-11 include hopelessness and anxiety, which unique to ICD-11 as part of the diagnosis. There is a higher threshold for those who experience bereavement within the context of ICD-11 diagnostic criteria. This contrasts with DSM-5 in which bereavement is considered to be a distinct category (APA, 2013).

The range of prevalence rates for major depression in those aged 65 and older is between 3.3% and 6% (Volkert et al., 2013; Byers et al., 2010; Andreas et al., 2017). This rises to approximately 7.2% in the oldest old (75 and over) (Luppa et al., 2012). In the UK, LLD affects 1 in 5 older people living in the community and 2 in 5 living in care homes (Luppa et al., 2012). Most concerning, suicidal ideation is commonplace when experiencing LLD. Completion of suicide is highest in older age groups over 60 years and is consistently seen within this clinical population across countries (Shah et al., 2016; WHO, 2018). As global life expectancy improves, people are living longer. The number of people living beyond the age of 65 is set to increase. With a high probability that an increase on worldwide life expectancy will see life expectancy age closer to 90 years and the largest age increases are found across females (Kontis et al., 2017).

Whilst in the DSM-5 or ICD-11, there is no unique or subset diagnosis for LLD, there is often variation in the presentation and symptoms for people with LLD. At times, LLD presents less with typical mood and motivational symptoms and more with somatic-like symptoms, particularly in those aged 70 and older. This can lead to under-diagnosis and then under-treatment (Reynolds III, Alexopoulos & Katz, 2002). When looking across the life span, the trajectory of displayed depressive symptoms also starts

to increase around aged 70 years and above, suggesting increased distress within this age group, which is not only attributable to factors such as comorbid illness and functional decline (Sutin et al., 2013). This is explained by the experience of higher somatic disease burden, more severe mood and motivational symptoms often being found within this age group (Hegeman et al., 2015), and can create a complex picture for diagnosis.

However, when treating LLD and assessing with standardised objective depressive scales, such as 17-item HAMD (Hamilton, 1961), the greatest change in symptoms seen were across 9 items which include both 'typical' mood and motivational and symptoms that might be interpreted as somatic: depressed mood, guilt, and loss of interest in work and activities; sleep particularly middle and late insomnia, anxiety and energy and suicidal ideation. These items account for around 92% of variance and are comparable to non-geriatric age groups (Nelson et al., 2005).

There is comparable symptom change when using the Montgomery-Åsberg Depression Rating Scale (MADRS) (Borza et al., 2015). An observational prognosis study looking at LLD in hospital found change over time, the largest effect sizes were seen in reported sadness, lassitude, and suicidal ideation. These are similar symptoms to those seen on HAMD despite there being some differences with assessment scales and type of population (i.e., hospitalised patients). Concentration difficulties improved the least, which could be accounted for, though a small sample of those with a diagnosis of dementia (Borza et al., 2015). Albeit symptom change in both standardised tools (HAMD, MADRS) can be used as a reliable means of measuring response and remission following treatment (Borza et al., 2015; Nelson et al., 2005).

The natural history of symptom duration and severity, clinical course types and the stability of the diagnosis of LLD highlights the poor prognosis, with nearly 50% of participants feeling depressed around two thirds of the time (Beekman et al., 2002). It is further reflected in the chronicity of the illness; much of the sample had a chronic or chronic-intermittent type of LLD (64%), with only 23%

with ‘true’ remission, meaning there was no further occurrence within the 6 years follow up period. In terms of severity of symptoms, this study found a clear expected gradient, with subclinical depression showing the least severity, followed by MDD, dysthymic disorder (DYSTD), then ‘double depression’ classified as meeting diagnosis for both MDD and DSYTD, with the latter group also showing the worst severity and prognosis. On average, there are around 17% with clinically relevant symptoms (Luppa et al., 2012) and this increase as age increases i.e., over 85, around 20-25%; for over 90’s, it is estimated in the region of 30-50% to have clinically relevant depressive symptoms. As seen in younger age groups, subclinical symptoms have the same likelihood of developing into a diagnosable affective disorder with similarities in their outcomes, when compared to healthy age-matched controls. Though what is unique to late-life groups is a higher percentage of diagnosable subthreshold or minor depression (15%), compared to MDD (2%). Further, subthreshold depression in late-life shows a closer alignment with a DSM diagnosable condition at their outcome assessments, has an interrelationship to stressful life events, among other factors and may suggest diagnostic tools are not wide enough when assessing depressive disorders in late-life and requires closer consideration of clinically relevant symptoms (Beekman et al., 2002; Van den Berg et al., 2001; Büchtemann et al., 2012).

Incidence and recurrence of MDD across the old age population show that those with a history of depression occurred at a higher rate than those with a first occurrence late in life and recurrence was 3 times as high than those with a later onset presentation (Luijendijk et al., 2008). Women were twice as likely to have a first and recurrent episode but risk of the development of LLD across sex were no different (Büchtemann et al., 2012; Luijendijk et al., 2008).

Somatic symptoms as well as motivational symptoms, over mood symptoms, have been associated with vascular and degenerative processes (Naarding et al., 2005). Though, this also highlights the importance of a differing symptom profile for LLD. There are as high as 90% of somatic symptoms

that are not explained by physical illness. There is a high potential that a considerable proportion of LLD population experiencing either an 'atypical' form of depression or express their symptoms in a somatic way, particularly in relation to the lower proportion of MDD diagnosis within this age group (Jeong et al., 2014).

Clinical importance of addressing LLD

Misidentification, reduced identification, and delayed treatment are clinical concerns in LLD (Mitchell, Rao & Vaze, 2010). As LLD can often be seen with co-morbid illness, symptoms often overlap. This may lead to complications during diagnosis if symptoms are solely explained by physical ailments rather than LLD. Potentially delayed treatment and an increase in the severity of 'baseline' symptoms (symptoms that are seen at the point of diagnosis and initiation of treatment) can be a consequence of these complications. Thus, identifying symptomology is important, as both baseline depression and anxiety severity are predictors for treatment outcome. Longer duration of episodes has been associated with poorer treatment outcomes (Tunvirachaisakul et al., 2018). Moreover, when looking at item-level depressive symptoms, there is a significant disparity across ethnic groups. Compared to non-Hispanic white participants, all other ethnicities have significantly more severe symptomology as measured by Personal Health Questionnaire Depression Scale (PHQ-8). Hispanic ethnicity was associated with 23% increased severity; other, multiple, or unspecified ethnic groups saw a 14% increased severity; and older Black groups showed a 10% increased severity. There was also 1.5 to 2-fold higher levels of anhedonia, sadness, and psychomotor symptoms in Hispanic and Black communities (Vyas et al., 2020).

Low QoL has been linked to increased morbidity and hospitalisation (Dominick et al., 2002; Tsai et al., 2007). Those experiencing LLD report QoL as negatively impacted and associated with higher mortality, typically through suicide or higher morbidity (Chang-Quan et al., 2010). Inevitably, a higher likelihood of accessing other health services proposes a higher economic burden on services than

those without depression (Bock et al., 2014; Katon, 2003). There is a strong correlation between physical illness, LLD and a lower disproportion of utilisation of mental health services ranging from 56%-79% (Kohn et al., 2004; Horackova et al., 2019).

Physical illness, but notably cardiovascular illness, has been highlighted as a negative predictor for treatment outcomes (Tunvirachaisakul et al., 2018). Importance is placed across ethnic minority groups, particularly where subset ethnic groups are at greater risk of vascular illness in later life with a troubling combination of more significant depressive symptom profile and reporting low levels of receiving treatment (Vyas et al., 2020). It is recognised that barriers to treatment are in both self and professional perceptions on the need for services as well as ageism and stigma imbedded within services (Burroughs et al., 2006; Bodner et al., 2018; Kim, Thyer & Munn, 2019). Further, frailty contributes to an attenuated response to antidepressant treatments, which was apparent after 8 weeks of treatment with escitalopram or duloxetine, but also persisted in the continuation of treatment. There was an association between those with frailty who did not respond at 8 weeks, and those not responding at 6 and 12 months (Brown et al., 2020), suggestive of increasing frailty and poor response to treatment.

With a higher likelihood of comorbidities in older age, an additional risk of developing treatment resistant depression (TRD) is discernible, and 80% of those who develop TRD in late life will be inadequately treated, either in form of poor response or slow response, or will show early relapse signatures and face augmentation of supplement treatments such as mood stabilisers or anti-psychotics (Whyte et al., 2004). Though, when adequately identified, the clinical response to standard treatment of depression in late life can be as successful as those within the 'working age' adult population i.e., 18-65 (Cuijpers et al., 2006; Nelson et al., 2008).

Lifetime LLD is associated with reduced hippocampal volume (Geerlings & Gerritsen, 2017). Cognitive

impairment is common in LLD, being observed in rates of 40-60% (Diniz et al., 2013) and persisting cognitive impairment is also a common clinical issue (Köhler et al., 2010; Panza et al., 2010). There is further association between cognitive impairment and vascular change which contribute the poor treatment response. This demonstrates the compounding effect MDD has in late life.

There is an association between depression and performance in episodic memory, executive function, and processing speed, as the severity of depression increased and cognitive functioning declined (McDermott & Ebmeier, 2009; Koenig, Bhalla & Butters, 2014). Deficits can often remain, even after treatment (Diniz et al., 2013). Köhler et al., (2010) found that half of participants showed generalised cognitive impairment 18 months post remission consistent with earlier reports, with some lasting as long as 4 years. In part, this was explained by information processing speed contributing to other domain deficits. There were greater deficits in those who developed depression later in life, compared with early developed depression group (<65) and a greater effect on executive functioning than memory deficit. It was proposed the potential for cortical, subcortical atrophy and white matter hyperintensities (WMH) all offer some contributions to these differences, as well as age of onset differences (Köhler et al., 2010). Further, in examining the characteristics of persistent cognitive impairment in remitted patients, Liao et al., (2017) found amnestic mild cognitive impairment (MCI), show significantly more severe deficits in global cognitive functioning, when compared to remitted LLD (Liao et al., 2017). Likewise, greater severity or volume of WMH, cortical thinning, cortical and subcortical volume, are associated with global cognitive deficits, executive function, processing speed, attention, and memory, when compared with healthy older adults (Khalaf et al., 2015; Kim & Han, 2021). While those with remitted LLD had deficits specific to executive functioning and memory domains but not attention and processing speed, relative to healthy control subjects. This suggests some cognitive changes were continued to be seen in those in remission, but the latter domains (attention and processing speed) are reversed by successful depressive treatment (Liao, et al., 2017) and that these are deficits are characteristic to a current

depressive episode. There are some important aspects to consider here; the assessment of cognitive functioning, the timing of depression (i.e., age of onset) and ability to differentiate between LLD and cognitive disorders such as MCI, as all of these can aid clinical assessment in understanding potential trajectories of illness and response to treatment. Further, it may be that combined effect with inadequate treatment contributing to reduced treatment response.

Higher WMH and increased rates of poor response to antidepressant medication have a known association; the greater the severity of deep periventricular WMH lesions was, the poorer the response to antidepressant treatment (Herrmann, Le Masurier & Ebmeier, 2008; Taylor, Aizenstein & Alexopoulos, 2013). WMH lesions reduced white matter integrity in regions of the brain related to fronto-striatal-limbic circuits, specifically in prefrontal, posterior cingulate, middle temporal cortices as well as hippocampus were associated with poor treatment response (Kim & Han, 2020). These regions are critical for multiple brain functions including emotion regulation, cognitive and executive function (Tadayonnejad et al., 2014). Further, there is an association with the accumulation of WMH, antidepressant treatment outcomes for LLD and non-remitting symptoms. An increase of WMH is associated with increased depressive symptoms, within the non-remitting group who have been treated with an antidepressant (escitalopram) and might be indicative of worsening of neural pathways necessary for recovery (Khalaf et al., 2015).

Further, deficits in planning and organisational skills had a significant nonresponse to antidepressant treatment, in contrast to predictions of verbal fluency and response inhibition (Pimontel et al., 2016). Problem solving or cognitive training protocol as part of training within these age groups might offer some mitigation to the effect of reduced or non-response from treatments (Pimontel et al., 2016).

Finally, some literature suggests there may well be a link among LLD, the development of mild cognitive impairment and dementia. There was limited data showing depression with the

subsequent onset and persistence of progressive memory decline. Those who have depression prior to the onset of MCI and dementia have been associated but only with those who developed depression later in life (Singh-Manoux et al., 2017). This suggested that depression could be a prodrome of dementia within the specific group who develop depression later in life, or that there is a common cause for LLD and dementia (Steffens, 2017).

Aetiology of LLD

This section will cover the aetiology for LLD include biological, neuropsychological, psychosocial, and genetic hypotheses. These include vascular hypothesis, inflammation hypothesis among others as well as genetic disposition and psychosocial risk factors.

Vascular hypothesis of LLD

This hypothesis proposes vascular changes not only precipitate but also predispose and perpetuate mood disorders in older adults such as LLD (Taylor, Aizenstein & Alexopoulos, 2013). Vascular risk factors, particularly stroke, diabetes and heart disease have a strong association with LLD (Valkanova & Ebmeier, 2013). Vascular changes (microbleeds, cerebral atrophy, lacunes, perivascular spaces and WMH) affect regions involved in affective processing and pathways linking frontal- subcortical regions of the brain (Wang et al., 2014; van Agtmaal et al., 2017; Rensma et al., 2018).

Van Agtmaal et al (2017) combined data from multiple measures of peripheral and cerebral microvascular dysfunctions across both cross-sectional and longitudinal analyses, finding generalised microvascular dysfunction is associated with depression; an aspect of vascular change not previously known to be implicated in development of LLD. However, assessing well documented risk factors to the cardiovascular process found no association between hypertension and LLD or between dyslipidaemia and LLD, and only a weak association between smoking and LLD. A positive association was seen between diabetes, cardiovascular disease, and stroke and LLD. This has demonstrated that

vascular illness, but not precursory risk factors of vascular disease, are associated with a higher risk for LLD episodes (Valkanova & Ebmeier, 2013).

There are two ways LLD may be identified and explained in the vascular hypothesis. The first is through brain imaging highlighting vascular changes, an advantage is this can offer such evidence as discussed above. Secondly, through neuropsychological change showing executive dysfunction (Alexopoulos et al., 1997; Alexopoulos, 2001).

Neuropsychological functioning, and brain imaging as demonstrated through the severity of WMH predict depressive scores using MADRS, following a 12-week antidepressant treatment with SSRI (Sheline et al., 2010). These have subsequently developed and diverged into 2 distinct hypotheses: the vascular hypothesis, which can often be described as a subset 'vascular depression' and 'depression executive dysfunction syndrome' hypothesis.

Depression executive dysfunction syndrome hypothesis

Depression executive dysfunction (DED) syndrome hypothesis of LLD has symptoms consistent with a fronto-limbic dysfunction. These include anhedonia, psychomotor retardation, mild vegetative syndrome that produce significant disability and a lack of insight (Alexopoulos 2002; Rapp et al., 2005). It is characterised by a deficient performance of executive function. WMH are found located within these regions (of frontal and subcortical areas) and have been associated with reduced executive function (Kim et al., 2011). Hypoactivation, low resting functional connectivity and metabolic activity have been identified as part of DED syndrome in LLD (Aizenstein et al., 2009; Alexopoulos et al., 2012). Poor response to antidepressants, and early relapse and a recurrence of illness, are predicted by executive dysfunction (Pimontel et al., 2016).

From this neuropsychological perspective, LLD is a dysfunction in the multiple networks across the brain, including the cognitive control, reward, and salience networks (Alexopoulos, 2019). Preceding cognitive control deficits is a slowing of informational processing which can be more notable in LLD, as natural aging will also slow processing speed. Reduced processing speed will affect attentional control, inhibition and working memory. Encoding becomes poorer and impacts short term memory, inhibition control, error monitoring, and cognitive planning; and increases the severity of LLD (Elderkin-Thompson et al., 2003; Lockwood, Alexopoulos, & van Gorp, 2002).

Inflammation hypothesis

The inflammation hypothesis advances the notion of age related and co-morbid disease-causing inflammation and then, predisposing older age to the development of depression. Conversely, it may predispose metabolic changes that lead to the development of LLD (Alexopoulos & Morimoto, 2011).

Cytokines induce an enzyme, indoleamine 2,3-dioxygenase, that reduces the production of serotonin, further cytokines can dysregulate the glutamate system and increase oxidative stress, damaging glial cells in prefrontal cortex and the amygdala. When microglia are persistently activated, this may lead to an inefficiency in the clearance of neurotoxins leading to neuronal loss and reduction of neurogenesis. Often in LLD, an increase in peripheral inflammatory markers is seen and antidepressant treatment can reduce these markers (notably, TNF-a, IL-6, IL-10, and CCL-2). Pro-inflammatory markers are also associated to an increase in physical illness, particularly in cardiovascular disease, and aging may exacerbate the effect of stress in the brain, leading to changes like that seen in depressive illness (Charlton et al., 2018). Further, chronic systematic inflammation in middle adulthood is found to have a greater chance of the development of LLD and an increased risk for clinically significant depressive symptoms during late-life (Sonsin-Diaz et al., 2020).

Dementia-prodrome hypothesis

LLD and a high conversion rate of MCI to Alzheimer's disease (AD; Gallagher et al., 2018), suggests that the role underlying this conversion could also affect LLD. The dementia prodrome hypothesis (Byers & Yaffe, 2011) indicate that those with LLD are at greater risk of developing dementia and can be explained through aetiological factors. The proposal of disruption of neural networks that occur in dementia are the same of that in LLD. Hippocampal atrophy provides an example of this. Very commonly seen in dementia and aging, hippocampal atrophy is also seen in and confers vulnerability to developing LLD. There is some cross-over from both vascular and inflammatory hypotheses. However, a unique factor within the dementia-prodrome hypothesis is the accumulation of amyloid beta protein. LLD appears to increase the risk of the presence of amyloid beta and antidepressant treatment seems to delay conversion from MCI to AD (Rapp et al., 2008). Thus, this presence of amyloid beta could have a role in LLD. Though to date, there has been no distinct findings between depression and AD pathology.

Hippocampal regions are vulnerable to stress and chronic illness, as they can induce ischemia and activation of HPA axis activity (Miller & O'callaghan, 2003). HPA activation may be an important observation for those with 'early-onset' LLD aetiology. Stress-related HPA activation can also affect other brain regions which are implicated in LLD, atrophy of the prefrontal cortex and hyperactivity of the amygdala. These regions play a significant role in cognition and may also offer explanation to the dementia-prodrome hypothesis.

Age by disease interaction hypothesis

Age by disease interaction hypothesis categorises LLD as a specific subtype of depression, whereby naturally occurring age-related gene expression directs specific biological processes that lead to the development of depression (McKinney & Sibille, 2013). This model posits gene expression as a main

driver for biological change. These changes lead to vascular, inflammatory, and neurotrophic processes that promote LLD, as well as dementia-related processes (McKinney & Sibille, 2013).

Genetic disposition

Of 23 genetic dispositions analysed in relation to LLD, 3 associations have been found to be significant: APOE, BDNF Val66 Met, and *SLC6A4* 5-HTTLPR. These are not determinant but represent genetic risk factors for the development of LLD. Particularly, APOE e4 may contribute to a vulnerability to LLD (an additionally high-risk gene for the AD). *SLC6A4* 5-HTTLPR S allele and BDNF Met allele present an increased risk factor for developing LLD (Naismith et al., 2012; Tsang, et al., 2017). Heritability in LLD ranges from 14%-55% (Tsang, et al., 2017). This compares to 'working age' MDD which is around 37% (Sullivan, Neale, & Kendler, 2000) and as in 'working age' MDD, a sizeable proportion of contribution is owed to psychosocial risks, over genetics.

Psychosocial risk factors

Psychosocial risk factors include life stress or social stressors, personality attributes or maladaptive traits (Aziz & Steffens, 2013). Comorbid illness and functional decline markers also seen in aging can be psychosocial risk factors in developing LLD, along with female gender, sleep disturbance and adverse life stressors such as bereavement (Cole & Dendukuri, 2003; Gertner, Domino & Dow, 2017; Sutin et al., 2013). Carer burden, poor social connections, physical health disability and rehabilitation are influences that can increase risk for the development of depression (Bruce, 2002).

Bereavement is strongly associated with LLD (Zisook & Kendler 2007; Thauvoye et al., 2018). Of those who were bereaved of their spouse, around 25% met criteria for a major depressive episode at 2- but also 7-month post bereavement, with 15% still meeting criteria over a year later (Zisook & Shuchter, 1991). Understanding pre-bereavement circumstances can be important to distinguishing different risk factors, clinical outcome, and treatment responses between LLD and the development

of complicated grief (Lichtenthal, Cruess & Prigerson, 2004). For example, understanding the type of relationship and attachment style the widowed had with their significant other may identify those predisposed for developing a complicated grief as opposed to a depressive episode. Further, the clinical course differs to that of LLD, appears more persistent and severe in complicated grief without response to antidepressant treatment (Lichtenthal, Cruess & Prigerson, 2004).

Social interaction contributes significantly to human wellbeing. Negative wellbeing is often cited as a consequence of having depression though is frequently assessed as subjective wellbeing, incorporating eudemonic, evaluative, and affective wellbeing (Vanhoutte, 2014; Becker, Kirchmaier & Trautmann, 2019). Older age groups are suggested to need fewer social contacts to protect against depressive symptoms compared to younger counterparts, with fewer than one close contact per month required to reduce a twofold incidence of developing LLD (Werner-Seidler et al., 2017). There is an importance of social support clearly highlighted in the literature. Social support is a predictor for the development of both MDD and suicidal ideation in older adults (Vanderhorst & McLaren, 2005). LLD, particularly in the older-old, often see sharper declines in QoL, attributable to poorer health or lower partnership through illness or mortality as well as child but not always grandchild support (Diener, 2000; Jivraj et al., 2014; Becker, Kirchmaier & Trautmann, 2019).

Functional ability remains a significant risk factor in LLD as increased baseline depressive symptoms and subsequent functional decline was found, when compared to those without depression. More important, physical functioning and the decline of physical function over time was an independent correlate with increasing severity of reported depressive symptoms, even when accounting for the symptoms occurring at baseline (Callahan et al., 1998). This suggests that the more severe the presentation of depression, the more significant a loss in QoL of those who experience LLD will be. A notable strength of this research was the large enrolment of primary care patients and as such, researchers had access to covariate information. As these participants were attending health-based

clinics, the authors posit whether there may have been an over estimation in functional impairment which warrants further research.

Age of onset: Early vs Late Onset LLD

LLD can be categorised into 'early-onset' (EOD) and 'late-onset' depression (LOD), depending on at what age the first presentation of depression occurred either before or after age 60 (Van den Berg, et al., 2001) and similarly, differences are seen with age of onset. Typically, the diagnostic name 'LLD' includes both EOD and LOD (Blazer, 2009), with around 52% presenting with a form of LOD; either LOD with severe life stressors or LOD with vascular risk factors (Brodaty et al., 2001; Van den Berg, et al., 2001).

There have been some suggestions that there are aetiological differences between EOD and LOD clusters (Gallagher et al., 2010; Grace & O'Brien, 2003; Van Den Berg et al., 2001). There were significantly more life events and bereavement in those with EOD, when compared to LOD and healthy controls. EOD were also significantly less likely to have a confidante, when compared with LOD and controls groups. Those with depression (EOD and LOD) showed higher neuroticism and lower extraversion when measured with Eysenck Personality questionnaire (EPQ) and compared with control group (Grace & O'Brien, 2003). This suggests that psychosocial risk may play a greater part for those with EOD, and it may be that neurobiological factors have greater impact for LOD type. Supporting this notion, Van den Berg et al., (2001) proposed 3 aetiological differences or subgroups. EOD with a psychobiological vulnerability, show higher neuroticism as well as a parental history of depression. Here, LOD is classified into 2 diverging groups: one being a clear delineation of presenting with significantly more vascular risk factors. Moreover, they tentatively propose a third subgroup, LOD as a reaction to severe life stressors, given the groups heterogeneity and their research only allowed for life stress 12 months prior, and introducing a recall bias (Van den Berg et al., 2001). A later review suggests no significant differences were found across aetiology or other

group aspects such as symptomology, or clinical outcomes other than a family history between EOD and LOD; it reports a sparse number of studies with inferior quality and there remains open discussion around potential differences (Grayson & Thomas, 2013).

Environmental factors which are specific to onset have been identified in a history of childhood abuse and the interplay with psychosocial risk factors. Wielaard et al., (2018) addressed this aspect and found psychosocial factors mediated the association between childhood abuse and EOD but not LOD. Loneliness was the strongest mediator, and its strongest mediation was within psychological abuse and emotional neglect. A smaller social network was also a mediator for association between childhood abuse and EOD. There were no group differences between age, sex, severity of illness or medication use in EOD and LOD, as well as no significant differences between education, socio-economic parameters, or life events (Wielaard et al., 2018).

Those with LOD were less likely to have a familial history of depression, lower cognitive scoring as measured by a mini-mental state examination (MMSE), or previous admission to hospital. A significant association between LOD and cognition, with a lower likelihood of admission, and family history. Further, LOD were less likely to report thoughts of not wanting to live or endorse guilt feelings (Gallagher et al., 2010). Additionally, biological differences were identified in LOD in cortical and subcortical structural regions are suggested but results did not differ across neuropsychological markers after a prospective treatment study using sertraline treatment for 12 weeks (Disabato et al., 2014).

2.1. Main treatments for LLD

NICE guidelines propose two main forms of treatment for LLD: antidepressant treatment and psychological therapies (NICE, 2022).

Antidepressants for LLD

The pharmacological treatment option often comes in different classes of antidepressants, such as SSRI, and SNRI and tricyclic antidepressants (TCA).

Antidepressant efficacy is demonstrated, when compared to placebo, with response and remission rates at 48% (OR 1.78 with 95% CI 1.42–2.24) with a number needed to treat (NNT) of 6.7 (95% CI 4.8–10) and 33.7% (OR 1.36; 95% CI 1.07–1.73) with a NNT of 14.4 (95% CI 8.3–50), respectively for all antidepressants combined (Kok, Nolen & Heeren, 2012). Remission was only significant with all class antidepressants are pooled together. At class level (TCA vs placebo; SSRI vs placebo; other vs placebo), results only remain significant for those in response group and not remission, defined as lower than cut off (<=7 on 17-item HAMD scale, <=10 on 24-item scale and ≤12 on MADRS) at their end point assessment. The authors explain this may be due to a type 2 error, meaning an incorrect rejection of a null hypothesis (Kok, Nolen & Heeren, 2012).

Antidepressants may not be as efficacious in older age groups though (Tedeschini et al., 2011). Short term use of an SSRI in LLD of up to 8 weeks, may not provide any benefit to LLD, when compared to placebo (Tham et al., 2016). Tham et al., (2016) reported that duloxetine, an SNRI, was superior in both response and remission but has an increased side effect profile (drowsiness, sickness, headaches, dizziness, and bowel disturbances). The number of studies included in response and remission is small (response group n= 2 studies, n = 352 active treatment, n= 247 placebo; remission group n = 3 studies, n = 549 active treatment, n= 342 placebo) and the quality of these studies were rated as low or moderate and as such, authors state that the results were provisional (Tham et al., 2016).

Baseline-severity predicted symptom improvement in mixed-age meta-analysis, with the effectiveness of antidepressant improving with increased baseline severity (Fournier et al., 2010).

However, an increase in mean change in HAMD is not found in LLD in response to antidepressants (Locher et al., 2015). This was likely because there were large placebo responses particularly after short illness. The inclusivity of a wide range of severity types (mild, moderate, severe) extends the current literature and contrasts to mixed-age meta-analysis that focuses on severe baseline markers (Locher et al., 2015). However, those with long duration do see severity as a moderating factor (Nelson et al., 2013).

Medication can become problematic specifically for this age group, experiencing side effects such as anticholinergic side-effects, anxiety, diarrhoea, nausea, dizziness, insomnia among others (Krause et al., 2019), or contra-indication to other treatments (Alexopoulos, 2011) may limited choice and endorse the rationale for those who may not wish to take antidepressant treatment. Primary care is often the preferred route of treatment sought for those with LLD (Unützer et al., 2003). However, there is a high non-adherence rate to antidepressant treatment for those with LLD who are treated in primary care, with a range of 11%-21% not starting recommended treatment, 12%-16% had a suboptimal prescribed dosage and 33-38% discontinuing treatment before it was recommended, however reasons for non-adherence were not discussed (Gum et al., 2006; Holvast et al., 2019). Whilst new medications are being investigated for MDD, often dedicated studies for this age group do not occur in parallel and there is a clear divergence in current research designed for older adults when assessing new antidepressant treatment or other novel modes of treatments (Patel et al., 2017).

Psychological therapies for LLD

There is good evidence that psychotherapy is an effective treatment for LLD and may be preferable specifically for this group (Unützer et al., 2003; Huang et al., 2015). However, a meta-analysis (Cuijpers et al., 2006) reported no significant differences between psychotherapy and antidepressant treatments, with a large effect size (0.72).

Holvast et al., (2017) address non-pharmacologic treatments provided in a primary care (cognitive behaviour therapy (CBT), exercise, and other (CBT-based bibliotherapy, problem solving therapy, bright-light therapy, and behavioural activation)) and community setting (CBT, bibliotherapy, life review, exercise, problem solving and other therapies: cognitive therapy, behaviour therapy, and brief psychodynamic therapy, as well as receiving postcards on depression). CBT intervention was highlighted as the main significant finding in primary care, with individual therapy more successful than group therapy. Bright light therapy showed some promise as an effective treatment in primary care, though this would require replication before any suggestions for recommendations can be made (Holvast et al., 2017). Among the reviewed treatments, life review therapy has some optimistic potential, which is a form of structured group therapy that addresses different life themes (Korte et al., 2012). When compared to care as usual, life review therapy as a treatment for moderate LLD was effective after the initial treatment but also at a 3 and 9 month follow up, post treatment. There were 2 moderating factors found, higher levels of extraversion and lower levels of boredom reduction found an increased benefit from the treatment (Korte et al., 2012).

CBT based interventions were statistically significant more effective as compared to active (education groups) and inactive (waitlists) control conditions (Thomas et al., 2018). A moderate effect was found when CBT intervention was compared to the combined controls groups, but a small effect was found for active control group comparison and large effect for inactive control comparison. Significantly lower symptoms of depression were seen at follow up after CBT based intervention across both comparison groups and suggest there may still be some benefit to have specific CBT based interventions in the active control group where the effect was small. Cognitive therapy performed best in subgroup analysis with large effect size and the worst performing was behavioural activation; behaviour therapy, problem solving therapy and CBT had comparable moderate effect sizes. Using clinician-based assessment tools (HAMD), larger effect sizes were

observed when compared with self-report tools (Beck Depression Inventory (BDI) and Geriatric Depression Scale (GDS)). The BDI showed the smallest effect which could be due to inclusion of somatic symptoms that are reported in higher frequency in this age group. Moderators include community intervention offering a moderate effect, and suggestive there might be more chronic or severe patients in clinical environments. Analysis using outcome (completers-only) was significantly higher than intention to treat analysis, a consideration for the interpretation of results. Meta regression showed gender, quality of the study and dropout rate were all predictive of the treatment outcome. Females had a higher percentage of overall effect than males; the higher the quality of the study to lower the effect size; those with lower dropout had higher effect sizes, with an association between dropout and gender, higher male ratio, showed higher dropout rates (Thomas et al., 2018).

Third wave mindfulness-based CBT (acceptance and commitment therapy (ACT) and mindfulness based- cognitive therapy (MBCT)) also show a moderate effect size on depressive symptoms (g = 0.55). ACT was significantly superior to control groups, which included waitlists and placebo psychology. MBCT was significantly superior to treatment as usual with both HAMD (weighted mean difference (WMD) = -4.31) and BDI scales (WMD = -7.33). It is noted there is more research required before these results are substantiated but shows promise for LLD (Kishita, Takei & Stewart, 2017).

LLD often presents with co-morbid health concerns and reduced functioning potentially impacting on treatment effect. Problem solving therapy may improve depressive symptoms for this group when rated by a clinician using HAMD (mean dif= -4.94, 95% CI [-7.90, -1.98], Z=3.27, p=0.001), in the short term (Frost, Bauernfreund & Walters, 2019).

The CASPER study offered a therapeutic approach, designed for subsyndromal depression as a preventative approach for more severe disease. This uses the idea of collaborative care methods by case managers (Gilbody et al., 2017) and may aid for those with co-morbid illness, involving 6

sessions over 7-8 weeks, 2 sessions were face-to-face and the remaining via telephone. At 4 months, PHQ-9 depressive symptoms were significantly lower in collaborative care group when compared to those who received care as usual (mean dif= -1.31, 95% CI [-1.95, -0.67], p=<0.01). Anxiety symptoms and health-related QoL outcomes were significantly better for collaborative care at 4-month and 12-month reviews (Gilbody et al., 2017).

Some limitations to the presented research might include few or low-quality studies (Cuijpers et al., 2006; Holvast et al., 2017) and an over-estimation across psychotherapy for adults of all ages has been demonstrated (Cuijpers et al., 2010b). For LLD with co-morbid physical illness, there was also only limited evidence for effect on function and improving QoL, and further suggests collaborative care did not affect depressive symptoms (Frost, Bauernfreund & Walters, 2019).

Both treatment options have their challenges within this age group and considering primary care as a preferred point of access for those with LLD, having novel treatments that can be accessed in this manner could be a principal factor (Hall & Reynolds III, 2014). Whilst there are some impressive results for the treatment of LLD, it appears limited to variations of CBT and require confirmatory research. In addition, any psychological therapy options often come with long wait times due to high demand in services (Trusler et al., 2006).

2.2 Transcranial direct current stimulation

Neuroplastic, functional and structural changes found following TMS may identify tDCS as potential new treatment, as discussed in chapter 1, p. 31. Bhandari et al., (2018) used a paired-associative stimulation (PAS) paradigm, a technique which can measure neuroplasticity with a single-pulse TMS protocol to induce MEPs. PAS protocol assessed associative plasticity and LTP, using TMS to induce MEPs as an indirect measure. Results showed PAS induced neuroplasticity was successfully reached in 68.8% in those with LLD and 47.1% of matched healthy controls. This did not reach statistical

significance (Bhandari et al., 2018). This differs to a previous study by Player et al., (2013), who found significant differences between 'working age' depressed group and healthy controls. Some differences to consider, first were 'working age' group baseline severity assessment was higher, at moderate rating (Bandhari et al., 2018 baseline scores: MADRS ≥15, Player et al., 2013 baseline scores: MADRS ≥20). The authors highlight nerve conduction timings, which can slow in aging, may act as a factor to consider to accurately representing PAS plasticity assessment and an inability to distinguish the neurophysiological profile of LLD from normative aging, an identified limitation of the study. Further, around one third of older group were taking antidepressant medication (n=16) which can also facilitate neuroplasticity. The remaining were not on antidepressant medication (n=31) but no group differences were observed (Bandhari et al., 2018).

Current research of tDCS in the older population

Current tDCS research in the context of adult participants show overall good levels of efficacy and acceptability for major depression (Mutz et al., 2018; Moffa et al., 2020; Razza et al., 2020). However, there is a limited research basis for tDCS in LLD, with no known randomised control trials dedicated to LLD and tDCS addressing the efficacy of tDCS as a treatment.

Of those that have included older participants within their studies, tDCS has been reviewed for cognitive effects. Remitted patients aged 60 and over were assessed in working memory and global cognition at 14 days and 90 days post remission. No improvements were seen in either working memory or global cognition when compared with placebo (Kumar et al., 2020). Similarly, on reviewing cognitive effect of tDCS in depression, Brunoni et al (2016b) found no significant effects, though post hoc tests showed older adults improved more than younger participants on TMT-A, again with non-significance (Brunoni et al., 2016b). In a further tDCS study by Brunoni et al., (2014) with combined cognitive control therapy (CCT), depressive symptoms were ameliorated by both CCT only, with CCT and tDCS combined, and are in line with previous results (Segrave et al., 2013).

Interestingly, there is a suggestion that combined CCT and tDCS may be beneficial for 'older adults' (aged 65 and over; Brunoni et al., 2014), though they have defined this age group as over 50 years. Both CCT and combined treatment (CCT and tDCS) improved depressive symptoms with a superiority for the combined therapy. Results vary across studies that include participants aged 65 and over, with some showing a significant difference in mood scores (Boggio et al., 2008; Loo et al., 2010; Brunoni et al., 2013b; Loo et al., 2018), some more modest (Loo et al., 2012), and without significance (Palm et al., 2012).

Providing an alternative to the currently available options, tDCS has some clear benefits for patients such as the potential to increase adherence to treatment, reduce drop-out, provide an option with a less distressing side effect profile and alleviating the burden on psychotherapy services. Meta-analyses including all ages show promising results and considerable potential for tDCS as an antidepressant treatment, as noted in chapter 1.

However, there has not been any meta-analysis of current research to address efficacy and acceptability in LLD and subsequently, what the effect would be in LLD remains unclear. This study investigates efficacy and acceptability using meta-analyses techniques, to assess IPD of LLD, extracted from randomised sham-controlled trials.

2.3 What is a meta-analysis?

Meta-analysis is a systematic process for synthesising findings from independent research studies and is done by calculating an absolute effect of what is being measured (Shorten & Shorten, 2013). The term 'meta-analysis' was coined by statistician and social psychologist, Gene Glass (Glass, 1976). In the 1970's, an increase in statistical methodology, particularly blending multiple studies and single studies were found to have difficulties detecting modest, though potentially clinically relevant differences in treatment, for example type I & II errors (Egger & Smith, 1997). The use of meta-

analysis in MDD research is as old as the term itself. An early meta-analysis including depressed patients was completed by Miller (1979) only a few years after the term was made, looking at the comparative effects of medication, psychotherapy and combined treatment of medication and psychotherapy. Hence, meta-analytic techniques were developed.

Strengths of meta-analysis

A meta-analysis is an objective review and synthesis of the available research, in comparison to narrative reviews which are often subjective both in the review and synthesis of the literature. Thus, it reduces bias and error to what and how data is added (Teagarden, 1989). Meta-analyses can be a cost-effective alternative to conducting large, and often expensive studies (Chalmers et al., 2014).

Meta-analyses offer a transparent process and can be better positioned to answer questions around generality, such as if an intervention might vary across subgroups, men vs women, older vs younger age groups (Egger & Smith, 1997). There is currently no fixed rule on when you should consider doing a meta-analysis. Cheung and Vijayakumar (2016) suggest consideration of several questions; the first being is there enough research available to do a meta-analysis. There is no upper limit to how many studies should be included in a meta-analysis and while not recommended, there is potential to conduct an effective analysis with just 2 studies being included. However, this may be suggestive the research topic may not be mature enough and it may be of more benefit to allow for further studies to be conducted as there may be some criticism from the research community that the meta-analysis is not robust enough. The second question of how critical is the data required for the subject area, is it important and urgent? If the answer supports significant importance and urgency, authors should offer their rationale to contribute to the literature, and this may provide some further insights into the converging points of the topic area (Cheung & Vijayakumar, 2016).

Limitations of meta-analysis

There are some potential limitations to meta-analyses (Patel & Bajaj, 2017):

1) Including low quality research papers. There is a standardised assessment published via Cochrane handbook for systematic reviews of interventions (Higgins et al., 2011). Here there is discouragement of using quality scales because evidence suggested that using certain scales of quality assessment created a bias towards certain effects due to the lack of an underpinning theoretical framework. A merge of competing concepts arose during the assessment of 'quality' such as bias, applicability, ethics among others (Jüni et al., 2001) and resulted in the development of Cochrane risk-of-bias (RoB) tool (Higgins et al., 2011), as documented above.
2) A tendency to oversimplify results. This is a critical point which lies with the authors. It is important to represent the results as they are, even if they are complex.
3) Results that disagree with published data. Whilst this is highlighted as a limitation. It may also offer the authors a position to review the dataset, methods of analysis and provide critical insight which adds to the literature.

2.4 Conducting the meta-analysis

Principles and procedures to ensure a 'well conducted meta-analysis,' include a systematic review, selecting studies and performing an analysis using the latest guidelines. Prior to any form of analysis, a systematic review of the literature is conducted which includes formulating a question, developing an *a priori* protocol and eligibility criteria, and a literature search of databases (Berstock & Whitehouse, 2019). When selecting the research studies to include, the ideal studies would be those who have appropriately randomised participants with blinding measures in place and include all participants initially included in line with intention to treat protocol (Lefebvre et al., 2021).

The Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines provide the minimum set of guidelines for reporting systematic reviews and meta-analysis in a transparent way,

including why it was conducted, how it was completed and what was found in the review or analysis. The purpose is to improve the reporting of systematic review and meta-analysis. PRISMA provide a statement and accompanying 27-item checklist to ensure a standardised approach to outlining why, how, and what (Page et al., 2021; Møller & Myles, 2016).

Quality

Quality in research can be referred to as rigour. This can be defined as the amount to which researchers have extended the quality of the research being conducted. Quality is then measured through the validity and reliability of the research. Validity and reliability are defined as the extent to which researchers have accurately measured a concept and instrument, respectively (Heale & Twycross, 2015).

Another rationale to use PRISMA guidelines relates to the significant improvement of the quality of meta-analyses that have been performed since their introduction (Panic et al., 2013). These improvements may be borne out of the increased quality seen across randomised trials following Consolidated Standards for Reporting Trials (CONSORT) guidelines. CONSORT provide standardised guidelines for parallel randomised control trials to ensure the design, conduct, analysis and interpretation, and validity of the results are adhered to and transparent (Schulz, Altman & Moher, 2010). This also ensures high-quality RCTs are then inducted into a meta-analysis (Rennie, 1996; Han et al., 2009). In addition to this, and specific for meta-analyses is an open-access prospective, international web-based register for systematic reviews called PROSPERO (Booth et al., 2012). The web-based register allows a sole source database of all systematic reviews that are occurring internationally, increasing transparency of methods prior to beginning the analysis, promoting high methodological standards, and reducing duplation of topics and potentially wasting finite resources (Davies, 2012).

Bias

There are different forms of bias which can be highly problematic to meta-analyses as this can threaten the quality and validity of the analysis. Publication bias is a statistical interest in meta-analyses. Well recognised and discussed, publication bias relates to decisions around how data is published. For example, a treatment may show effect as only significant results are published, whereas those that do not have effect are not published. This create a bias in publication (publication bias) and a mild level of publication bias presence has been found within psychology (Van Aert et al., 2019). While publication bias is the bias most recognised, it is noteworthy to mention other forms of bias such as location bias, as locally reported studies may be published in the local language, thus limiting a search to 'English language only' could introduce bias (Moher et al., 1996). Multiple publications can add further bias, as significant results are at a higher likelihood of being published, it could also mean there is a higher likelihood of duplicate data and thus being included in a meta-analysis (Easterbrook et al., 1991). There are specific tools available to assess and report for bias found in the publication and a chapter laid out in the Cochrane handbook for systematic reviews of interventions, Chapter 7 (Boutron et al., 2021). Cochrane risk-of-bias (RoB) tool (Higgins et al., 2011) is an example of assessing bias and validity. Bias can also be addressed using a funnel plot, significance in an Eggars test can identify bias (Egger et al., 1997).

Individual-level participant data

IPD is one method of conducting a meta-analysis. It involves contacting authors to collect the data of each participant across each study that meets a specified criteria and these raw data are then included together in the meta-analysis. Advantages of IPD meta-analyses over aggregate meta-analyses include increased ease with controlling eligibility criteria more precisely by allowing for raw scores and increased sensitivity and specificity, and identifying data sets which may be overlapped or duplicated more easily; statistical analysis can be standardised across studies and the use of more appropriate or advanced methods such as using one-step analysis which can increase the power of the study; meta-analytical results for specific subsets can be achieved such as differential treatment

effects across groups which can reduce heterogeneity (Riley, Lambert & Abo-Zaid, 2010; Debray et al., 2015).

Standardised Assessment Measures

Standard measures to assess the severity of depressive symptoms are typically used in randomised controlled trials. Managing symptom severity has been a consistent goal in research. Though historically there was not standardised measures which meant up until late 1980's and early 1990's, large inconsistencies were seen in research for depression (Prien, Carpenter & Kupfer, 1991), with the use of an operational criteria to evaluate and describe the change of symptom severity, whereas others used outcome categories such as scales like the HAMD (Hamilton, 1961) and MADRS (Montgomery & Åsberg, 1979). These are example assessment scales used across age groups, including for LLD, to assess if an antidepressant treatment has efficacy. Despite each scale addressing different symptoms, they are highly comparable for LLD (Heo, Murphy & Myers, 2007). There is a challenge particularly in accuracy, when attempting to compare and combine studies using different scales, such as signalling questions, unit measurements or direction. If the construct is the same, in this case – depression severity, it is possible to pool the results and convert these scores (Murad et al., 2019).

Definitions for outcomes were proposed by Frank et al., (1991) for response, remission, relapse, recovery, and recurrence. This provided uniform terminology and enabled more useful comparisons for different clinical trials (Keller, 2003). These are categorical measures and are defined as a binary measure of either meeting the threshold. For example, in 17-item HAMD, remission would equal to a score of ≤ 7, a period for 'full remission' would be ≥ 2 weeks but less than 6 months, and those with ≥ 6months would be considered in recovery (Frank et al., 1991). Though, these can appear to vary depending on the version of the form you might use, all 'cut off' ranges equate to the 17-item

HAMD. Across versions, 'cut off' ranges from score of 12 – 6 or less for HAMD versions, or a score of 15 -8 or less for MADRS for example (Mulder, Joyce & Frampton, 2003).

When defining remission, for 17-item HAMD, a score of 7 or lower has been accepted as the cut-off for remission (Frank et al., 1991; Zimmerman, Posternak & Chelminski ,2004). Zimmerman et al., (2006) found self-report symptoms and psychosocial function are highly correlated, 17-item HAMD ≤7 allows for some residual symptoms to be present and there may be other factors that could be considered in terms of remission such as personal ability to cope, general well-being and positive attributes like optimism and self-confidence. Whilst there has been demonstration that having a 17-item HAMD of ≤ 7 means it would be improbable that one would be in a depressive episode, it might be symptoms may continue to feel problematic for the patient (Zimmerman et al., 2006). Similarly, having a hard cut-off such as 17-item HAMD ≤7 will inevitably mean those very reaching the definition are discounted, yet may be assessed as clinically remitted.

An alternative means of measuring treatment outcome is the continuous measure of percentage improvement. This is typically measured as a 50% improvement from the baseline measure to end point and an empirical approach to using groups of responders and non-responders can be achieved (Mulder, Joyce & Frampton, 2003). Though this approach comes with the same challenges for reaching cut-off not being included. As a measure, it takes into consideration the baseline and can demonstrate the improvement over time without those who may have reached remission stage. This is particularly important within the older age group, where they are harder to treat or may have longer periods of depressive episodes (Wu, Schimmele & Chappell, 2012). This might be addressed by looking at the improvement along with number of sessions to see if a longer course has a differing effect compared to shorter treatment courses.

Statistical models

There are two main statistical models to analyse effect sizes, using fixed or random effects models. There is an important distinction between these two models. A fixed effect model will assume *a priori* that the population value is homogenous (the same across all studies), whereas there are allowances for variation in study parameters within a random effects model (Hunter & Schmidt 2000). It has been found that results depend on which model is used. Both methods can experience a type 1 error (a false positive result), though using random effects found the error rate risk falls within an appropriate margin (5% for the designated alpha 0.5), fixed effects can have higher values if the population parameters vary across the studies (Hunter & Schmidt 2000; Schmidt, Oh & Hayes, 2009). Heterogeneity is used in the decision on which model to use. The absence of heterogeneity, fixed effect model will be used. If heterogeneity is present, a random effects model can be used. However, if the heterogeneity is significant, a meta-analysis should not be performed (Egger, Smith & Phillips, 1997; Borenstein et al., 2010).

The effects are called the summary estimates, where the outcome specified in an analysis is extracted from different studies and pooled together as an average effect size index (i.e., odds ratio – OR, relative risk – RR, weighted mean difference – WMD, standardised mean difference – SMD).

Choosing the right approach: Frequentist vs Bayesian

The Bayesian approach provides a conditional probability using Bayes Theorem. Bayesian inference is based on the prior and posterior belief distribution. In the case of no established priors, 'uninformative' priors are determined. Then, it can establish parameters and models (parameters are factors in the models which affect the observed data; models are the mathematical equation of observed events). In a frequentist approach, 2-step approach will use independent analysis such as a linear regression model to produce aggregate data. The aggregate data will then be synthesised into the meta-analysis. This differs in Bayesian 1-step approach, including the ability to complete more

sophisticated analyses of the data. The data from all individual participants are analysed concurrently under one assumed model (such as applying fixed or random effects). This occurs while the participants are clustered to their trial (Carlin, 1992; Riley, Lambert & Abo-Zaid, 2010).

Software

There are several options of software for meta-analysis, which is how the analysis is performed and as such is informed by the analysis that is undertaken. One of the most subscribed packages are with STATA. Though, if looking for open access sources, R (Metafor, R package v2.4-0; Viechtbauer, 2010) offers an advantage in accurately reporting the process of analysis. There are also published guidance for conducting such analyses (see Beath, 2016; Balduzzi, Rücker & Schwarzer, 2019). This provides a step-by-step process on how to conduct the meta-analysis. For those who may be new to meta-analysis and require a simpler user interface, Cochrane collaboration offer Review Manager (Rev Man, 2014), which also provide step-by step guides and online training literature.

Describing the results

Once data is collected and processed as defined by the parameters of the meta-analysis and before running the meta-analysis in the software, descriptive analysis can be conducted. This involved using text to describe results and findings. The flow is described using PRISMA guidelines, this would include how many databases were used and reviewed, how many abstracts and journals were found and reviewed. A description of the characteristics of the meta-analysis data found can also be added, such as the population, protocol and parameters of interventions and placebo measures. At this point authors decide whether the data collected can be used for meta-analyses (Muka et al., 2020; Page et al., 2021).

Statistical results: Effect size, means and probability.

The effect size is calculated to demonstrate the size of the difference between two groups; in a meta-analysis, the author combines and compares the estimated effect size.

For example, a calculation of Cohens *d* effect would look like this:

$$\text{Effect size} = \frac{\text{[experimental treatment]} - \text{[control treatment]}}{\text{Standard deviation}}$$

The estimates are presented with 95% confidence intervals. Confidence intervals (Cis) are the margin of error and calculated to assist with interpreting the result or significance of the effect size. Both heterogeneity and effect sizes can be presented in forest plots.

Recognised statistical techniques address differences in the study such as the sample size, variability, and the findings of each study. A categorical end point will be reported by an odds ratio (OR) or relative risk (RR). They are both acceptable measures of effect though they represent different concepts. OR represents the ratio of two different odds and relative risk is the ratio of two probabilities. Whereas a continuous end point would be reported as the difference of means between treatment and control groups (Egger, Smith, & Phillips, 1997). Continuous measures (i.e., severity of depression) require standardised measure such as SMD or ratio of means (ROM) before being pooled into a meta-analysis. These can be transformed to both relative and absolute measures such as risk relatives, or differences or odds ratio (Murad et al., 2019). There is a requirement for the studies included in meta-analyses to have a standardised outcome measure to allow for comparisons.

Bayesian approaches take into consideration prior and posterior data information combined as probability distributions and draws an inference as a probability. As such a 95 % credible interval would suggest “95% probability that the population value exists within the limits if the interval” (van de Schoot et al., 2014, p. 844).

Heterogeneity

Heterogeneity shows how much variation there is across the studies. The importance of heterogeneity is shown in its guidance on whether results can be combined and assist in the choice of effects model to be used. Heterogeneity can occur at several levels across any stage of the research process (study or population characteristics, methods, and differences in analyses) and is mostly conducted by using Cochranes Chi squared test (Cochrane’s Q) which assumes a null hypothesis that all studies examine the same effect but does not always accurately identify heterogeneity. An alternative is to use Higgins I^2, this represents the percentage of variance between the sample estimates because of heterogeneity (Ioannidis, Patsopoulos & Evangelou, 2007). The index of heterogeneity is indexed by (I^2), whereas the chi squared test will reported as (X^2) if this is statistically significant (Higgins & Thompson, 2002). More typically, Cochrane’s Q is used as a non-parametric test (Burke, 1998). If heterogeneity is found, an attempt to explain it should be made (Bailey, 1987; Egger, Smith & Phillips, 1997).

Forest Plots

Forest plots are the way the results are presented. The title of the forest plot will inform the reader what data has been reviewed (i.e., OR outcomes for tDCS in depression). Below the title will show a list of titles contributing to the analysis, most typically in alphabetical order, occasionally chronological order. The mean standard deviation and n data for treatment arm then placebo arm

for each trial will follow and a contribution percentage will be present to show the level of contribution each study has in the analysis, finally the weighted mean difference (WMD) with 95% CI and a pictural representation as a diamond represent this number on x-axis (Lewis & Clarke, 2001).

Summary

This section has provided a summary understanding of what a meta-analysis is and how to conduct on using evidenced based methods, touching on strengths and weaknesses. From quality, statistical models to standardised assessments and choosing the right approach to unsure the data collected is analysed in the most appropriate way to answer the research question. This next section will present the research questions and hypotheses. It will go on to present the materials and methods, results, and discussion.

2.5 Research Questions

In this section, the research questions are presented, IPD were extracted from randomised sham-controlled trials to examine the efficacy and acceptability of tDCS. The results will be presented using meta-analyses techniques.

Research Question 1

Is active tDCS over DLPFC efficacious in LLD compared to sham, as measured by an improvement of depressive symptoms?

Hypothesis 1: Active tDCS over DLPFC will improve symptoms associated with LLD compared to sham.

Research Question 2

Is *active tDCS over DLPFC* considered acceptable in LLD, when compared with sham tDCS?

Hypothesis 2: Active tDCS over DLPFC will be considered acceptable in LLD compared to sham conditions.

2.6 Materials and Methods

Systematic review

This meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (The PRISMA-IPD statement; Stewart et al., 2015) and supported by PRISMA 2020 statement: an updated guideline for reporting systematic reviews (Page et al., 2021). The meta-analysis has been registered on PROSPERO (CRD42019137488).

Two authors (KJ and RR) performed independent literature reviews under supervision (CF). Any differences were resolved by consensus. We systematically searched PsychSource (EBSCO), Medline (PubMed) and PsychINFO (EBSCO). We searched for articles from the first date available to 20 October 2021.

Search criteria were: ((“bipolar disorder” OR “bipolar depression” OR “major depression” OR “unipolar depression” OR “unipolar disorder”) AND (“transcranial direct current stimulation” OR “tDCS”)) in all fields.

Inclusion criteria were: (1) adults aged 65 years of age or older; (2) a DSM or ICD diagnosis of MDD or bipolar disorder currently experiencing a major depression episode; (3) randomised, sham-controlled trials of tDCS, which used a parallel-group or cross-over design; and (4) a clinician-administered depression rating scale, such as HDRS (Hamilton, 1986) or MADRS (Montgomery & Åsberg, 1979).

Exclusion criteria were: (1) a primary diagnosis other than MDD or bipolar depression; (2) studies limited to a specific subtype of depression (such as postpartum depression, psychotic depression, or dysthymia) or in which a major depressive episode was a secondary diagnosis (i.e. heart disease and

major depression), (3) co-initiation of any other form of treatment, such as pharmacotherapy or cognitive control training, and (4) the study not being published in English.

Titles were reviewed to exclude studies not meeting the inclusion criteria, and remaining abstracts were examined. From abstracts meeting inclusion criteria, full-text articles were reviewed, and relevant studies carried forward for data extraction. Reference lists of review articles and included papers were checked for additional publications.

The authors of the original studies were contacted to request a line-by-line IPD comprising of any information from (1), (2), (3) and (4) that was not provided in the published sources. Figure 1. Shows the flow diagram of identification, screening, and eligibility of included studies.

Quality assessment

Each trial was assessed for methodological quality, using a standardised checklist: the Cochrane risk of bias tool in Figure 2. (Higgins et al., 2011) that evaluates studies based on selection, performance, detection, attrition, and reporting biases (reported as low, high and unclear risk).

Outcome measures

The outcome measures were:

(1) Categorical measures of clinical response defined as ≥ 50% improvement of clinical response from baseline to end point for each study

(2) Remission, defined as MADRS ≤10, HDRS-17 ≤7, HDRS-21 ≤8 or HDRS-24 ≤9 at end point, according to standardised criteria (Keller, 2003; Rush et al., 2003; Zimmerman et al., 2004).

(3) Continuous measure of depression improvement, estimated as the difference in z-scores (a measure for standardising each result) from baseline to endpoint.

(4) Acceptability (number of participants who dropped out in the active and sham groups at endpoint).

The primary outcome scale was used to measure depression score change over time, regardless of if the study used more than one scale. For crossover data, only data from the parallel (between-participant) phase was used. Analyses used the last observation carried forward (LOCF) for imputing missing data.

2.7 Data Analysis

Descriptive results include the baseline variables, using mean and standard deviation for continuous variables and rates for categorical variables. Individual participant data will be analysed. Trial-level and participant-level characteristics of included studies have been described. Advice was sought from a statistician (SC) and a one-stage hierarchical statistical model (or Bayesian multi-level modelling) was used to synthesise all data, as described in 16.8.2 of Cochrane Handbook for Systematic Reviews of Interventions. This will allow meta-regression and co-variate analysis. Specific statistical software was used for this task (R Core Team, 2018 found at: R: The R Project for Statistical Computing (r-project.org)). There are different analysis techniques for continuous outcome data (Higgins et al., 2001) and binary data (Turner et al., 2000). Statistical heterogeneity will be evaluated (χ^2).

The Bayesian one-step approach has been chosen to analyse the data. As a well-accepted approach for this form of analysis, the benefits over a two-step approach are increased control of factors around study eligibility and added flexibility for several extensions. There are many advantages to using this method; one relates to increased power and sensitivity to detect treatment effects and treatment-covariate interactions, by allowing testing of different assumptions about model structure and adjustment for multiple covariates. A second advantage arises from the capability to gain

deeper insight into the data. Finally, an ability to control for aggregation bias. Statistical expertise is advised for this approach as there is an added computational complexity that allow for the potential advantages when compared to a more traditional two-step or frequentist approach (Stewart et al., 2012; Turner et al., 2000; Fisher et al., 2011; Bowden et al., 2011).

In a multi-level meta-analysis, at level 1: observed overall effect size, variances, and distribution. Level 2 will address variance between-studies, can explore the moderating effect of characteristics of studies (such as treatment resistance, number of sessions and duration of illness), if there is significant variance, multi-level model can allow for mixed-effects analysis; Level 3 will address variance between groups of studies (Van Den Noortgate & Onghena, 2003). This can be achieved by using e.g., random effects regression model, log odds ratios, maximum likelihood or restricted maximum likelihood estimations and likelihood ratio test (Bryk & Raudenbush, 1992)

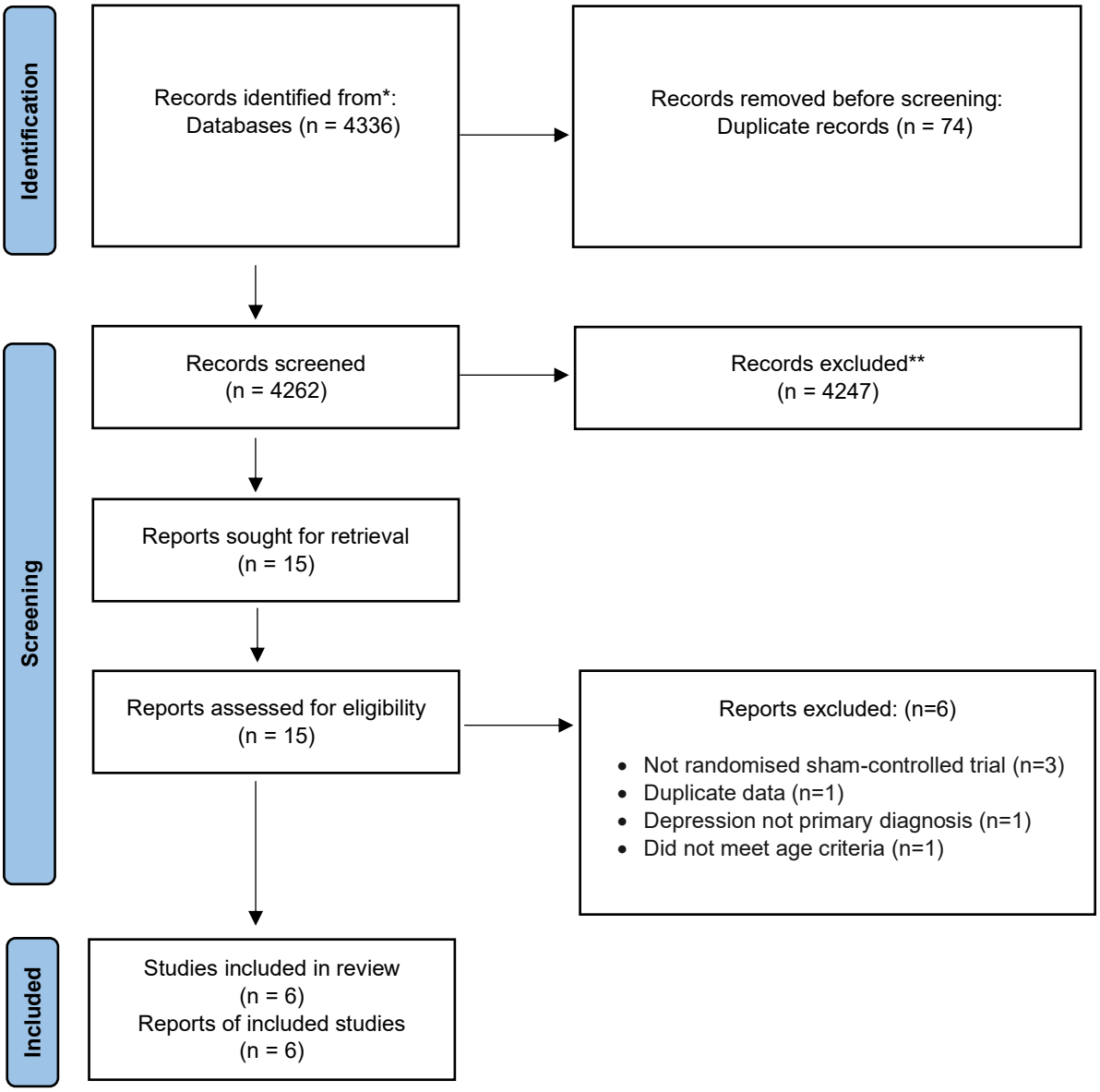
2.8 Results

A total of nine papers met the inclusion and exclusion criteria consisting of fourteen independent participant samples in six studies. Three papers did not respond to requests for data. Six studies included (Brunoni et al., 2013b; Brunoni et al., 2017; Loo et al., 2010; Loo et al., 2012; Loo, et al., 2017; Palm et al., 2012) (Figure 1). Table 2. Summary of the included studies gives an overview of the study characteristics and tDCS parameters of each study included in the analysis.

For the continuous outcomes (depression scores), the standardized mean difference was calculated and the corresponding pooled standard deviation for each group. The Hedges' g was used as the measure of effect size.

For categorical outcomes (response rate, remission rates, and adverse events), the odds ratio (OR) was used as the measure of effect size.

Figure 1. *PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only*



The following demographics and clinical information were extracted:

sample size in each group sample size, age, gender, years of education; depression characteristics (illness duration, baseline severity scores and end point scores; use of antidepressants; degree of refractoriness; scales, interviews and checklists used for depression diagnosis).

The total sample was total n = 43 tDCS patients, mean age ± SD, 69.28 ± 4.22 years; n = 23 sham control tDCS, (22 females (51%), with unipolar depression (n=33) or bipolar depression (n=10). Table 3. Clinical and Demographic Characteristics of included IPD gives a study-by-study breakdown of the demographic information.

For two studies that had a concurrent treatment arm, only tDCS and sham/placebo were selected (Brunoni et al., 2013b; Brunoni et al., 2017). Most participants were considered treatment resistant (n=27, 82%; Palm et al., 2012; Loo et al., 2012; Loo, et al., 2017).

The primary tool for measurement of depressive symptoms in the studies were MADRS (n = 4 studies, n = 29 participants; Brunoni et al., 2013b; Loo et al., 2010; Loo et al., 2012; Loo, et al., 2017), 17-item HAMD (n = 1 study, n = 7 participants; Brunoni et al., 2017) and 24-item HAMD (n = 1 study, n = 7 participants; Palm et al., 2012), as noted in Table 2.

The mean number sessions: 18.2 (range: 5-22); with anodal (F3) and cathodal (F4/Fp2/F8) positions, electrode size (25cm² or 35cm²), current (mean 2.1mA, median 2mA, range 1-2.5mA) and density (mean 0.056, range 0.029-0.080), as noted in Table 2.

Cochrane Risk of bias showed high quality across all studies and a low risk of bias. (Figures 2 & 3).

Figure 2. *Cochrane Risk of Bias Graph*

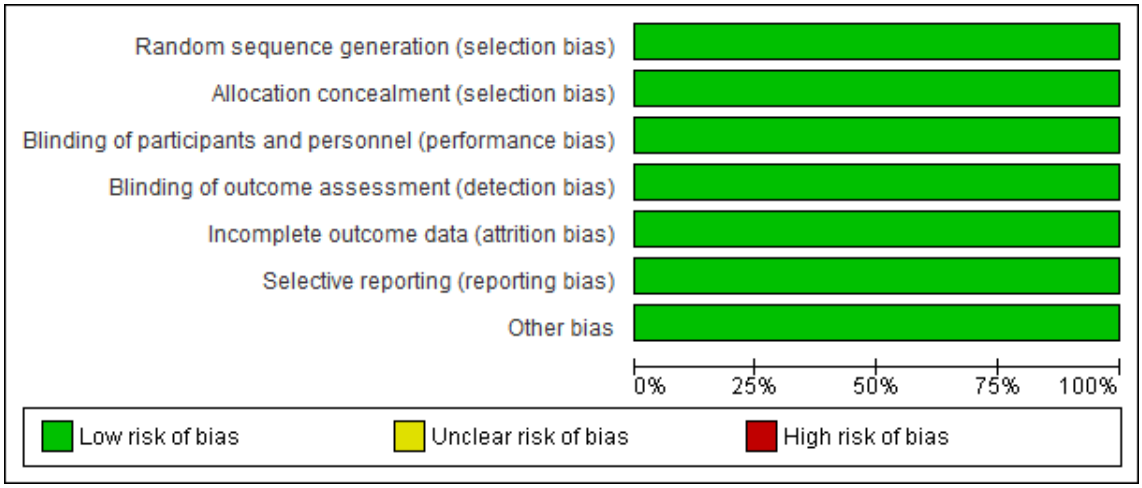


Figure 3. *Risk of Bias Summary*

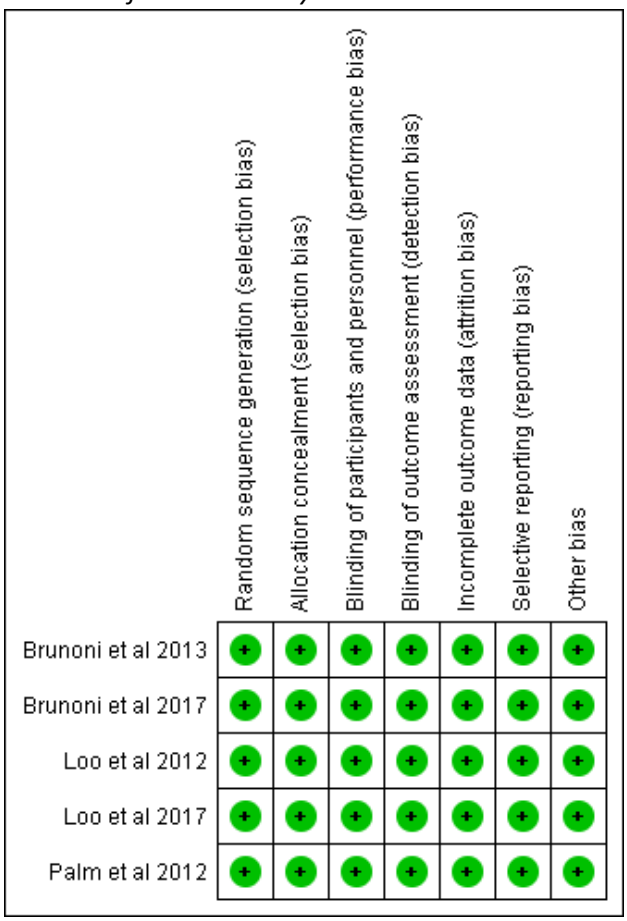


Table 2. *Summary of the included studies*

	Study Characteristics					
Study	**Palm et al (2012)**	**Loo et al (2010)**	**Loo et al (2012)**	**Loo et al (2017)**	**Brunoni et al (2013b)**	**Brunoni et al (2017)**
Study design	RCT, crossover	RCT	RCT	RCT	2-arm RCT	3-arm RCT
Main inclusion	MDD	MDD	MDD ≥3 years	MDD	MDD, low suicide risk, AD free	MDD
Depression cut off	HDRS-24 ≥ 18	MADRS ≥ 20	MADRS ≥ 20	MADRS ≥ 20	HDRS-17 ≥ 17	HDRS-17 ≥ 17
Bipolar disorder	Excluded	Excluded	Allowed	Allowed	Excluded	Excluded
Main exclusion criteria	Other Axis I disorders, suicidality, neurological disorders	Other Axis I disorders, Failure of ECT, neurological disorders	Other Axis I disorders, ECT failure, neurological disorders	Other Axis I disorders, >3 failed meds, ECT failure, neurological disorders	Other Axis I disorders, Axis II disorders, neurological disorders	Other Axis I disorders, Axis II disorders, neurological disorders (Anxiety not excluded)
Primary outcome measure	HDRS-24	MADRS	MADRS	MADRS	MADRS	HDRS-17
Age range, years	36-79	18-65	23-78	18-81	18-65	18-75
Total Sample Size (n)	22	40	60	130	120	245
tDCS Device Stimulation Characteristics						
Device	Eldith DC	Eldith DC	Eldith DC	Customised device	Chattanooga Lonto device	Soterix device
Anode	F3	pF3	pF3	F3	F3	F3
Cathode	FP2	RSO	F8	F8	F4	F4
Frequency, No sessions	10	5	15	20	10	22
Weeks, stimulation	2*	2	3	4	4	10
Current density	0.28-0.57	0.29	0.57	0.83	0.8	0.8
Session duration (mins)	20	20	20	30	30	30
Total charge (mA)	1-2	1	2	2.5	2	2

(AD= antidepressant, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale; all studies completed an intention-to-treat analysis, *crossover +2)

Table 3. *Clinical and Demographic Characteristics of included IPD*

	Clinical and Demographic Characteristics						
Study	**All patients**	**Palm et al (2012)**	**Loo et al (2010)**	**Loo et al (2012)**	**Loo et al (2017)**	**Brunoni et al (2013b)**	**Brunoni et al (2017)**
Size (f)	43 (22)	7 (5)	1 (0)	5 (2)	19 (10)	4 (2)	7 (3)
Age m(sd)	69.3 (4.22)	70 (4.83)	65	70.2 (5.17)	70.4 (4.29)	65 (0.00)	68.3 (3.45)
Age range	65-81	65-79	65	65-78	65-81	65	65-73
Education m(sd)	16.72 (3.57)	NR	NR	NR	18 (2.89)	NR	14.3 (3.62)
UP* (n)	33	7	1	4	11	4	6
BP** (n)	10	0	0	1	8	0	0
Medication (n)	15	7	0	1	5	0	2
Duration, months m (sd)	145.33 (151.48)	219.4 (110.57)	6	64 (81.28)	213.89 (166.00)	11 (9.42)	87.17 (169.68)
Treatment resistant (n)	27	7	0	1	16	0	3

(*unipolar disorder, **bipolar disorder)

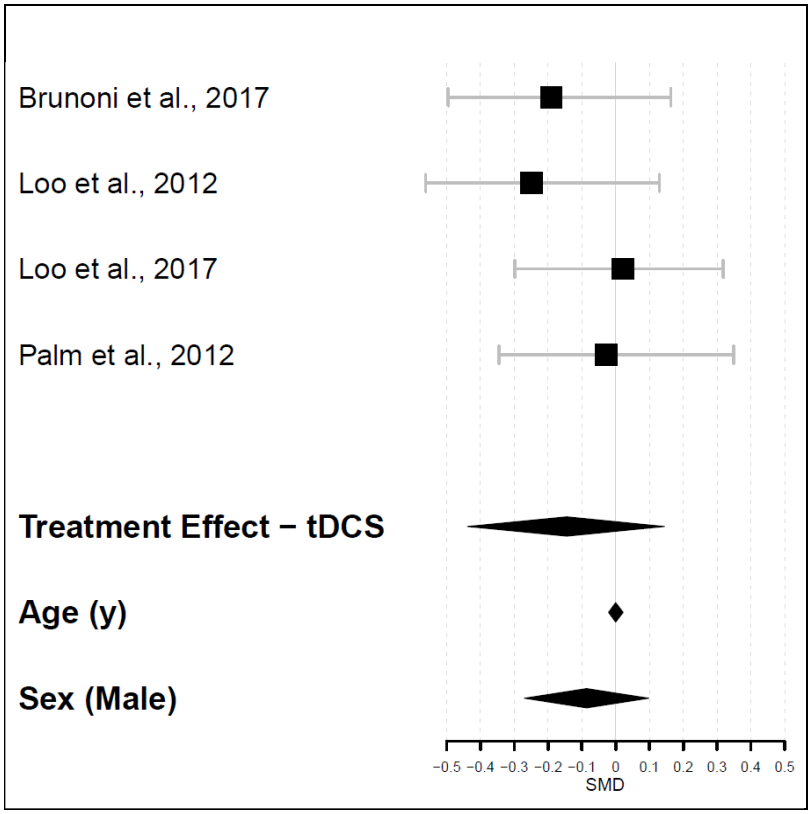
Depression scores reduced in both active tDCS (HDRS: -8.7 points; MADRS: -7.6) and sham tDCS (HDRS: -5.7; MADRS: -6.9). Response rates were 21.0% for active tDCS (4/19) and 16.7% (4/24) for sham. Remission rates were 10.5% for active tDCS (2/19) and 12.5% for sham (3/24).

The analysis was conducted using Bayesian multilevel modelling for IPD of the 6 RCTs. Treatment with active tDCS was associated treatment with tDCS was associated with non-statistically significant modest reduction of SMD = -0.14 (95% credible interval [-0.44; 0.15]) on validated depression scale scores before and after treatment, relative to sham tDCS.

Based on these SMD estimates, there is a probability that tDCS treatment reduces depression scores in older adults is 82% as a small effect (score change <0).

Sensitivity analysis using a two-step IPD frequentist meta-analysis with LOCF showed similar results, with tDCS treatment associated with a reduction of -0.12 (95% confidence interval [-0.34; 0.12]) (Figure 4).

Figure 4. *Forest Plot (Frequentist analysis)*



Tests of heterogeneity

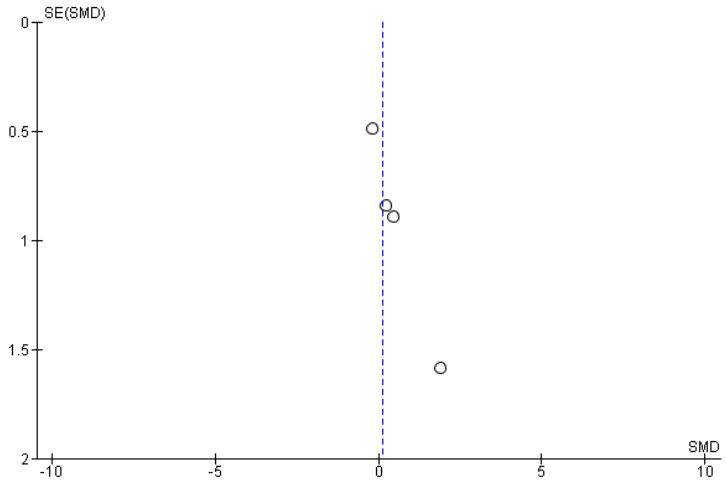
Statistical heterogeneity was assessed by utilizing the *I*2 statistic and evaluated using the I^2 test (35% for heterogeneity) (Higgins et al., 2003).

According to the studies heterogeneity, a random-effects model was used for conducting meta-analysis for each outcome.

Acceptability

Most participants completed treatment (n=39; 90.7%). Discontinuation rates were 15.8% (3/19) for active tDCS and 4.2% (1/24) for sham tDCS, which was not statistically significant (OR = 4.3, 95% CI 0.41- 45.28, p=0.31).

Figure 5. *Funnel Plot of tDCS depression improvement*



2.9 Discussion

To our knowledge, this is the first individual patient level meta-analysis of the efficacy of tDCS in LLD. Individual participant data was collected across 6 RCTs, compiling of 43 participants. With regards to clinical response and remission, our findings also did not show any significant effects for active tDCS. Though there is a modest, non-null effect for improving depressive symptoms with tDCS. The main conclusion from this meta-analysis suggests there may some effect, however more research is needed. In particular an sham-controlled RCT focused on efficacy of tDCS in LLD.

Efficacy of tDCS in LLD

There have been no studies to date that focus on efficacy of tDCS in LLD only clinical groups. There are 2 case studies with results showing reduction of symptoms over time have been reported in of LLD samples (Palm et al., 2009; Shiozawa et al., 2014). Shiozawa et al., (2014) found a lasting effect after 3 weeks in a case-study. This case might be of interest as at aged 92 years; firstly, there are limited cases of old-old population within any tDCS studies; the participant presented with a current depressive episode, which was not treatment resistance and the depression did not seem to appear to be vascular in nature, however it is unclear whether this was a first episode in late-life or a recurrent episode. In either case, it may offer insight that whilst age does have a complex relationship with depression, tDCS may remain effective at any age and, in depression that is not treatment resistant (Mutz et al., 2018). How age and age of onset might impact on tDCS efficacy in LLD requires more research.

Across the current literature, there are multiple meta-analyses that include old age groups within their sample such as a large meta-analysis (including n= 27 studies and n=1204 participants) by Zhang et al., (2021). This analysis used both continuous and categorical outcomes. It demonstrates active tDCS was superior in the modulation of depressive symptoms with significant effect (g = 0.46,

95 % CI 0.15−0.76) and when looking at active tDCS over sham tDCS for both in response and remission, active tDCS was superior but results were not significant ($OR_{response}$ = 1.75, 95 % CI 0.85–3.58; $OR_{remission}$ = 1.29, 95 % CI 0.59–2.83; Zhang et al., 2021). There may be 2 rationales for this; not reaching the optimal current (2mA) and session length (30 min) may offer some explanation to why response and remission were non-significant, but treatment shows reduction in symptoms. The first explanation may be related to the sample was largely treatment resistant. Our findings are in line with results from those defined as treatment resistant within working age population (Blumberger et al., 2012; Palm et al., 2012), showing results were not significant in these clinical trials. It is now established treatment resistance is associated with reduced efficacy in predictor models (Brunoni et al., 2016a).

Another explanation might relate to different variables across study results within the meta-analysis that vary from the optimal current (2mA) and session length (30 min). This may offer some explanation to why response and remission were non-significant, but treatment shows reduction in symptoms (Zhang et al., 2021). Specific tDCS parameters have been found as moderators to outcome, as well as possibly contributing as predictors (Meron et al., 2015). Instead, dose was identified as a significant and independent predictor, which could be calculated as a combination of the above two parameters. There is not currently any consensus on how to calculate, whether this be current, or number of sessions. It may be more feasible to increase number of sessions over stimulation level due to potential side effects (Brunoni et al., 2016a). Although many of the studies varied in tDCS current level, number of sessions and timing, there was no significant heterogeneity (Zhang et al., 2021).

Other meta-analysis which included LLD within their samples show significant effect in clinical response and remission (Shiozawa et al., 2014; Razza et al., 2020). Using a more conservative end point, depressive symptoms as a primary continuous outcome showed significantly improved in the

active tDCS group when compared to sham (Hedges' g= 0.37; 95% CI 0.04–0.7), as well as a significant effect in categorical outcomes of clinical response, remission (Hedges' g= 0.40; 95% CI 0.07–0.73). The authors highlight that although parameters such as current level, number of sessions, dose do vary over time and across studies, this is not significant enough to alter results as their106artict size remains like that of an earlier meta-analysis (Shiozawa et al., 2014). This suggests and was confirmed a subsequent meta-analysis reviewing follow up data following tDCS treatment for an acute depressive episode, there is an established cumulative effect of tDCS, but the overall effect was modest (k = 13, g = -0.81, 95% confidence interval [CI]: -1.28; -0.34, I^2 = 84.0%; Razza et al., 2020).

Additionally, continued improvement in depressive symptoms over time has been observed across adult age groups, (Brunoni et al, 2016a). Once tDCS treatment has finished, improvement has continued to be seen in follow up sessions for as long as 6 months post treatment (Razza et al., 2021). This has been suggested as evidence that tDCS follows a similar mechanistic trajectory to antidepressant medications. And as such, the results seen in this meta-analysis may not be demonstrate the full potential effect of tDCS within the IPD scores that were available. Future studies looking at LLD should consider incorporating long term follow ups within their design.

In terms of acceptability, there were a small proportion who did not complete, this could be reflected as an overall drop-out rate of 10%; (Active 15.8%; Sham 4.2%). However, rationale for non-completion was not stated. Thus, this analysis was unable to capture the reasons for non-completion and this would be a consideration to incorporate for future research to see if this is a replicable effect across this specific age group, if there are differences between old and older old and to help understand the rationale for any differences found. Sekhon et al., (2018) propose that acceptability

of treatment is multi-faceted beyond all cause drop-out. Further, understanding acceptability in this framework can assist the success of future interventions.

Strengths and limitations of analysis

This is the first meta-analysis to address the efficacy of tDCS in LLD. It has been able to highlight a potential benefit for a subset of LLD by reducing the severity of symptoms experienced within this age group. Compared to an aggregate approach, using IPD meta-analysis techniques has allowed for precise estimates and were able to calculate the percentage improvement by transforming scores to z-scores and analyse this as an independent variable. There was a low risk of bias. The quality of all the studies included were high and this supports the validity of the results found in this meta-analysis. A limitation is the small sample size due to the lack of sham controlled RCTs within LLD that have been conducted to date. This research is still in preliminary stages when looking at the treatment for the age group. It may support tDCS for LLD as a treatment for depression It is known that a small sample is likely to have low statistical power and thus lower chance of finding a statistical effect but also reduces the chance that statistical significance truly reflects the reported effect (Button et al., 2013). To mitigate both outcomes, the choice of analysis has offered increased power and sensitivity to detect treatment affects, treatment-covariate interactions and an ability to control for aggregation bias (Stewart et al., 2012; Turner et al., 2000; Fisher et al., 2011; Bowden et al., 2011).

It is a balanced sample within categories of age and gender; including those 65-75 and the older old (75+), the small sample can be explained to an extent, as with older old less likely to consult mental health care (Crabb & Hunsley, 2006), and may in part contribute to a restricted sample because of the lack of access to research.

With increased vulnerability for female sex, it is very typical there is a higher proportion of females represented across depression research (Albert, 2015). Though supportive of incident being twice as high, when specifically looking at old age population, gender difference for the risk of depression tends to disappear (Luijendijk et al., 2008). However, there is an equal sex ratio in this sample (f:m = 56%:44%).

The small amount of available IPD is a limitation. This also highlights pressing need to further research in this age group and to consider factors that may uniquely impact this clinical group such as the impact of vascular risk factors, age of onset as well as potential tDCS moderators. TDCS has shown efficacy in those with a first episode or recurrent type disorder (Meron et al., 2015; Brunoni et al., 2016a; Mutz et al., 2018). This can be complicated by the above factors in this clinical group and as such, it may be beneficial to address these with future studies of LLD. A small sample also may mean there is a lack of generalisability and any future research to include older participants would strengthen the research base. Studies with a small sample size that are included in the meta-analysis may create a sampling error, causing a bias across all effect sizes including the standardised mean difference, odds ratio, risk ratio, and risk difference to varying extent, though the mean difference was unaffected (Lin, 2018). Overall, each included sample had a considerable size in the original studies. However, this is worth considering given the IPD data has effectively taken a sub-group sample from these and it is not clear whether this has significantly impacted the results.

No data was available on the age of onset for any 108participants, as well as no historical data around social support. As presented in the introduction, there are some aspects that can be considered as part of the analysis such as age of illness onset, psychosocial risk factors and particularly for LOD neurobiological status. All these factors could affect the understanding of the effectiveness of tDCS within this age group. Further, it meant that these aspects were not able to be included into any moderator analyses, which might have provided insights into the findings. It would

be advised to include these in future studies. Co-morbid physical illness and level of burden were not assessed in the meta-analysis due to non-availability of data.

Anxiety is a known factor in relapse and 15% had a co-morbid anxiety disorder. Andreescu et al., (2007) examined the effects of co-morbid anxiety on response and relapse, reported those with co-morbid anxiety took longer to respond to treatment and had a higher occurrence of relapse (Andreescu et al., 2007), which undoubtedly is a factor within this subset. Both co-morbid anxiety and medical illness are highlighted as moderating factor in treatment outcomes for those with LLD (Lenze et al., 2001).

Future directions

Novel approaches to see greater effect are needed that extend beyond focal stimulation, or longer or more sessions. Specifically, for LLD, investigating current established treatments as potential concurrent treatment such as collaborative care might be of benefit. Any research to include potential moderating factors such as age of onset, biological history, psychosocial history, and co-morbid illness would be well-judged. In addition to brain imaging and possible inflammatory markers, to allow for co-variate analyses of these factors, consideration for samples which include first presentations in late-life or recurrent episodes which have previously responded to treatments would be of great benefit to the research base.

To address impacts on the depression course and efficacy, there is value in completing longitudinal assessment of tDCS beyond 6 months; most notably in this group, it would also aid monitoring for prodromal cognitive changes or development of vascular risk factors, in a prospective design.
High definition tDCS (HD-tDCS) is a novel approach for this age group (Wong et al., 2019). HD-tDCS typically has a smaller surface area to provide a higher, more focal current density and is designed as

a 4x1 electrode montage. The treatment was for 2 weeks as an augmentation treatment with antidepressants. Not only did they find a satisfactory level of tolerability, marked by no dropouts, the team found a reduction in symptoms and severity and further found global cognitive improvement and verbal fluency (Wong et al., 2019). Due to limitations of a small sample (n = 15) and an open label pilot design, interpretation of the results is limited but this could mark a potentially promising treatment protocol for further future research, particularly in a randomised controlled trial (Wong et al., 2019).

Concurrent tDCS with other treatments, for example cognitive control therapy and tDCS (Segrave et al, 2014; Brunoni et al., 2014), may also specifically benefit LLD given the cognitive changes. There might also be a consideration for taking a novel approach in this direction such as assessing tDCS with a successful treatment with LLD such as incorporating a primary care approach, collaborative care approach or a form of community psychological intervention to see if the efficacy improves.

Chapter 3: Investigating the feasibility and acceptability of at-home tDCS, using a new paradigm for qualitative analysis of acceptability.

Chapter Overview

Prior to this chapter, the thesis has followed a positivist, quantitative line of inquiry to investigate novel research areas of tDCS that include a meta-analysis of tDCS in LLD and tDCS effects on neuropsychological assessment.

This chapter will be describing the qualitative analysis on data taken from a feasibility and acceptability clinical trial for at-home tDCS. This study is detailed in the previous chapter (p. 46-50). A distinction is made between the previous quantitative approach versus the current qualitative approach as the presentation, format, tone, and terminology may change accordingly.

The chapter begins with differentiating between feasibility and pilot studies, then a description of feasibility uses to investigate acceptability are presented. In the next section, acceptability is discussed in the context of healthcare, with a discussion on definitions of acceptability and how they vary in their complexity. A history of assessment tools for acceptability and the development of a new framework are presented and discussed. Factors concerning acceptability, its importance in healthcare and a rationale for this study, including the current knowledge base of acceptability of tDCS are then discussed. For this chapter, acceptability will be understood as a complex construct.

Examples of how tDCS as a methodology can assist in deconstructing the elements of acceptability and a new perspective of understanding acceptability in tDCS are then provided. The research question is restated and after briefly introducing qualitative methods, I will discuss the methodological, epistemological, and ontological concerns. The final sections will review the analytical approach (thematic analysis), the findings and conclude the chapter.

3.0 Introduction

What is feasibility?

According to the SAGE Encyclopaedia of Educational Research, Measurement, and Evaluation, feasibility "*is the extent to which those who implement a research study, or an intervention can practically do so within an identified authentic setting*" (Gagnon & Barber,.2018, p. 668). The term feasibility is typically used to describe small, confirmatory studies and has been used interchangeably with 'pilot study' (Lancaster, Dodd & Williamson, 2004). Though, the interchangeable notion is only used in around 14% of studies. More commonly, the terms are used individually with approximately 63% and 31% of studies using the terms feasibility and pilot, respectively (Billingham, Whitehead & Julious, 2013), which might suggest there is a rationale for using them independently.

Feasibility and pilot studies are recommended by the Medical Research Council (MRC) as an aid in identifying the problems that might occur when investigating new or novel complex interventions (Craig et al., 2008). Making a formal distinction between the two terms might support what the most appropriate terminology and approach for novel intervention research (Arain et al., 2010). Though until recently, despite numerous definitions for feasibility, pilot studies, there remained a lack of clarity in the definition (Lancaster, Dodd & Williamson, 2004; Thabane et al., 2010).

A key distinction identified a pilot study as a smaller, more cost-effective version of the main study to ensure all components work together as expected. Whereas the alternative (a feasibility study) tests the characteristics of the study such as number of eligible participants, standard deviation of an outcome measure and can offer a more flexible methodology (Arain et al., 2010). More extensively, a feasibility study has a main objective to evaluate recruitment capability and sampling characteristics, any procedures relating to data collection and outcome measures, acceptability,

intervention, study procedures, available resources, implementation, and preliminary response of the intervention (Orsmond & Cohn, 2015).

The definition offered by the National Institute for Health Research (NIHR), a funding body across the United Kingdom (UK), also use these definitions to differentiate between terms. It further states both are undertaken to see whether an intervention can be researched, and if and how to proceed with it, with the difference that a pilot study uses a specific design (NIHR, 2021).

A feasibility study is described as an overarching term that includes pilot studies as a methodology (Eldridge et al., 2016a). Notably, when preparing for an RCT such as randomised and non-randomised pilot studies, those feasibility studies that are not classed as pilot studies. An example of studies not classed as pilot would include all other trials which do not have efficacy as a main outcome and are designed to support a future RCT (Eldridge et al., 2016a). This definition is also compatible with MRC guidance for investigating novel, complex interventions (Eldridge et al., 2016a; Craig et al., 2008).

Feasibility studies are used to test the acceptability of an intervention among other attributes of the study and intervention. When investigating interventions in healthcare, acceptability should be considered during the design phase of a study and right through to implementation and evaluation (Sekhon, Cartwright & Francis, 2017).

Acceptability is an important facet of feasibility which can often be skimmed over or even 'overlooked' (Eldridge et al., 2004). Literature can use inconsistent labels for outcomes of the same construct occasionally but are particularly noticeable with feasibility and acceptability constructs. For example, being feasible is meant as the guidelines produced in an article are recommended as implementable and acceptable are 'attitudes, perceptions, and reactions' of an intervention. So,

despite have clear delineation, feasibility, and acceptability constructs are often used interchangeably or individually. The variation in labelling has created an overlap between acceptability, and feasibility (and accessibility) being used interchangeably (Proctor et al., 2011). Identifying each construct as its' own specific and unique entity aids the researcher position in several ways. The first by stressing the importance of not conflating these concepts. Second, it offers additional understanding for a novel intervention within that construct (i.e., acceptability). This, in turn, proposes to offer quicker resolutions when the researcher understands acceptability of the intervention versus the nuance of accessibility and what the feasibility is of conducting the study. Further, there are wider implications on what methods of analysis might be most appropriate, using individual level or aggregate data and the validity of the proposed investigated construct if not appropriately and transparently defined (Proctor et al., 2011).

The CONSORT was designed to increase transparency in RCTs. The CONSORT issued a statement to establish a standardised report of what is required for pilot and feasibility studies. In this instance, there is no distinction made between the guidance for a pilot or feasibility study. The CONSORT for feasibility studies have given an alternative layout of aims and objectives which apply specifically for these studies (Eldridge et al., 2016b). Further, provides the required clarity is maintained around the definition of feasibility and means all feasibility studies will have a high standard of conduct and reporting (Eldridge et al., 2016b).

Acceptability in healthcare

A clear understanding of what a feasibility study is has been presented. To understand the how acceptable a novel intervention is in the context of feasibility, requires a) an understanding of acceptability as its own concept and b) how to appropriately examine this within a feasibility study in a healthcare setting. The next section will look to address these points.

What is acceptability?

Acceptability can be defined in simple terms from as an inference from a person's behaviour, mainly 'the level of consent in the study, degree of uptake, adherence, or engagement (with an intervention)' to a more complex and personal experience of patient perception, intervention satisfaction, absence of harm and positive effect, perceived benefit, and usefulness (Sekhon, Cartwright & Francis, 2018). However, there was no clear definition on acceptability that encompasses the construct as a complex entity until recently (Sekhon, Cartwright & Francis, 2017).

Acceptability studies have typically defined acceptability as a quantitative, binary measure like discontinuation rate or drop-out rate, counting the number of participants who do not complete the study (Furukawa et al., 2016; Simmonds-Buckley, Kellett & Waller, 2019). Early definitions of acceptability within the confines of treatment describe the appropriateness of a treatment as a social validity construct (Kazdin, 1980). This forms the basis of acceptability as a construct. The component, social validity, was described as the social significance or 'acceptability' of a treatment procedure and the resulting behaviour change (Miltenberger, 1990). Using this definition has led to researchers to infer acceptability through the lens of participant behaviour as engaging with the study, for example through adherence, engagement, or discontinuation rates (Sekhon, Cartwright & Francis, 2018).

Using a dropout method to measure acceptability does provide some useful information for quantitative researchers looking for raw, binary data. A criticism of having the narrow definition of acceptability as a singular factor means the understanding of acceptability ends here. It does not provide any insights or explanation for adherence, engagement or drop out (Sekhon, Cartwright & Francis, 2017). A more nuanced comprehension cannot be extracted from this data such as why there was or was not engagement in an intervention. Therefore, a clear definition of how treatment acceptability is interpreted may assist in both the understanding of what is required to assess

acceptability and what benefits and barriers arise around the engagement with a treatment or intervention.

It is now understood discontinuation or dropout rates are just one representation of acceptability and acceptability is acknowledged as a complex construct (Elliott, 1988). Acceptability is a powerful aspect to the success of a treatment and the potential to dismiss an efficacious treatment with low acceptability is possible (Carter, 2007; Sekhon, Cartwright & Francis, 2018).

A working definition of acceptability has been proposed and is used for this research as "*a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention*" (Sekhon, Cartwright & Francis, 2017, p. 4).

An array of acceptability rating scales are available to assist in teasing out specific tenets of acceptability such as manipulation of the treatment (level of intrusiveness, apparent appropriateness and time required for intervention), of treatment user (age, gender, diagnostic label of user and severity of illness) and manipulation of the rater (rater knowledge of treatment and rater affiliation), along with more complex aspects such as ethical consideration, intention and opportunity costs (Carter, 2007; Sekhon, Cartwright & Francis, 2018).

Assessing acceptability

Converse to an empirical assessment of attrition rates or drop out, structured approaches to the assessment of acceptability have been approached using rating scales (Carter, 2007). The first structured approach to treatment acceptability was developed by Kazdin (1980) called Treatment Evaluation Inventory (TEI). Kazdin (1980) defined acceptability as appropriate, fair and reasonable for the treatment and the patient, as judged by the patient, lay people and others (Kazdin, 1980).

This definition signifies acceptability may be dependent on the perspective was judged from and a consideration researchers should make is where they place the importance of this perspective, i.e., on the researcher or the participant that can be led by the research question.

TEI, initially created for parents to assess children's behaviour, was a 7-point Likert rating scale. The questions asked were 1) how acceptable treatment was, 2) how willing they would be to carry out the procedure, 3) how suitable the procedure would be for children with problems other than those described in the study, 4) how cruel or unfair treatment was, and 5) how much the student liked the procedure (Kazdin, 1980, p. 261). This has been used in subsequent parent studies (Calvert & McMahon, 1987) and adapted for undergraduates (Kazdin 1980) and within health settings (Burgio et al., 1995). In addition to a modified short form version being created (Kelley et al., 1989). These adaptations led the way for the development of several different acceptability forms to assess social validity as a construct for acceptability. Examples such as the Treatment Acceptability Rating Form (TARF; Reimers & Wacker, 1988) and the Intervention Rating Profile-20 (IRP-20; Witt & Martens, 1983) have provided extensive comparative critique of the content, purpose, psychometric properties, and their use within research (Finn & Sladeczek, 2001).

As acceptability expands within healthcare research, so too have the tools of measurement. Treatment Acceptability and Preferences (TAP) is a psychometric measurement that aims to identify treatment preference focused on patient preferences (Sidani et al., 2009). TAP includes a description of the intervention and participants were asked to rate the intervention as acceptable (or not). The description may have provided some clarity to what was being assessed. Questions were framed around a) appropriateness (does it work for the symptom/illness experienced); (b) suitability to individual lifestyle; (c) effectiveness (for managing symptom/illness); and (d) convenience of its' use. The 5-point Likert scale (higher scores equate to high acceptability) rate each attribute which allowed for a quantitative analysis of different attributes. The clinical group sampled were

experiencing insomnia and were given 4 different treatment options including sleep education and hygiene (SHE), stimulus control instructions (SCI) sleep restriction therapy (SRT) and a combined therapy called multi-component intervention (MuCI), which comprised of 3 prior options (SHE, SCI, and SRT). This demonstrated the use of comparative perceived efficacy could be made meaning a researcher can compare the efficacy as perceived by the participant for one intervention against other interventions (Sidani et al., 2009), an aspect considered in acceptability.

The TAP provided some understanding of acceptability as a construct from the perspective of 'patient' (Sidani et al., 2009). It can be argued limiting complex or novel healthcare interventions to the 4 attributes above only provide part of what makes an intervention acceptable. It does not fully include items such as burden of the treatment, which could augment attributes like participant intention; self-efficacy as an explanation for uptake of treatment or intervention against another and can be viewed as a limitation of using a rigid Likert scale. Further, opportunity costs are not considered in the TAP, either for those who pay for healthcare or the potential cost of a healthcare establishment endorsing it as cost-effective. In addition to the extent of any benefit, or values required to engage with the treatment (Sekhon, Cartwright & Francis, 2017).

Standardised assessment has limited ability to reflect the complexities of acceptability and thus does not allow understanding of the construct. While inconsistencies between earlier forms of assessment (i.e., TEI, TAP) may have contributed to the ambiguous nature of acceptability definitions, the lack of theory development is a more pivotal aspect (Sekhon, Cartwright & Francis, 2017). Using a flexible, inductive-deductive approach to theory development and analysis, conceptual elements of acceptability can flourish and allow for a better understanding of the complex, multi-faceted component to healthcare intervention success and expanding knowledge base (Shaw, Larkin & Flowers, 2014).

An inductive-deductive approach was used to catechize acceptability from a new perspective (Sekhon, Cartwright & Francis, 2017). The TFA encompasses 7 categories to assess acceptability: (1) affective attitude, (2) burden, (3) ethicality, (4) intervention coherence, (5) opportunity costs, (6) perceived effectiveness, and (7) self-efficacy (Sekhon, Cartwright & Francis, 2017). Multi-timepoint assessments: prospective, concurrent, and retrospective acceptability assessments taken from a temporal position, (i.e., what is the experience up to this point, what is the anticipated experience from this point onwards), can allow for real-time alterations particularly within a feasibility study (Sekhon, Cartwright & Francis, 2017).

Collecting data in this structure will invariably alter the knowledge gained around the intervention in question and how acceptability of the intervention is understood. The increasing frequency of quantitative methods to establish participant or consumer preference have been applied, for example to inform regulation (Ho et al., 2015) but more typically, the understanding and acceptability of a new intervention is initiated through using a qualitative approach (Huls et al., 2019).

There is a juxtaposition around health research which follow an increasing attempt to use linear models of causality within research, while health policy is identifying rising levels of complexity and diversity with the same population. Qualitative approaches are more suited to lending themselves to addressing this conflict. Though in conducting the research, it would require a variety of methodological approaches, that are both sensitive to and encompasses the diversity of acceptability constructs across different sectors and topics (Meyrick, 2006; Shaw, Larkin & Flowers, 2014).

Factors affecting acceptability

The initial recognition of acceptability as a multifaceted construct was found when devising a short form version of an established assessment tool (TEI; Kelley et al., 1989) and represent the first consideration of factors affecting acceptability.

Determining the relevant factors of acceptability rating scale transcends any definition of acceptability. Initially TEI was published as a 'one factor' assessment tool, assessing acceptability as one, simple construct. However, further analysis during the development of a short form of TEI devolved this into 2 aspects, one being how acceptable the intervention is considered and a second specific factor of perceived side effects and posed the question of its' now known complexity (Kelley et al., 1989). However, acceptability ratings can be influenced by several differing factors. These include how acceptability is rated, the role of stakeholders such as patient and professionals, how and where the data is collected, for example the level of intrusiveness and the environment will impact intervention acceptability, in addition to a summary of what does not affect acceptability.

A factor affecting acceptability relates to an identified gap between what is known about a treatment, and what is provided and experienced in practice. The lack of evidence around implementation can mean a lack of understanding or a misunderstanding of treatment acceptability (Proctor et al., 2009). This can frequently occur when research around acceptability has been based on vignettes rather than having experienced the treatment first-hand.

Stakeholder viewpoint is another factor affecting acceptability. Both patients and healthcare providers or professionals are highlighted as stakeholders within acceptability assessment (Borelli, 2011). Patient involvement in acceptability have been associated with improved quality outcomes, and patients have been encouraged to act as an expert of their experience and preference to treatment options (Department of Health, 2001; Greenfield et al., 1985; Say & Thomson, 2003). The

proposed acceptability of a treatment or intervention can further be informed by the healthcare provider or professional perception of the intervention (Borelli et al., 2005). Often treatment history is summarised by professionals and severity is rated by professionals, both of which can impact acceptability ratings (Kalfus & Burk, 1989; Kazdin, 1980; Spreat & Walsh, 1994).

Further, the setting of the intervention and the characteristics of the raters such as rater education and contact with patient impacts how acceptability is rated (Burgio et al., 1995). In this study, nurses with special interest in older adult care were asked to consider 3 different treatment types, behavioural interventions, positive reinforcement and a 'time out' as a mildly punitive and haloperidol in response to vignette conditions. The vignette presented behavioural problems, living situations and cognitive levels of the patient with the TEI used as a method to rate acceptability. This study yielded a response that preferred positive reinforcement with the highest acceptability. Responses were modified by the educational background of the nurses rating, with those who had received specialised training rating medication for a behavioural response as lower in acceptability, suggesting training provides other skills and approaches to successfully remediate behaviour that appears problematic. In this case, moderating factors included specialised training, in addition to the aforementioned stakeholder viewpoints and the experience of the intervention. Other moderators were clinical factors, i.e., cognitive levels of the patients and where the patient resided, (Burgio et al., 1995) which may seem apparent as this was part of the information presented in the vignette.

It may be posited from this that information could act as a moderating factor for acceptability. The information on positive outcomes of treatment can impact acceptability ratings, specifically the reported strength of a positive outcome significantly affected how the interventions were rated in terms of acceptability (Clark & Elliott, 1988). How restrictive a treatment might be or is perceived can also affect acceptability ratings (Kazdin 1980; Spreat & Walsh, 1994).

In contrast, increasing raters' knowledge of treatment (Rasnake et al., 1993) age, gender or severity of patients (Elliott & Fuqua, 2002) have not been found to affect acceptability ratings. The former expands on the earlier point raised on the gap of knowledge to experience and may emphasise the experience is paramount in being able to accurately provide an account for acceptability. Though, in the latter study, authors stipulate this may be due to a lack of definitive language in the vignettes provided or an occasion specific to acceptability for the treatment and illness examined in this study (Elliott & Fuqua, 2002). While typically any treatment provided received some level of acceptability, some emerge as having no effect. It seems when provided with options between treatments, social are preferred over and punitive or pharmacological options in acceptability levels (Miltenberger, 1990).

Qualitative research methods

Qualitative research is a methodical process of investigation to gain new knowledge, concerned with the understanding of people's experiences, seeking to make or access meaning of those experiences, and can be involved in taxonomy or theory development to describe these experiences (Curry, Nembhard and Bradley, 2009; Willig, 2019). Though, definitions for qualitative research are more 'what it's about' instead of what it is and can be referred to as an umbrella term of processes (Aspers & Corte, 2019; Flick, 2007). The process to understanding and meaning can take different paths depending on the investigative approach taken. Qualitative research pursues knowledge as an exploration and naturally leads to generating novel insights (Pope & Mays, 1995). Forming categories of meaning known as 'themes' develop in the words and actions of participants (Willig, 2019) These categories of meaning can be both a prerequisite and complimentary to quantitative research (Pope & Mays, 2009). The overall aim of the research guides the decision of the approach taken (Kalu & Bwalya, 2017). Balance is struck between theoretical approaches and what is referred to as 'a broad spectrum of concrete methodology'. In the development of a qualitative research

project, theory, methodology and procedural conceptualisation are concerned with going beyond that of empirical studies (Flick, 2004).

The design and process are made up of components and should be considered (Flick, 2004, p. 146):

- **the goals of the study**, either description, testing of hypotheses, theory development.
- **the theoretical framework**, including a detailed description or evaluation of current practice
- **its concrete questions**, meaning questions are formulated to be answered
- **the selection of empirical material**, and availability will inform the design
- **the methodological procedures**, such as selection of sampling and formation of groups.
- **the degree of standardization and control** relating to loose vs tighter designs.
- **the generalization goals** (versus representational goals)
- **the temporal, personal and material resources that are available**

Good qualitative research uses accountability, transparency and reflexivity through a well-defined research question, and a valid justification on the choice of approach; accurate reporting of any adoption of theory, research design, sampling strategy and data collection, ethical considerations and evidencing data trustworthiness and reflexivity (Kalu & Bwalya, 2017; Toye et al., 2016). In addition to these criteria, providing clear interpretation and exploring the experience beyond the research study that is set in an impact plan is critical (Toye et al., 2016).

Qualitative technology research in healthcare

The use of qualitative approaches (QA) in healthcare research has been limited when compared to RCTs. Qualitative methods are reported to be underutilised and overshadowed by RCTs, though qualitative research could offer an innovative and novel perspective to complex healthcare interventions and the potential for learning using this method may be undermined by this gap (Mannell & Davis, 2019).

A wide array of QAs has been used to understand a variety of topics across healthcare and importantly can be brough together in the same way RCTs are systematically reviewed. Systematic reviews are employed to establish a diverse range of countries, settings, and interviewee perspective on the organisations. One review addressed struggles to improve the levels of quality with their healthcare systems (Vaughn et al., 2018). The review found 5 domains that could be identified as a healthcare organisation struggling to improve quality: (1) Poor organisational culture, (2) Inadequate infra-structure, (3) Lack of a cohesive mission and vision, (4) System shocks and (5) Dysfunctional external relations. Some of these are translatable across constructs (Vaughn et al., 2018) and may specifically relate to the form of clinical trial that was conducted within this thesis. For example, inadequate infrastructure was defined in the review as poor levels of staffing (recruitment and retention) or resources, including poor technological or quality improvement infrastructure (Vaughn et al., 2018). For the thesis clinical trial following COVID-19, there was a heavy reliance on technology for videoconferencing. Both having access to technology and the technology working to an approved standard proved pivotal to the success of the study. This is equally a factor that could have affected acceptability for those seen in lockdown conditions, quite uniquely to those in comparison who had access to an in-person researcher early in the study. Another example is point 5: Dysfunctional external relations, defined as organisations having poor relationships with key stakeholders or governing bodies, or lacked well-functioning systems for collaboration with other healthcare facilities infrastructure (Vaughn et al., 2018). At clinical trial level, one of the key stakeholders is the participant and the relationship the researcher holds with them could directly affect acceptability, both positively and negatively.

Addressing the use of outcome measures within healthcare research could translate across to acceptability studies in different ways. Whilst this project is not directly addressing patient outcomes on treatment, it is worth considering practitioner-clinician perspectives. Four themes were identified

in a study addressing professionals experience of patient-reported outcome measures for quality improvement (Boyce, Browne & Greenhalgh, 2014). The first was around practical considerations such as workload around data collection, dissemination, and implementation. This could directly relate to the reduced amount of qualitatively data studies on acceptability, as it is never known what might arise from participant interviews and could potentially lead to extensive change requirements to studies and/or treatments (Boyce, Browne & Greenhalgh, 2014). The second and third themes were around value and meaning of the collected data, often requiring follow up focus groups or individual interviews for clarification. Another consideration is the additional time placed on participants to collect and review the data and other requirements such as any additional training that might be required, which is a universal in most qualitative studies (Boyce, Browne & Greenhalgh, 2014). The final theme found patient outcomes were related to the impact of care. Invariably, the impact should be null. However, the study identified mixed views. On one hand, it can be used to promote professional development and complement any clinical judgement. Conversely, the process may narrow the focus towards opportunity costs towards aspects considered to be more or less important. In addition to the intrusiveness of privacy towards the patient (Boyce, Browne & Greenhalgh, 2014). Again, each are valid considerations within the realms of acceptability of a novel treatment such as tDCS.

A review of methodologies on the patient perspectives of art as an intervention in healthcare demonstrated grounded theory and phenomenology alongside mixed methods were most popular in approaches, variation of content or thematic analyses as most common and semi-structured interviews most frequently cited method (Moss, Donnellan & O'Neill, 2012).

Despite underutilisation and overshadowing, there is a growing interest in using qualitative methods alongside RCTs, particularly to assess complex health care interventions (Mannell & Davis, 2019; Lewin, Glenton, & Oxman, 2009). Using differing timepoints (i.e.., pre and post intervention) can

support in the goal of extracting personal experience and meaning, as well as changes in condition (Midgley, Ansaldo & Target, 2014). Though a criticism of this often cites poor integration with the overall trial findings (Lewin, Glenton, & Oxman, 2009). The experience of post-intervention included in the method the present study uses provides the space to identify unintended outcomes and help to interpret findings, though a stress on pre-trial assessment has been made particularly for acceptability of the intervention and the trial in principle, accuracy and development of measures and the breadth of outcomes (O'Cathain et al., 2014).

The voice and perspectives of the consumer, usually the patient experiencing the intervention, are frequently 'back-grounded' as opposed to 'fore-grounded', when it comes to looking at outcome research within the healthcare sphere of traditional clinical environments (Simmons-Mackie & Damico, 2001). Patient involvement or engagement can be key to enhancing quality. Patient engagement, in form of personal experience, goals, perceived problems and concerns, has been described as a revolutionary concept to guide healthcare planning and interventions through promoting 'patient-centred' care delivery (Maxwell, 2008; Carman et al., 2013). All patient engagement should incorporate the patient wants, needs and preferences (Carman et al., 2013) and it is at this intersection where acceptability finds a firm seat. Involvement can include areas across service delivery, quality improvement and research (Mead & Bower, 2000) and should filter through every aspect of the organisational structures from research to policy (Carman et al., 2013). Research, specifically, has been highlighted as a specific area of interest for improvement in patient engagement (Majid & Gagliardi, 2019). Though it is recognised participants and patients have limited power or authority towards decision-making (Carman et al., 2013).

The landscape of acceptability with tDCS as a treatment for MDD is thin and there are limited studies that provide a qualitative review. A rapid review of qualitative research for MDD and generalised anxiety disorder (GAD) to 2019 identified 29 studies detailing perspectives on pharmacological and

psychotherapeutic interventions. Most include patient perspective (n=28), with treatment studies making up only 12 (n=6, pharmacotherapy, n=5, psychotherapy, n=1 combined pharmacotherapy and psychotherapy) where acceptability is included as part of the study objectives (Kandasamy & Campbell, 2019).

The considerations in the rapid review document the use of qualitative approaches within the specific clinical groups (MDD and GAD) has typically been low. Further, leans towards psychological interventions (Kandasamy & Campbell, 2019). The eligibility criteria included both MDD and GAD, which can present with similar clinical features. However, for the purpose of this thesis, it would be difficult to extrapolate any findings specific to the clinical group of interest (MDD) (Kandasamy & Campbell, 2019).

From the pharmacology sampled studies, none of the studies report the construct 'acceptability'. One study taken from a professional perspective (pharmacist), one chosen excerpt describes 'social acceptance' (Guillaumie et al., 2015). The reference to 'acceptance' is found in 2 other studies, one which uses the interview questions to discuss long term use of antidepressant and the patient perspective of 'accepting treatment' (Bosman et al., 2016) and the other describes the adolescent understanding of acceptance is experienced differently to adults (Maroun, Thackeray & Midgley, 2018). Disease severity and ability to engage with treatment impacted acceptability (or accepting treatment) across both psychotherapy and pharmacological treatments. There were also organisation-level factors that reduced acceptability such as lack of time, and practice setting changes (Kandasamy & Campbell, 2019).

In a brief review of the literature in the more recent years (Stark et al., 2018; Cao et al., 2019) there continues to be a limited amount of published research on acceptability with MDD, or across more

specific clinical groups within depression such as anhedonia in MDD (Cao et al., 2019) or LLD (Stark et al., 2018).

In line with the technological advances available within the home and on mobile devices, an increase of acceptability research merging with the field of digital health interventions (DHI) such as technology, using technological aids, apps, and technology to enhance current therapies or completing therapies via tele-health (online).

On the use of digital app for treatments such as CBT terms like "useful", "flexible", and "helpful" were used. Digital treatments such as CBT were reported to be easy to use at a chosen location and rated highly for privacy, both aspects were also rated as important by participants. There was a point from authors for the need of internet safety (in particular as this study was addressing adolescents). Another key aspect rated as positive by participants and professionals was the scope to use digital tools to monitor ongoing mood assessment scores and flag any pending crises (Rasing et al., 2020).

One review utilised single-item Likert scales, questionnaires, or user feedback interviews to address usability and acceptability outcome across multiple varying digital health tools such as internet based CBT and widely available apps such as Headspace, MoodGYM and SilverClouds Health (Lattie et al., 2019). The results overall were favourable towards usability and acceptability. The authors reported a difficulty with establishing a true acceptability of these interventions due to response rates being low. There were some indication interventions were helpful with good levels of usability in those who continued to engage with the study procedures. The studies could have benefited from higher use of validated scales (Lattie et al., 2019).

A literature review synthesised literature addressing the acceptability and usability of digital products within clinical groups with mood disorders (Patel et al., 2020). The authors established 3

mains themes 1) initial motivations and approaches to DHIs. 2 subthemes came from this, i) Initial motivations: hope, accessibility, and cynicism and ii) Participant Approaches to Engaging With a Digital Health Intervention: Active Versus Passive. Participants describe feeling empowered and a sense of responsibility towards their illness by engaging in this form of treatment. When participants had a self-determined active approach, the outcomes were more positive, in comparison to those with a more passive approach preferred face-to-face as digital health interventions present increased difficulty, and 'stress' (Patel et al., 2020).

The second theme Patel et al., (2020) found was personalization of treatment, had 3 subthemes: 1. Flexibility and autonomy. 2. Stigma and privacy. 3. Functionality, content, and interface. When some found a sense of autonomy and flexibility others struggled with the lack of formal structure that a face-to-face therapy session would bring. Again, mixed reviews around stigma and privacy, some participants embraced the sense of anonymity using digital health technology can bring though for other a lack of space to engage with challenging and difficult topics made the process feel unsafe (Patel et al., 2020).

The third theme, the value of receiving personal support in DHIs, had 4 subthemes: 1. Support for understanding DHIs. 2. Support to enhance commitment and motivation. 3. Suitability and desire for additional support. 4. Support to develop a virtual therapeutic relationship. This theme encapsulates the acknowledgement of increased access and empowerment for self-management. Establishing empowerment is also important for bridging the gap between dichotomous and asymmetrical power relations that exist between the researcher and participant (Ben-Ari & Enosh, 2012). However, highlights the personability of having access to human contact through this therapeutic process. It reported having increased support, simultaneously increased motivation, and commitment to the treatment. The additional support would have enabled a quicker understand on the use of digital health equipment as well (Patel et al., 2020).

Effectiveness of treatment is an apparent aspect of acceptability, and this becomes important when reviewing study outcomes. Exploring a combination of perspectives of patient, caregivers, and professionals has given a broad spectrum of domains to focus in on expected treatment outcomes around functioning (elementary, social professional and complex functioning) and symptoms (physical, cognitive, mood and emotional symptoms; auto-aggression symptoms and perception of self) (Chevance et al., 2020). Focusing on symptoms and functioning in addition to technology uses, may benefit both the patient and researcher in the understanding of effects and side effects in the context of acceptability.

3.1 Rationale for this study

Acceptability in tDCS

Until now, the acceptability of tDCS within depressed clinical groups has been understood in the context of quantitative measures such as drop out, all-cause drop out and discontinuation measures (Moffa et al., 2020; Mutz et al.,2018, 2019; Razza et al., 2020; Zhang et al., 2021). It is suggested with low dropout rates, as found with tDCS in this group, this would imply a high rate of acceptability. Dropout is assigned by the clinician and is assumed to be related to how tolerable the treatment and adverse effects are, creating a direct inference of acceptability being related to side effects (Brunoni, Loo & Nitsche, 2016). However, without discussing with the participants their rationale for 'dropout', it is difficult to state whether this would be the case.

Perceived risk, which includes a person's belief, attitude, judgement and feeling towards a potential hazard, has been reviewed in the context of rTMS (Cabrera et al., 2021). It was appraised as having minor risks and side effects which was based on the information they had been provided with prior to the interview. When compared to psychological interventions they were grouped as both having perceived risk one physical, one emotional. In addition to the potential 'ongoing risk' of permanent or long-lasting damage from the usage (Cabrera et al., 2021).

A retrospective questionnaire on side effects of participants who received transcranial focused ultrasound, form of neuromodulation, revealed only 5/64 participants who responded to the questionnaire reported neck pain, problems with attention, muscle twitches and anxiety as a mild or moderate side effect during the study of brain stimulation (Legon et al., 2020). There were also some unrelated symptoms (sleepiness and neck pain) that were reported. Of the initial transient reports of mild neck pain, scalp tingling and headache were not present at follow-up with no new symptoms up to 1 month after treatment (Legon et al., 2020).

As discussed above, acceptability includes many other aspects and this form of assessment of acceptability for a novel treatment is limiting. To widen the knowledge base and understanding of tDCS within this clinical group taking a qualitative approach could therefore be beneficial.

Current knowledge of tDCS acceptability in MDD

There is limited knowledge for understanding tDCS acceptability in MDD from a qualitative perspective. Further, a limited understanding of using tDCS as a treatment at home for this clinical group.

The usage of tDCS has been explored using a survey by Wexler (2018) who found there was a significant relationship between usage purpose and perceived success of tDCS, from those using tDCS to self-treat MDD. An online survey containing questions on usage, beliefs, attitudes, and demographics was sent to tDCS consumers across 7 different companies in United States. A total of 339 participants were included, 83.5% of respondents were male, with an age range 20-87. One third of responders (n=131) self-treat with tDCS, of those 74% are using tDCS for depression and treaters felt it was effective to treat MDD. This was in comparison to other users using for non-treatment purposes (cognitive enhancement/restoration) who overall rated the device as ineffective. Further, it was noted there was a greater number reporting 'somewhat' successful in comparison to 'totally' successful, suggesting there was some effect but possibly not complete or total removal of symptoms (Wexler, 2018).

In a qualitative rapid review on treatments for MDD, external factors such as those found at organisational level, are an important consideration for the acceptability of tDCS. This is particularly noted as tDCS as a treatment can be used on an at-home basis. One study also addresses the importance of societal representation. While reviewing currently available scientific evidence for the use of tDCS while pregnant, a review of media articles was completed. It found both limited scientific

evidence (3 case studies) demonstrating promising results, and this was replicated across media publishing, a sparse but promising and as such no significant importance had been attached (Kurzeck et al., 2018). Firstly, this gives an insight into how potential patients are socialised to treatments and could be a factor in acceptability ratings. Additionally, it may extend to the understanding of the treatment through the eyes of media rhetoric and have a bidirectional effect on acceptability. Furthermore, the wider social acceptance (others' opinions and attitudes) of testing and maintaining a novel treatment may impact the uptake and acceptability of tDCS.

Self-administered at-home tDCS has been conducted with some success (Alonzo et al., 2019). Participants were provided with a device to self-administer tDCS of 20-28 sessions over 4 weeks. An 'excellent' adherence to protocol was reported with 93% completed planned sessions. Mood significantly improved from baseline and side effects wither minor and transient (Alonzo et al., 2019). An at-home protocol has been demonstrated as encouraging option and the tDCS devices are developing to become more technologically advanced. With this, a risk for technical issues developing increases. Across at-home studies in other clinical groups, technical issues have been cited (Palm et al., 2018). A review of literature of using telehealth options for at-home tDCS suggests an enhanced reduction in technical issues and facilitate compliance through real-time monitoring and with the use of videoconferencing can be done remotely to observe administration and offer troubleshooting solutions (Hordacre, 2018). There have been identified clinical groups who may find at-home tDCS with telehealth monitoring acceptable, of which depression is included (Alonzo et al., 2019; Hordacre, 2018). Further, age and familiarity with the technology are not conditions that affect the acceptability. However, users of at-home tDCS who have used videoconferencing before had preferences with this form of telehealth. Suggestions to include training to increase engagement and for generic telehealth considerations; providing a version of telehealth to those familiar with a set method was also presented. For example, those who might be more experienced in laptop teleconferencing preferred using this method in favour of the use of an IPad (Hordacre, 2018).

There are limitations to the use of telehealth with at-home tDCS. These include the requirement of stable access to internet services, the cost of implementing telehealth such as purchasing hardware or videoconferencing technology could be burdensome for the research team. This also requires maintenance and updates. It could appear intimidating for those who aren't familiar with this form of interaction and may require additional training (Hordacre, 2018).

There has been one study conducted with at-home tDCS using remote supervision (Alonzo et al., 2019). Though the approach to acceptability is that of previous meta-analyses using drop out as the measure. No study has completed a qualitative approach to acceptability to understand patient perspective of tDCS in MDD clinical group. When acceptability is reflected through set categories (overall concept, helpfulness, side effects, effort and burden, ethicality, self-efficacy and recommendation, and design) (Sekhon, Cartwright & Francis, 2017), quantitative measures can provide an accurate rating of helpfulness and side effects, but less is known about why this is the case. Using the qualitative methodology will provide more detailed understanding of these categories, as well as other categories of acceptability and provide the space for participants to express new aspects of acceptability.

3.2 Research Question

This research aims to understand the patient perspective of acceptability through the following question using a series of pre-defined categories related to this topic:

How do patients with depression describe the acceptability of using a novel treatment, at-home tDCS?

The pre-defined categories will include acceptability as an overall concept, helpfulness, side effects, effort and burden, ethicality, self-efficacy and recommendation, and design under the TFA (Sekhon, Cartwright & Francis, 2017).

3.3 Methodology

Overview

In this section, the methods will be discussed to include the research paradigm and epistemological position. The ethical considerations will then be discussed which will include ethical approval, informed consent, confidentiality, and distress.

Research paradigm

Ontology, epistemology, methodology and methods are the four components of a paradigm (Scotland, 2012).

Ontology relates to the understanding or belief a researcher holds around the nature of reality and humanity. For instance, this project takes an interpretative stance, where the experience of reality is a human construct, which is socially constructed and that people make sense of their worlds individually (Cohen, Manion & Morrison, 2000). This means each experience is personal and unique to that person.

Epistemology relates to the theory of knowledge, the nature and form of knowledge, and assumptions consist of how knowledge is produced or 'what it means to know' and examines the relationship between the knower and what is known (Goertz & Mahoney, 2012; Scotland, 2012).

Whilst there is a relationship between ontology and epistemology, prescribing a specific directional relationship can undermine reflexivity and critical analysis (Bates & Jenkins, 2007). The epistemological position of this project, interpretivism-constructivism as a theory understands a world that is constructed, experienced, and interpreted by people through social interaction (Maxwell, 2015). More specifically, the position held as a researcher for this project is critical

realism. Critical realism holds an objective reality which exist beyond our awareness and belief and can also be observed and measured (Willig, 2016). There is an acknowledgment of history, political and social context and proposes multiple dimensions within reality. There is a subjective reality existing alongside the observed experience of the research participant and this acknowledges influence from the researcher (Willig, 2016).

Methodology is strategy of the data collection. There are different methodologies that could be adopted to conduct a qualitative analysis. These include grounded theory, social constructivist approaches and phenomenological approaches (Scotland, 2012). There is a logical connection between the ontological and epistemological position researcher take and the methodology can be impacted by these positions. Whilst there is a directional relation between ontology, epistemology, and methodology, this does not mean one concept determines the other (Kant, 2014). For example, with this research, the methodology has a focus on phenomenology, that is the participants lived experience within the world (Neubauer, Witkop & Varpio, 2019), yet epistemologically, the critical realist would also consider the socialisation of the participant, as the world exists around the participant.

3.4 Methods

Design

Participants and recruitment

All participants were enrolled in at-home tDCS feasibility and acceptability study and were enrolled to take part in the acceptability interviews as part of this study. The participants completed a written 7-point Likert acceptability scale at visit 1 prior to the commencement of the study, then at V21 (end of the tDCS treatment sessions) and V23 (6-month follow up appointment). They were all provided with the opportunity to give a recorded interview at V21 and at V23 follow up, where the qualitative

data has been derived from. As an open-label study, some participants had continued use of tDCS during the follow up period.

The demographics of participants who agreed to a recorded interview. 15 participants agreed to a recorded interview at the end of treatment, with 14 participants at the 6-month follow up, 11 participants were women with an age range 19-73 years. Participant ethnicity was mostly White British (9 participants), 3 participants were of Mixed heritage (Black and White), and other ethnicities included Black British Caribbean, Sephardi Jewish, Chinese, and White Other. The educational background ranged from 12-18 years. During the trial, 11 participants were on antidepressant medication (citalopram, fluoxetine, venlafaxine, sertraline) 5 participants were engaged in psychotherapy (CBT or online CBT -Living Life to the full course). 12 participants disclosed history of various treatment including antidepressant medication and psychotherapy.

Ethical considerations

Ethical considerations are integral in healthcare when conducting qualitative research though any research goal maintains a secondary position to patient wellbeing (Sheikh, 2007). Challenges can arise from the participant-researcher relationship when establishing an open and honest dialogue, maintaining respect towards privacy, confidentiality, and avoiding a misinterpretation of data. There is always a potential for conflict to arise at all stages of the research, research design, data collection, and analysis (Sanjari et al., 2014) and this can be managed through addressing informed consent, anonymity, and confidentiality (Richards & Schwatz, 2002; Sanjari et al., 2014).

Ethical approval

Ethical approval was sought and granted from the University of East London ethics committee and the London - Fulham Research Ethics Committee, Health Research Authority. It was also registered as a clinical trial (ClinicalTrials.gov ID: NCT03632434).

Informed consent

Informed consent was sought as part of the screening process through the means of a participant information sheet (PIS) and a verbal discussion. In the PIS, information about the study was provided in advance, potential participants were given adequate time to read and digest the information provided about what to expect in the study. Information was also provided in relation to data protection, and confidentiality. Participants were aware they could withdraw at any time, without reason or consequence. They were given time and space to ask questions and provided with contact details of the study. Each section of consent was checked verbally with a researcher. Verbal consent was taken to conduct the assessment as either a video or voice recording.

Anonymity and confidentiality

Anonymity and confidentiality were discussed with all participants. It was explained to participants their data would be anonymised and the research team would maintain confidentiality throughout the study. Participants were informed that their GP would be contacted about their enrolment in the study and a summary GP letter would be sent at the end of the study, and at follow up sessions. All transcripts were anonymised and stored in a password protected secure file, in which access has been limited to those researchers on the study (RR, RW, CF, SC).

Power dynamics

Distortion of power exists within healthcare and could be argued to be more prevalent within mental health settings and this area has been under most under debate and scrutiny (Molodynski, Rugkasa & Burns 2010). For example, the use of legislation to compulsorily detain patients albeit legal is often the most overt display of power dynamics. However, there are more subtle positions that are taken such as engaging in 'coercive practices' (O'Brien & Golding, 2003). Coercive practices can be as broad as gentle persuasion to manipulation, threats, or physical acts of force (O'Brien &

Golding, 2003). The challenge of coercion is often placed within hospitalised settings and historically, under the use of mental health legislation which is not relevant to this thesis. Though, some argue for a clear moral justification or a form of paternalism, any form of coercive practice should be avoided in research, as it is understood differently dependent on your position, professional vs patient (participant) (O'Brien & Golding, 2003; Lorem, Hem & Molewijk, 2015).

There is a relevant power imbalance that should be explored. Such imbalances can lead to agreeing or accepting treatments such as directed decision making. Patients (or participants) might find it difficult to speak up and develop a sense of passivity (Joseph-Williams, Edwards & Elwyn, 2014) or resistance or resignation, when a patient (participant) does not feel heard (Lorem, Hem & Molewijk, 2015).

Power imbalance or power dynamics become visible following the process of self-awareness that reflexivity brings and in understanding the position of the researcher (Finlay, 2002a). There is a shift between the knowing (the researcher) and the not-knowing (the researched) which contributes to power dynamics through the power of defining a body of knowledge (Råheim et al., 2016) but also in that to some degree the researcher is a part or shares the story with the participant (Finlay, 2002b). Concealed power dynamics may exist through methods such as caring, empathic, and instilling equality through an empowering nature could be deemed as ethically questionable (Brinkmann & Kvale 2005). Introspection of personal reactions and emotion is valuable as a preoccupation of personal emotions may give preference to the researcher in any findings, rather to give an explicit link between the new knowledge, the links between the participant and researcher within the social context (Finlay, 2002b). The practice of participant trust to gain their story can be another act of counteracting power imbalance if used as a strategic instrument (Råheim et al., 2016). In addition to intersubjective reflection, which allows for a deeper understanding of unconscious processes, social critiques and how these structure the relationship between the researcher and participant (Finlay,

2002b). The 'researched' are not in complete powerlessness, as this position provides the researched to control what information the researcher encounters during the research. As informants, the ability they hold "to control, deploy and manipulate. . .raises questions around the notion of the researcher's exclusive power" (Råheim et al., 2016, pp. 8). Certainly, there are power dynamics that exist between the researcher and the researched and both can be deployed, both discreetly and overtly, as the role of researcher, recognising these dynamics and ensuring balance where possible to prevent any bias should be paramount. Later in the chapter, reflexivity and its' role in this research is discussed.

Data collection methods

There are different forms of data collection which can be used to conduct thematic analysis. A semi-structured interview is an overarching term to describe interviewing in different forms (Brooks & Normore, 2015). How and what sequence the questions are asked and, if and what areas are followed up and developed with different interviewees should be considered with flexibility (Ryan, Coughlan & Cronin, 2009). As with all data collection methods, there are both advantages and disadvantages to interviewing as a data collection method. Some advantages to using interviews are their usefulness in gaining context, insight and generating quotes and stories, along with asking more complex questions. When conducted well, interviews can see the researcher developing a rapport with the interviewee, the interviewee can give more detail and the researcher probe more when appropriate (Doody & Noonan, 2013). Disadvantages to interviewing can mean the interview can seem intrusive, time consuming and expensive when compared to other methods, when talking on sensitive subjects such as mental health, there is a requirement for sensitivity and care for the interviewee. There is also a risk of bias, the interviewee can want to 'please' the interviewer or not feel open to say what they feel, with a desire to want to please, hampering interviewees giving honest answers (Doody & Noonan, 2013). Under bias, sits power dynamic of knowledge creation. There is bifold creation with the participant having knowledge of the experience (in this case the

level of acceptability of tDCS as a treatment), whereas the researcher holds knowledge of research process and will set the agenda. This can come in form of the structured or semi-structured questionnaire. There is an inherent bias with this approach, with the interview being led by the researcher (Ben-Ari & Enosh, 2012). The participant does hold the position to withdraw at any point without obligation and holds power in the very fact they hold the experiential knowledge and thus controls what knowledges is accessed, even when directed by a researcher (Ben-Ari & Enosh, 2012).

There is special emphasis placed on the form in which interviews are conducted to try to manage and mitigate these potential disadvantages, for example semi structured interview can also explore new avenues which may have not been considered in quantitative initial phase of research (Gray, 2016).

Semi-structured interviews

Data collection consisted of a series of set questions with a 7-point Likert scale, scored between 1-7 and these questions were delivered in a semi-structured format to offer further discussion on their answers to the Likert scale question. There was an initial questionnaire completed at the beginning of the study (classed as V1) which delivered using pen and paper, so participants were familiar with the layout of the questionnaire. At the end of the study (classed as V21) and at the end of the follow up phase of the study, (classed as V23), the option to complete a recorded interview were given. The questions were constructed to be specific to this study, using categories of acceptability, in Table 4. (Sekhon, Cartwright & Francis, 2017). The questions were asked in order and sufficient time was given for them to consider their answer and to give a further explanation. Some points were expanded on for clarity or to give context.

All interviews were recorded as optional, with a further choice of video or voice-only recordings. These were conducted by 2 researchers (RR & RW). 16 participants engaged in the interviews, with a

total of 30 interviews were conducted over 2 timepoints (timepoint 1 -Visit 21 n=16, RR=10, RW=6; timepoint 2- Visit 23, n=14, RR=9, RW=5). Prior to the interviews, RR and RW discussed the format and structure the interview would take to try and ensure continuity. Alternatively, participants could provide written feedback or decline if they wished. Written feedback and Likert scores were not included in the analysis, as this would require mixing methods. Several challenges can arise with this approach. The most prominent is a loss of flexibility, data can become limiting which may jeopardise the qualitative process and the process of transforming data which includes quantitative and multiple forms of qualitative data can be complex and time consuming, particularly for a novice researcher (Driscoll et al., 2007).

The interviews were all conducted online via Microsoft Teams videoconferencing. The participants had access to the questions as a form in front of them on screen and the interviewer was the same person at all time points of assessment. Furthermore, the interviewer was the same person as the person who gave the intervention in the trial, which meant there was an established rapport between the participant and the interviewer. However, this could also introduce bias to allow the participant to express any discomfort or negative feedback which may be perceived to harm the rapport. Whilst the researcher remained visible throughout, it was not always possible to see the whole of the participant therefore observation of full body language was not always possible. These could be seen as invisible barriers of conducting the interviews online. Lack of body language and difficulties in expressing emotions have been cited as barriers to effective use of teleconferencing (Almathami, Win & Vlahu-Gjorgievska, 2020). Where an astute interviewer may pick up on non-verbal bodily cues for example, this may not have occurred due to the interviews being conducted online.

Other barriers include technological challenges such as difficulties in using software, poor quality connections, slow internet speed, privacy and security concerns, and a general resistance to technology (Almathami, Win & Vlahu-Gjorgievska, 2020).

Thematic analysis

Thematic analysis (TA) is a form of qualitative analysis that identify themes through a process of identification, analysis, and interpretation, using pattern recognition emerging from the data (Clarke & Braun 2017; Fereday & Muir-Cochrane, 2006). TA offers a systematic approach to analysing the shared meanings and experiences that are relevant to the research question can reduce the data crossing over with other analytical methods such as Content Analysis, IPA, and Grounded Theory (Guest, MacQueen & Namey, 2012; Vaismoradi, Turunen & Bondas, 2013). One advantage TA offers is a method – a tool or technique, that is not bound to theory, as opposed to methodology, which is theoretically informed and confined. As a method, TA has a degree of flexibility with sample size, data collection and in the generation of meaning (Clarke & Braun, 2017).

TA can be completed at different time points, for example pre- and post- intervention (Alhojailan, 2012). TA is accessible and flexible as a method and as such it lends itself well to novices in qualitative research and to research that takes a multimethod approach (Braun & Clarke, 2012).

Owing to the flexibility of this method, it can be used inductively and deductively (Boyatzis, 1998; Crabtree & Miller, 1999). Using the inductive process, the analysis begins with specific content and broadens to more generalised themes and can go onto theory development (Alhojailan, 2012). The inductive approach might be employed when there is little known about the phenomena or there is limited literature. An inductive approach may also be utilised for investigating a new construct mechanism which underlies relationships and boundaries, or during the investigation of a specific phenomenon where the data collection is very difficult (Huy, 2012). Finally, might involve processes such as how groups feel, think and act, in contrast to 'how much does it matter' (Langley, 1999). This form of rich description of the data or the decision to provide a detailed description of a particular focus on the data is informed by the type of analysis and investigation that is conducted (Alhojailan, 2012; Braun & Clarke 2006).

Table 4. *Participant Questionnaire*

Categories (Sekhon, Cartwright & Francis, 2017 p.8)	**Questions Asked for Acceptability Form**
Acceptable/Affective Attitude	How acceptable were the tDCS sessions?
Helpfulness/ Perceived Effectiveness	How helpful do you think the tDCS sessions were for improving your depressive symptoms?
Negative Side Effects	How bothered were you by negative side effects from tDCS sessions?
Ethicality	How ethical do you think the tDCS sessions are?
Effort/Burden	How much effort do you think you need to put in for the tDCS sessions?
Recommendation/ Self Efficacy	Would you recommend tDCS sessions to others?
Study Design	What were the most successful parts of the study? What were the least successful parts of the study? Are there ways the study can be improved? Any other comments

The deductive approach takes prior knowledge such as pilot study findings, prior research, or a conceptual framework and uses these within aspects of the analysis to code and identifies themes. As a result, it can be more prescriptive (Nowell et al, 2017). Typically, the deductive coding process

can begin with a set of *a priori* codes, which are more analytically based and tend to produce fewer rich datasets (Neuendorf, 2018; Braun & Clarke, 2006).

A hybrid approach of both inductive and deductive process can also be adopted and have principally been proposed by Fereday and Muir-Cochrane (2006). This incorporates a top-down and bottom-up methodology which supports a rigorous approach. Logical consistency of in-depth planning and a step-by-step process to analysis can demonstrate transparency. This process provides interpretative rigor, making clear where and how interpretations have occurred. Adjunctively, member checking of codes or formulations add to the rigorous process. With the hybrid model, this can occur on two occasions, member checking inductively and then deductive followed by any relevant additional (Fereday & Muir-Cochrane, 2006).

There is a generalised way of conducting the thematic analysis which consists of 6 stages which include active stages of analysis as well ensuring rigor and trustworthiness (Braun & Clarke, 2006; Fereday & Muir-Cochrane, 2006; Nowell et al, 2017). There are further recommendations that can increase credibility through transparency, transferability through including sufficient detail for the reader to decide if your results are transferable, dependability through the demonstration of consistency and reproducibility. Finally, confirmability that findings have been generated through the data and not through biases (Castleberry & Nolen, 2018). Transferability, reproducibility, and confirmability will enhance the quality of the research conducted and are areas criticised in thematic analysis (Attride-Stirling, 2001).

When conducting the analysis, there is an assumed return of power to the researcher. At this stage, the researcher holds privilege to interpret and report what the interviewees have reported within the interviews (Kvale, 2006; Anyan, 2013). There is an opportunity to invite the interviewees to review some of the analysis, however few researchers will afford the interviewee a 'final' say', to

ensure the intellectual pursuits meet the research community expectations rather than the participant agreement (Kvale, 2006; Anyan, 2013).

Table 5. provides an overview of the stages of thematic analysis that were conducted and evidenced in appendices (Braun and Clarke, 2006). Stage 6 is evidenced in this thesis and acts as the report and is being drafted as a scholarly report for publication.

Thematic analysis has been used widely to review acceptability across healthcare topics that have used technology (Dohaghy et al., 2019; Ebert et al., 2015; Ross et al., 2016) and tDCS (Riggall et al., 2015; Smits et al., 2021; Tedesco Triccas et al., 2018). Specifically, in tDCS, exploring views and experiences within specific patient groups (Tedesco Triccas et al., 2018), from researcher perspectives addressing ethical and scientific views or as part of a mixed method approach across groups (Smits et al., 2021). All can fall under the larger umbrella of acceptability.

Table 5. *6 Stages of Thematic Analysis*

Stages of Thematic Analysis (Braun & Clarke 2006 p.87)
Stage 1: Familiarizing yourself with your data: Transcribing data (if necessary), reading and re-reading the data, noting down initial ideas.
Stage 2: Generating initial codes: Coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code.
Stage 3: Searching for themes: Collating codes into potential themes, gathering all data relevant to each potential theme.
Stage 4: Reviewing themes: Checking if the themes work in relation to the coded extracts (Level 1) and the entire data set (Level 2), generating a thematic 'map' of the analysis.
Stage 5: Defining and naming themes: Ongoing analysis to refine the specifics of each theme, and the overall story the analysis tells, generating clear definitions and names for each theme.
Stage 6: Producing the report: The final opportunity for analysis. Selection of vivid, compelling extract examples, final analysis of selected extracts, relating back of the analysis to the research question and literature, producing a scholarly report of the analysis.

Method of Analysis

Transcription

Stage 1: familiarization with the data. Part of this process is transcribing data, reading and re-reading the data, and noting down initial ideas (Braun and Clarke, 2006). Initial transcription was conducted using the Microsoft Stream word transcription, which required some manual editing for example accuracy of pronunciation. The recording was listened to by the researcher(s) and edited to reflect who was speaking, with (I) used for interviewer and (P) used for participant. Identifiers were placed at the top of the transcript to include the visit number, date, participant ID and researcher initials. A researcher (RR) when through each transcription, corrected errors and added conventions. These were then annotated for exploratory comments and the initial themes were developed (Bird, 2005) on a master draft word document. As a novice qualitative researcher, I began loosely drafting a research journal (Watt, 2007) as part of the reflexive process.

Coding

Stage 2 involves generating initial codes and coding interesting features of the data in a systematic fashion across the entire data set, collating data relevant to each code (Braun and Clarke, 2006).

Coding and categorising can be enhanced by the forms of data collection chosen, such as the interview conducted in this study which has the potential to reflect the 'reality' of the experience (Braun & Clarke, 2006) more accurately.

The initial codes were developed intuitively to begin with and refined through a process of systematically collating similar codes together for example in Appendix 2 the exploratory codes can be seen down right. This process was initially done without the idea of themes as a first draft to attempt to remove any researcher influence. A review and reflection of the initial codes were conducted under supervision from the lead researchers (CF & SC) which allowed for me to also reflect on my predetermined outsider status may impact on the coding process (Merriam et al.,

2001). All supervision sessions were conducted via Microsoft Teams and all team members had access to generated codes via a word document.

Theme Development

Stage 3: Searching for themes and Stage 4: Reviewing themes are stage of theme development. After generating a thematic 'map' of the analysis, the generated themes were reviewed within a supervised session with lead researchers (CF & SC) on the project. All supervision sessions were conducted via Microsoft Teams and all team members had access to the thematic map.

Theme Identification

Stage 5: Defining and naming themes identifies the themes. Theme development was made with supervisors (CF & SC). The initial codes were brought to together and discussed at length with supervisors, a visual example found in Appendix 3. The themes were agreed by all parties and there was ongoing analysis even after stage 6 (writing the report) to refine the specifics of each theme. This was to ensure the themes truly reflect the content of what was developed from the analysis and the overall story the analysis tells, generating clear definitions and names for each theme. The second researcher (RW) had also reviewed the themes.

Quality standards

Some of the challenges when undertaking qualitative methods include trustworthiness, rigour, and appropriate quality criteria (Dickson-Swift et al., 2007). Criticisms of qualitative research suggest a lack of reliable measures or the lack of objective and replicable findings, in additions to a failure of representative sampling (Yardley, 2000). Yardley (2000) provides some countercriticism that this measure may not be appropriate or applicable. The role of a qualitative researcher, Yardley argues,

is to offer a single interpretation when there might be multiple, that would have implications for reliability and reproducibility. It is preferable to analyse and review samples that are of special interest (Yardley, 2000). In terms of quality indicators, Lincoln, and Guba (1985) established 4 principles that qualitative researchers can use to demonstrate quality in their research (Lincoln & Guba, 1985). These include credibility, confirmability, dependability, transferability. Bradshaw et al., (2017) further developed the 4 principles to add meaning and practical demonstration. For example, credibility can be demonstrated through an established rapport and trusting relationship prior to the interview, being able to express compassion and empathy with prolonged engagement (Bradshaw, Atkinson & Doody, 2017). Examples of these using the Stages of Thematic Analysis (Braun & Clarke 2006 p.87) are included in Appendix 2-4.

Reflexivity

Reflexivity is essential to quality in research. I, as the researcher, was involved in data collection, analysis of text and reporting, thus should be a transparent about the process through examining my position, perspective, and presence during data collection (Finlay, 2002). A realist approach taken toward the collection of the data.

The points below are raised for reflexive interest as potential influencers on the data and will be explored as part of the discussion:

- White British female from a single-parent, working-class background, with personal and familial experience of mental ill health who can be averse to treatments, particularly novel treatment, and some elements of mistrust in professionals within healthcare. In part, this has been a driver for my interest in these topics.
- Professional history of working in both the NHS and private sector, as a support staff or student for 5 years and registered nurse (mental health) for 12 years which has involved working extensively within the realms of assessment and treatment of people belonging to a

wide range of class, ethnicity, age range and risk level with varying degrees of distress relating to severe mental illness. I would also be part of the workforce potentially providing the novel treatment.

- Though I am positioned as an outsider for the purpose of this project, prior to the doctoral training, I have conducted 6 years of formal education at various institutions, learning about mental illness and psychology. Currently, a PhD student and main researcher for the projects in the thesis, conducting in-person or remote treatment with the participants, who were interviewed on their acceptability of the treatment I provided. I also recognise I hold a fair amount of what might be considered as 'insider' knowledge.

In recognising my own insider/outsider status of this community, I have been positioned in both at different times and different levels during my life experience, as patient, relative, carer, mental health nurse and researcher (Merriam et al., 2001). To the first point, the recognition of my own and family experience provides an outline or backdrop to the cultural community that I have belonged to growing up. This will have shaped some of my ideas and understandings around health approaches and the level of trust in empirical data, which has changed over time. In yearning to understand a conflict between my experiences taken from family and my experiences within my early career working in a hospital, I sought formal training as a nurse, which inevitably changed my positionality both from the various formal training I have received and the experience of working with different groups of patients and staff. Research outcomes and results can be influenced by the positionality of the researcher (Holmes, 2020), and the above information is helpful to gain an insight on the fixed and fluid nature of the researcher from a reflexive position (Burman, 1991). Added with the understanding of the research process being influenced by these factors such as age, gender, class, and ethnicity (Burman, 1991). It can be more pertinent to identify the researcher positionality around these three aspects (1) the subject being investigated, (2) the participants being researched, (3) the context and process being studied (Chiseri-Strater, 1996). Further, to consider a space in

between ‘insider/outsider’ rather than view the position as a dichotomous one (Dwyer & Buckle, 2009).

For this project, I positioned myself as PhD researcher researching tDCS as a novel treatment for MDD. The insiders are classed as all participants that met the criteria for MDD and the outsiders are those external to the study so I will act as a bridge, a qualitative researcher conducting an interview to understand their perspectives of using a novel device for this disorder. Further, to accurately represent and reflect these views of the insider participants through this thesis.

This does not discount my background knowledge but did offer a positionality with less bias to assume the researcher may/may not know or expect what the experiences might be for everyone (Holmes, 2020).

3.5 Findings

Overview:

In this section, a summary of the findings that have been developed from the analysis which answers the question: *How do patients with depression describe the acceptability of using a novel treatment, at-home tDCS?*

Introduction to findings:

Four overarching themes were identified: (**1)** Side effects, **(2)** Effectiveness **(3)** Time commitment **(4)** Support, feeling held, contained, which were gathered through semi-structured interviews. These are presenting in Table 6. and below, a more detailed overview of those findings and meanings.

Table 6. *Themes and Subthemes from the Thematic Analysis*

Themes	Subthemes
Theme 1: Side Effects	Subtheme 1.1: Physical Sensation of the treatment
	Subtheme 1.2: Side-effects from the treatment
Theme 2: Effectiveness	Subtheme 2.1: Expectation of tDCS as a treatment
	Subtheme 2.2: Recovery & enhancement: the extent of the effectiveness
	Subtheme 2.3: Un/certainty & novelty
Theme 3: Time commitment	Subtheme 3.1: An everyday commitment
	Subtheme 3.2: Convenience of having sessions at home, improving acceptability (gaining time)
Theme 4: Support, feeling held, contained	Subtheme 4.1: Feeling connected by daily visits by the same person
	Subtheme 4.2: Being observed feels safe versus feels anxiety provoking

Theme 1

Main Theme 1: Side Effects

The first main theme was rooted in the expression of what is typically known as 'side effects'. For participants who experienced side effects, there were 2 subthemes, 1.1. Physical sensation of the treatment and 1.2 side effects from the treatment. These two sub-themes were differentiated through how participants spoke about side effects. There was a relative high report of a generalised sensation of the tDCS, in that it appeared new but was time limited. Conversely, there were some reports of side effects which occurred as a direct result of using tDCS, for example, immediately after use, small patches of redness were seen at the site of the electrode in the forehead region.

The physical sensations of the treatment and side effects which manifested in physical form at times presented together. As the extract below shows, this participant found adjusting to the treatment "as a sensation" and encountered what would be classed as a side effect (redness).

> **'**. . .You know there is the slight burning sensation that, you know, didn't ever last through the full session just a few minutes. Yeah, right at the beginning. I think. There was a bit redness [after the session], but you know, yeah, it, it was all fine.' [ID: 049, F, pp]

The initial sensation here is described as 'slight burning sensation'. This appears to dissipate after a few minutes. Typically, side effects with non-invasive treatments have been appraised as having a lower perceived risk and side effects that transient which supported increased acceptability. tDCS has a low side effect profile (Brunoni et al., 2016a; Matsumoto & Ugawa, 2017). As well as other forms of novel interventions, tACS or transcranial focused ultrasound participants reporting a transient experience of side effects (Matsumoto & Ugawa, 2017; Legon et al., 2020). Additionally, non-invasive treatments have a lower perceived risk compared with more invasive techniques for example electroconvulsive therapy (ECT) (Cabrera et al., 2021; Loo, McFarquhar & Mitchell, 2008). Whereas a novel sensation is something that is new, not previously reported.

Under quantitative measures, a category is created and a binary count tally those who did or did not experience this sensation. However, it has allowed an exploration whether it might be possible to draw a distinction between an initial novel sensation from a novel treatment and a recurrent and or persistent side effect, as experienced with the redness. Nearly all participants reported varying degrees of redness, and this was managed to a greater or lesser extent with saline supplied by the study team. To explore a distinction between a new sensation and a side effect would require a

definition of what constitutes a side effect. Though, the participants seem to themselves draw their own distinction which is discussed below.

Subtheme 1.1: Physical sensation of the treatment

Here the 'sensation' is described as a new experience and the sense of needing to 'get used to it' came through. Around 7 participants (out of 15) spoke specifically to a 'sensation' of the treatment that did not last.

> '… there was a slight discomfort at the beginning of the session. Which is something I had to get used to. You know, with the. The headgear, heat sensation, stimulation sensation. But it calmed as I got used to it just because my brain wasn't… something completely new. Which I have never done before' [ID: 022, M, pp1]

This extract was clear this was something that occurred at the beginning of the session and felt a sense of needing to 'get used to it'. The participant goes on to speak about adjusting to this sensation. On the surface, this could appear as simply a reported side effect. When conducting the analysis, it was apparent there was something in participants reporting a 'sensation' which transcends the scope of a side effect. The sensation could be conceptualised under the idea of taking part in a novel treatment as this treatment has not been widely accessible for most people prior to the trial. Though available on the free market, it is not within most of the participants pricing range. Therefore, it is reasonable to assume there is not a widely understood experience of what tDCS feels like and indeed when first experienced, it was occasionally described as unique. This does, of course, fall under the category of side effects in the traditional sense. Though it may have merit to consider a more in-depth discussion in any future qualitative research looking at side effects and the experience of side effects in the context of tDCS to develop any nuances.

Subtheme 1.2: Side effects from the treatment

All participants spoke about side effects, whether they experienced them or not as this was defined as a category within the questions. This extract describes both redness and dryness and feeling this wasn't 'enough to stop doing it'.

> '. . . I'd say, uh. Bit affected and that was just the redness and dryness of the skin, but generally it didn't really bother me too much, like enough to stop doing it or anything". [ID: 027, F, pp7]

All adverse events were recorded and there were no newly established side effects from this data (Brunoni et al., 2016a). The side effects experienced were part of the information provided in advance to the participants. On one hand, it may be argued as leading or restrictive. However, there was space held for any other reported experience or event to recorded after every session and more formally once per week using a standard form (Brunoni et al., 2016a).

For the purposes of this analysis, differentiation between the two subthemes were established: the sense of an expectation of change in sensation, and potential of independent improvement, versus the increased degree of discomfort that required some level of management for improvement, i.e., observation, repositioning, increased saline, contact checking. This has created a novel and interesting perspective as a main theme around acceptability, as side effects would typically only be measured by tolerability, and adverse effect drop out.

Theme 2

Main theme 2: Effectiveness

The second main theme identified in the analysis was effectiveness. This relates to how effective tDCS was as a treatment and what other features of the study may be interacting with effectiveness. This was expressed as 3 subthemes: 2.1 Expectation of tDCS as a treatment, 2.2 Recovery & enhancement: the extent of the effectiveness, 2.3 Un/certainty and novelty.

The first subtheme discusses expectation, relating to, if, and how the treatment would resolve symptoms; if and how the result of the study meet those expectations and whether the expectations felt realistic or 'reasonable'. The second subtheme reports on the reflection on recovery and enhancement, and distinctly different to the expectation of how treatment would resolve symptoms. The third, un/certainty and novelty, might be positioned between these two themes around the process of reaching recovery (or not). The latter two points could also speak to the efficacy of the treatment, or bias from the researcher or participant. During the research, participants were given time to discuss their symptoms with the researcher, which formed part of the mood assessments. A process which could be inferred as a loose form of unstructured therapy, through combining researcher interviewing as loose form of psychotherapy that supports participants in identifying their symptoms. The position of the researcher is also important here, as they are typically rating mood to quantify the success of a treatment. This could mean the act of interviewing in a therapeutic form could be the rationale for an improvement rather than the equipment. Equally, it is not unreasonable to suggest the potential for bias in the researcher rating the mood as more positive, either for an increase in rapport or an apparent improvement in mood. Moreover, the participant reporting more positively due to the impact of rapport with the researcher. This qualitative approach has allowed some understanding of the recovery process and as such, other factors that might have been contributory.

Subtheme 2.1: Expectation of tDCS as a treatment

The first subtheme describes participants' expectation of how they anticipated the effectiveness of the treatment. Some of the participants suggest wanting a regeneration, transformation, or a complete removal of the distress that they felt during a depressive episode.

> '. . .hoping for a new me, a brand new me, a happy you know. Sunny Sunshine, rainbow roses. Not thinking that I'll still haven't been, this cloud hanging, but the cloud [depression] is obviously reduced but still there. I thought I'd probably completely. Decimated. Or destroyed [the depression] but. But I think I just need to know the hard work has been done'. [ID:022, M, pp4]

> 'I mean I, I always goes back to the sort of. Idea that you're, you're looking for 100% wonder, wonderful results at, this wonder drug or in this. In this case, a device and. I think we all have that reasonable expectations' [ID:048, M, pp103]

The first participant gives a noticeably clear example of an expectation which he felt was not met, although he does also say the cloud (depression) "obviously is reduced". Reflecting on his initial thoughts of believing he would have a "brand new me" to his current improvement, the participant felt to a degree the treatment had not met his initial expectation. In the moment, there is the reflection moving from whilst the whole feeling has not dissipated or "Decimated. Or destroyed" as it is described, the description of "the hard work has been done", suggests a large part of the symptomatology is resolved, and recovery will be easier. This could also represent a feeling of adjustment and wanting the happiness to feel 'happier', after a prolonged period a negatively based emotion.

Both examples speak about wanting an 100% result, “completely. Decimated”, “100% wonder, wonderful results”. This may speak to the perception of novel treatments having a higher efficacy rate which could initially and superficially boost the level of acceptability and subsequently lower acceptability at the end of the trial due to unmet expectations rather than the true efficacy of the treatment.

Taken from a clinical perspective, the notion of wanting 100% results may infer the development of an insight of the symptoms that are experienced and the changes across mood and personality that are experienced during a depressive illness. All interviews were conducted post treatment and provided the ability to reflect on any changes that may have been experienced. What is lacking is a precursor interview to see if the opinion or expectation has changed across the course of treatment.

However, the level of recovery is directly related to acceptability through the category of effectiveness. There is an effect of perceived effectiveness on the outcome of the treatment which relies on treatment orientation (Bride et al., 2013) and active perception and approach towards a novel health intervention improves the outcomes (Patel et al., 2020). Participants may be appraising the effectiveness of tDCS here against their expectation, rather than a neutral base which the researcher is inclined to be positioned. As such, there is an awareness of depressive illness prior to treatment and there is an awareness of improvement and/or change in the symptoms experienced post-treatment but there has not been a complete removal of their symptoms and/or this has not met the view or perception or expectation of what “happiness” might have been perceived.

There is also an adjacent line of thought that could be taken in future interviews or research. Firstly, those who have recovered appraise social support and group membership more highly (Richardson & Barkham, 2017) which could have an impact on how acceptability is assessed within this trial design. Second, a concept of a ‘reasonable recovery’, where it is generally accepted that all current treatments may not completely resolve symptoms and that relapse is somehow ‘inevitable’ due to

the nature of the MDD. It is known that perception of recovery varies across clinical and patient perspectives and their priorities towards recovery also differ (Richardson & Barkham, 2017). Nonetheless, it may be the currently available treatment do not adequately treat MDD and the recovery that is discussed above is acceptable to the researcher (or clinician) but possibly not the participant. At a societal level, there is a degree of those experiencing mental distress being consigned to poor treatment options and a recurring/relapsing health as acceptable. This may be something to explore in future trials of novel treatments of whether what is seen by participants as partial recovery is in fact an acceptable response.

Subtheme 2.2: Recovery & enhancement: the extent of the effectiveness

Here there is a clear description of an enhancement of symptom-by-symptom changes that this participant has noticed and how symptoms interact with one another, resulting a mood change and lifting of depression. The second quote is more succinct but conveys a similar change or enhancement in mood and goes further to suggest recovery.

> ‘I mean, for me, it's actually everything, um you know, my sleep has improved completely. You know, I've kind of gone from being up, um, several times a night, not being able to sleep at all, um to kind of getting restful sleep every single night, so that's been one of the massive differences. And um worry a lot less. And also, I um. I don't know, I kind of, I don't wake up feeling hopeless or depressed I kind of wake up and I can just kind of deal with the day. So yeah, they've, they've been the most major, major things that I've, I've kind of noticed and everything else then kind of seem to fit into place. Like you know, the kind of eating better and um, yeah, I kind of feel like once, once one thing sorted then the other thing you know. And then obviously that having better sleep then makes me more interested to wanna read. You know, and that kind of thing. So, I feel like once one thing gets into place to the next

thing. So yeah. So definitely. But yeah, having the sleep the less worrying. Not waking up feeling rubbish and that's made a massive difference' [ID:040, F, pp37]

'Yeah, I just did feel the shift in my mood by, at the end of all the sessions. So, I would. And that's what, you know, there are other things going on as well, but I do think it had a big part to play in that...I definitely still feel much better. Erm, A bit more enthusiastic about life. Erm. So yeah, I would say it's still present now.' [ID:027, F, pp60]

Here, the first extract describes a classical recovery with an improvement in sleep, which if disturbed is known to impact mood. Sleep improvement has also impacted on other typical symptoms known to be disturbed in depression (appetite, and motivation, "makes me more interested to wanna read"). The extract also conveys the extent she feels this, describing "they've been the most major, major things" and "that's made a massive difference". In the second excerpt, the participant notices a shift in her mood, "more enthusiastic" and the extent is conveyed differently "I definitely still feel much better". This is more suggestive of the results being lasting over time.

As part of the study, researchers were directly asking about mood which covered biological and psychological questions. Again, there could have been an added benefit through the application of researcher interviewing and encouragement as a form of supportive psychotherapy by supporting the participants in identifying their symptoms. There is some acceptability data around embracing the sense of anonymity using digital health technology to afford space to speak freely that for others brings difficulties with speaking around challenging and difficult topics in a lack of space left them feeling unsafe (Patel et al., 2020). It is possible that additional factors are occurring here, the research project is limited in time and there is no expectation to meet outside of study parameters, the participant having the space and time given to them may encourage open, dialogue, and

increase understanding. Then, increasing the participants ability to process the symptoms of a depressive illness which may have promoted recovery. This could be another example of the researcher-participant interaction could have had a possible overarching effect on effectiveness, which directly impacts acceptability.

These both approach the level of effectiveness that has been experienced. In terms of response and recovery, the study reported nearly all participants clinically responded to the treatment. These excerpts provide more on how the recovery has occurred and to what extent, even the persistence of mood recovery. The second excerpt was during a follow up visit, in which the participant described a lasting effect. This was an open label study, and this participant did not have any further follow up sessions. Here it may have been worthwhile to collect both an initial interview and a prospective interim interview alongside possibly teasing out more information on the existing qualitative interviews as there is mention of "other things going on" in one of their responses. Some disparities between clinician rated and participant rated experience of response and remission already exist in the literature (Zimmerman et al., 2006), which may arise from poor inferences. So, although clinically rated as "responded" or "remitted" via scoring inferred effectiveness from a quantitative position, here is an example of where more information around what causes success or hindrance in effectiveness has surfaced. Further discussion on what response was felt, whether participants feel it is directly related to the tDCS as a treatment or other factors, such as the concurrent treatments all participants were engaged with as a condition of the trial, having specialised 1-1 support from researchers through the study or the personal quiet time the study provided.

Subtheme 2.3: Un/certainty and Novelty

The final subtheme identifies an uncertainty about the treatment intervention, though despite this uncertainty, recognises a change in mood. There is also a feeling there is an effectiveness but offers

caution regarding attributing it to tDCS treatment. The second extract describes novelty in terms of modern scientific perspective which they infer means there will be effectiveness in the treatment.

> '. . .I was saying to my flat mate, like I was like, I'm not sure if it would be like, I would still be feeling bad right now if I wasn't like doing these things. But like I'd be feeling worse. Literally and so yeah, but I I don't know. I feel like generally I've been like kind of doing better than I have done before and that like, um and the kind of times I've been feeling low haven't been quite as bad as they have been before in my life also. [ID:036, F, pp6]

> 'There is a scientifical. Erm truth behind it. It's very futuristic, very advanced, very digital with the control of the app so. That definitely will work' [ID:022, M, pp3]

Though, these two points are polarised in certainty, the first participant appears unsure what and where the effect has come from and the other is sure the effect is from a new 'scientifical, advanced, digital' product. Presented here is a commonality, both in espoused effectiveness and of using a new device, though this may not be mutually exclusive.

The first extract points to other potentials that may explain or assist their improvement. The latter a more definitive explanation towards science. This is important to distinguish as there is certainly an understanding that there are likely mutable factors that lead to a recovery in MDD. This can be a combination of treatment, engagement in a trial, of itself is effortful and potentially meaningful and rewarding. In addition to scientific explanations. There is an undercurrent of participants' socialised understanding of treatment here that could also have impact of their perceptions both effectiveness

and in turn the acceptability depending on whether their ideas of treatment effectiveness support or violate their social and moral dispositions.

Theme 3

Main theme 3: Time commitment

The third main theme is associated with time commitment. An element of the study requires allocating time for required daily sessions which are 5 x weekly, this then reduces to 2x weekly. The commitment is seen in comparison to currently available treatments. The study required an overall commitment of 6 weeks. The first subtheme is, therefore, 3.1 An everyday commitment. There is a separate subtheme for time commitment which relates more to gaining time and has been titled 3.2 the convenience of having sessions at home, improving acceptability (gaining time).

Subtheme 3.1: An everyday commitment

The extract below makes a comparison of time commitment to available treatments (antidepressants and talking therapies). The nature and design of tDCS and associated monitoring required scheduled appointments through the week and would be a consideration for those with external commitments such as childcare or work commitment.

> **‘**Well, just because even though they [tDCS sessions] were quite straightforward and relatively easy with what it is, you need to do, uhm, you know, just thinking about other. Forms of you know. Looking after your mental health. If you’re taking pills, you just have to think about taking a pill or you know if you're doing therapy. Generally like some sort of talking therapy. Generally that's maybe once a week, so you're blocking out one time in your

> diary a week. Scheduled um whereas because this had to be sort of daily at first and then sort of every other day. So you, you have to think about that time and commit to that time. And that's not always, um, that can take effort.' [ID:049, F, pp8]

There is also an element where this participant talks of 'effort'; for those who are feeling unwell even without commitments, there is a consideration for the level of effort required as the treatment starts with an increased level of commitment. It felt more effortful with the process of meeting with a researcher (or staff in real terms) each day for 3 weeks, then regularly x2 week for 3 weeks when compared to simply taking a tablet or engaging in therapy once per week or less. It was found those with a more passive approach preferred face-to-face as digital health interventions present increased difficulty, and 'stress' (Patel et al., 2020). Therefore, it might be those with 'passive' traits at the start of the study rate an increase in effort. However, a passivity may point to a power imbalance in decision making and the researcher should be positioned to ensure that there is an active process of shared decision making to reduce and prevent any form of coercion (Joseph-Williams, Edwards & Elwyn, 2014). This is in the context of a study and there were other activities which could have impacted on the sense of effort required. Additionally, all participants were diagnosed with MDD, in a current episode at the point of enrolment so would be a further consideration to what is asked of the participant in terms of 'effort' or burden of treatment. This is an at-home treatment so if it was deemed safe to do so being more remotely supervised might decrease the sense of effort and increase acceptability. Though, adherence may also reduce in this scenario. Further clarity would be required to establish if trial activities make the sessions more labour intensive or if this is limited to what is entailed for tDCS treatment only.

Subtheme 3.2: Convenience of having sessions at home, improving acceptability (gaining time)

The subtheme discusses the converse experience of the convenience of at-home sessions and a dedicated 30 mins to complete the tDCS that appeared to give the sense of gaining time. In addition to this, the extract below describes a feeling of calmness and peace which is perceived because of having time to relax.

> 'I didn't have to go anywhere. So there was not much effort involved. And erm. And because you know, I had to switch off other things. It was actually, I found a very pleasant, the time for myself. . . It serves two purposes for me. It served two purposes, one that time. I had to force me to make time for myself to relax, to do to, dedicated to me, and switch off and also come. You know, I. Maybe that was a consequence, you know that followed after, which is this kind of like calmness and small sense of peace within' [ID:042, F, pp5]

Contrarywise to subtheme 3.1, effort was reduced due to the sessions being run at their home. This viewpoint is contrasting with the idea of going somewhere to get treatment (i.e., GP for medication, or a clinic for therapy). With rising demands on primary care services, it has been increasingly more difficult to gain access to GP appointments and to low level therapy services.

The study appeared to facilitate the participant in gaining a sense of time, both in being at home for the study activities but also having a set, allocated period of 'time for myself' and resulting a 'sense of calmness' which contributed to their recovery. This point provides a positive benefit and speaks to recognising recovery in real time and would boost the sense of commitment to engaging with the treatment and eliminating any sense of effort that may have been perceived.

It was regularly mentioned in the interviews having 30 minutes for the treatment was beneficial to some degree. It was perceived as having an allocated time to relax and unwind and may hold some

benefit of its own like meditation (Goyal et al., 2014). Participants generally had other commitments such as academic courses, work, family. It is widely advocated by clinicians that engaging in and maintaining a sense of routine plays a supportive role in recovery, particularly during COVID-19 (Murray, Gottlieb & Swartz, 2021) and it can be a coping mechanism or accompanying anxiety which leads to overexertion. It may be possible that this could be a contributory factor to the maintenance of depression. Not to conflate these 3 ideas however, encompassing a 30-minute break, meditation or tDCS or a combination of them may act in a role that promotes the recovery process.

Theme 4

Main Theme 4: Support, feeling held and contained

The fourth main theme is support, feeling held and contained. The participants contact with the same researcher (as treatment support and research interviewer) was viewed as a benefit. In the first extract the participant discusses some quite intimate things about how they are feeling through the course of a depressive episode. The rapport with the researcher and the ability to feel comfortable was important to them. The second extract describes both the benefit of having 1 on 1 sessions but also the practical explanations of the activities this entails. The first subtheme is 4.1 Feeling connected by daily visits by the same person, helps to describe the positive rapport that had been established. The final subtheme centres around observation and warranted being divided into 2 further subthemes as they are in fact conflicting and opposed to each other. Nevertheless, two contrasting positions brought together: 4.2 Being observed feels safe versus feels anxiety provoking.

Subtheme 4.1: Feeling connected by daily visits by the same person

This subtheme discusses the therapeutic relationship and how for participants, it was established through a repetition of meeting the same person daily for the period of the study. The participant

below described their experience of MDD as personal and disturbing. So having someone they felt comfortable with was important to them.

> ‘As you know we met regularly. And because I was meeting with you. Repeatedly, it's sort of like you build up. A bit a relationship, where you feel comfortable with someone and a, you know because you have to talk about it. Quite. Sometimes you know quite disturbing things and. erm You know around depression, and you know things that have happened to you. So, you do need to feel comfortable with the person that you're talking to, and I think. I did feel comfortable, and I did feel like you were very supportive, and I think that having that dedicated person who. Who can support you through the process is really important. . . it's like really personal and you know sometimes really hard to talk about stuff like depression. So definitely you know, having somebody you feel comfortable with, made it easier’. [ID:041, F, pp83]

The main theme touches on feeling connected. This seems to have occurred because they were able to establish a ‘therapeutic’ dyadic relationship with the researcher. This is where they were able to discuss those personal and disturbing experiences relating to their experience of depression.

In terms of acceptability, therapeutic relationships may be an enhancing factor, particularly as participants had tailored support as an addition (Norcross & Wampold, 2018). Feeling comfortable, having trust to disclose and how this transfers to having trust in a novel treatment. There is an overriding impression that the level of support the participant received which was discussed under Theme 2. Though, what is unique here is the reference to the same person throughout the treatment. The participant has identified this as a factor for them in building a good relationship. They also mention having regular session with the same person and having a feeling of being

supported by this person. With the potential anxieties of starting a new treatment having these things seem to go a long way to enhancing acceptability and may be a crucial factor for those looking for additional support. In addition to this, the presence and observation of the researcher as a mechanism of support could have had an overall effect on treatment. There have been reports of a fondness and acknowledgement of attentiveness to having an observer and a sense of loss when this relationship ends (Papoutsi & Fu, 2021). Observation has also supported participants to create a 'third space' in which participants within study conditions can reflect, which could add to the effect of thinking about / reflecting on their symptoms. This could increase the sense of feeling held (Papoutsi & Fu, 2021).

In the following excerpt there is discussion about 1-on-1 sessions with the researcher and being able to speak about the emotions they were experiencing. The participant also reports having a 'complete understanding' which may also add to the benefit they feel.

> 'Also the one on one talking. Talking. And in reviewing how I spend. . ., I found that too really beneficial to me. And it's, it's maybe a little bit of aware of my emotions and why I was feeling certain, certain way. . . What is really beneficial to Me, I was having a like a thorough explanation of the process is what we were going to go through on a day-to-day basis and, and I, you know, having had complete understanding. If there were any anything that was unsure I felt confident enough to ask further questions.' [ID:030, F, pp5]

The excerpt describes being able to talk about how they have been feeling and adding meaning and understanding to these feelings, 'it's a little bit of aware of my emotions and why'. All visits were discussed with a consultant psychiatrist, and this allowed for expert-tailored support and advice both from the researcher in the immediacy and then from the consultant in the background which

could be relayed at the next visit. They seem to express an acknowledgement of the level of support provided within the study later when stating “having a thorough explanation . . .and complete understanding”. It conveys detail, which has been specific for them and due to the frequency of the sessions this occurred daily.

Taken together, both feeling supported and having confidence in the treatment and service that has been offered appear to be a key aspect to acceptance of the treatment success. There is also a sense of being cared for and contained.

Subtheme 4.2: Being observed feels safe versus feels anxiety provoking

The subtheme begins with the notion of being observed as a positive experience. Maintaining a sense of safety through a trial of a novel treatment, having access to the researcher through observation that ‘things were done properly’. The excerpt below goes on to add some detail around a feeling of being part of a wider network of supportive colleagues and through community services like the GP, it felt like interaction with a human, against what could potentially be quite mechanical.

> ‘I mean, the fact that it's supervised. And as well just makes it safer. Uhm, uh, and it was part of a wider. Uh. Sort of you're part of a wider network of things. . . I think with depression and anxiety, a human face. I commu-, interaction with a person makes you feel more reassured. That things are going. You're doing things properly and. Sometimes er. Yeah, I that's why I even know that this was all done virtually. I knew that I was being aided by an actual person rather than a rather than an app’ [ID:048, M, pp7]

The subtheme ‘being observed’ has been interpreted from the phrase ‘the fact its supervised’. It seems the choice of lexicon may have been more of ‘keeping watch’ or being ‘held’ over rather than

observation. In this case, there may be something nurturing in this expression of observation and perhaps is aligned with a connection or reduction of loneliness. Being in the presence of another person who is discretely available for an extended period can offer an aspect of holding and even feelings of wider community connection (Papoutsi & Fu, 2021). The research occurred during a national pandemic due to COVID-19 and this theme reflects a unique experience of the present study design. However, there were limited opportunities to meet face-to-face. For those less inclined to reach out for social occasions using videoconferencing or and those expressing a general fatigue towards videoconferencing, increased isolation inevitably occurred. These 1-2-1 meetings seem to boost the efficacy, 'I knew I was being aided by a person rather than an app'. Although largely it is technology in form of treatment 'doing the heavy lifting', again there is the notion of human connection, that felt safe.

Additionally, this subtheme has an acknowledgement for the 'necessity' of observation. For some participants, the experience of observation was negative and somewhat intrusive. The study protocol meant we were not able to engage with the participant during the tDCS treatment which meant a discussion before, along with study activities, then a period of silence during the treatment (whilst being observed) then discussion again.

> 'I would say probably one of the more uncomfortable things is that whilst you're participating, you do have someone watching you, erm, that can be just an odd thought and an odd feeling. I don't want to say that it's unsuccessful because at the same time I recognize that it's a necessity for, for, for what it was, you know' [ID:049, F, pp112]

The natural course of a conversation does not usually contain a 30-minute period of silence and so is perceived by the participant as 'uncomfortable' this gives a clinical overtone. The researcher sat in

silent observation, whilst the participant sits in inactivity with a device on their head is certainly not a 'natural' situation and this gives a clinical overtone. It is understandable to have an 'odd' thought or feeling, even anxiety-provoking or a feeling of being judged or being imposed in some way. Due to a negative bias, some of these thoughts or feelings may already be present and are being amplified through this experience (Ito et al., 1998). This would undoubtedly reduce acceptability for those who experience this and consideration for concessions in observations with this treatment in real world scenarios may be worthwhile if it increases acceptability.

3.6 Discussion

This chapter has presented the views of participants who have received a novel treatment for depression that is currently not available via their GP as the main source of treatment for primary care, directly or via referral. The aim was to assess the feasibility and acceptability of this treatment using a qualitative semi-structured interview through the research question: *How do patients with depression describe the acceptability of using a novel treatment, at-home tDCS?*

A structured questionnaire formatted from a TFA by Sekhon et al., (2017) was used with each question relating to what is understood to be an aspect of acceptability as defined by TFA and some answers were given that were specific to these categories of acceptability. However, the analysis was conducted both inside and outside (cross sectionally) of the framework, in line with TA approach, which meant that we were able to develop some main and sub-themes that transcend these definitions of acceptability categories. In this case, themes that were taken cross-sectionally from the data were identified as main themes.

The first theme, Side Effects, relates directly to the experience of the intervention and 4 potential constructs from the TFA where side effects may fall under 'affective attitude, burden, opportunity

costs and perceived effectiveness'. The most appropriate category might seem 'burden' to categorise the theme 'Side effects', by English definition 'to cause someone worry, distress, hardship'. TFA has defined burden by the amount of effort required that is perceived by the participant to engage with the intervention. Experiencing unwanted adverse effects of a treatment can be considered a burden however patients can be poor reporters of side effects (Moosa, Jeenah & Kazadi, 2007). Though, side effects of an intervention or treatment can reduce compliance to that treatment (Bloom, 2001) which may impact on opportunity costs. Psychoeducation can improve attitudes by improving affective attitude and a perceived effectiveness and in turn, improve adherence to a treatment protocol (Lin et al., 2003), and all of which appear to be important to the acceptability of tDCS.

The second main theme, Effectiveness, is slightly more apparent in its relation to TFA and links directly to the construct of perceived effectiveness. Perceived effectiveness may also impact the outcome of acceptability (Bride et al., 2013), in that perceived effectiveness relies on the orientation of the treatment, which will differ from researcher to participant but also across the participant group. This can be important for both the participant and the researcher as this can lead to a biased approach to effectiveness (or efficacy) and invoking positive (or negative) symptoms based on how it is perceived to work. In terms of acceptability ratings, there should be a consideration for the established relationship between the participant and the researcher. Participants may not always feel comfortable to say they have not recovered if there is an established rapport with the researcher. The notion of novelty arose under the second main theme of effectiveness. General public attitudes towards neuromodulation have been explored both for enhancements and treatment (Sattler & Pietralla, 2022). Using a web-based survey, moral acceptability was found to be 25.5% for brain stimulation devices and 28.7% for brain-computer interfaces. Further acceptability for use within treatment was higher than for cognitive enhancement. Higher moral acceptability was found for less invasive products (Sattler & Pietralla, 2022).

Time commitment was the third main theme and relates to TFA categories of self-efficacy and burden. Self-efficacy is defined as participant confidence they can perform the behaviours required to participate in the intervention. This was achieved by a large percentage of the group (96%), with supervision and in this study, self-efficacy in the truest sense was not established due to the trial guidelines of requiring researcher observation. The idea of commitment was contextualised around everyday tasks that are required to co-occur, such as childcare, chores etc. In this sense, it gave a realistic viewpoint of what one may contend with when conducting this treatment at home, though time commitment in this context relates closer to burden. Burden, as described above, relates to effort. Time commitment was seen by some participants as an effort but then also seen conversely, as again, that they had gained personal time which previously they did not have, due to other commitments (i.e., demanding work life, family commitments).

Whilst there are a lot of benefits to using a framework (Sekhon, Cartwright & Francis, 2017) to assess the acceptability of a novel treatment, it can be the case that because of there were predefined apriori interview categories, these aligned to the framework themes developed from this data into multiple constructs of the framework used. Conversely, a theme can also be developed that does not (because of the semi-structured interview technique), the fourth theme is an example of this. There was a unique factor to this study, in that supervision of the treatment at each session by the same researcher and there were weekly reviews of mental state and safety. This different protocol undoubtedly contributed to the experience of the participant of this intervention and therefore to the development of this theme. The final theme was **(4)** Support, felt held, contained. Here the excerpts speak of the supervision as an aspect of support and offering comfort and feelings of ease. To further this, the second excerpt directly describes a feeling of connection to the wider community. It is likely this is an example of a benefit to having trained professionals and expert external guidance from the chief investigator. This was a unique aspect of the study which gave the participant real time supervision. However, I must identify being part of this community, that my motivation was to offer the research treatment as directed in the protocol but also to monitor for its

effects. This would be an important point to reflect on as this could add some bias into review of the participants, particularly if hoping for a positive outcome. It may be the benefit came from external support offered outside of the study such as the free Facebook support group or free app support they could complete in their own time, or simply an altruistic sense of taking part in a greater cause than themselves. It could equally reflect a motivated and engaged sample of participants.

The role of the researcher, itself, was also a source of support that was external to any experience held by the researchers. There is the potential for inherent or unconscious biases to have a role in how I conducted or analysed the research. The history of familial mistrust with novel treatments and those in perceived authority could have led to me abandoning power within the research analysis. An unconscious bias towards this thinking had the potential to influence what was drawn out myself leading to a harsher review of the literature (Lazard & McAvoy, 2020). Thinking around the wider socio-political landscape, a renewed wave of antiracial movements had occurred during the time the interviews were being conducted and led me to be engaged with antiracist groups as an extracurricular, which undoubted shaped my position and a keenness to give a voice to marginalised groups (Lazard & McAvoy, 2020). My own professional history of working extensively within institutions designed to support and care for patients with MDD and other conditions. These comes with a set of professional codes may have offered a benefit to a practiced impartiality. Though, equally, skewed power imbalances and at times, prejudices from working within this sector could have been presented (Molodynski, Rugkåsa & Burns, 2010). As a novice researcher, all codes and themes were reviewed by experienced researchers, who were providing guidance along with the use of a reflexive research journal (Braun and Clarke, 2006).

This study was completed online, which meant we were able to increase access to certain groups, such as those living outside of the geographical location limits of commuting to home visits (i.e., outside London). The study setup also allowed for those who are in gainful employment to take part, as the study was offered outside office hours. A comment from participants around being part of a

wider society of support and that it could be argued that any support may have been as equally beneficial. Particularly as this was completed under COVID-19 pandemic national lockdown conditions, which invariably heightened the experience of connection even through videoconferencing. In the context of this study being conducted during a COVID-19 lockdown, it seems the supervision given during the intervention offered more than just safety and ensuring trial parameters are met, this was felt by the participants in a way that were described as “being held” or protected.

There is some evidence that both age and gender may have moderating effects on the use of technological devices within a treatment format. Older participants report a lower willingness to use either technology (brain stimulation or brain-computer interfaces). Older participants were up to 89 years. With an average mean age of 53 in experiment one and 54 in experiment 2, the older participants reported lower willingness to use either technology (Sattler & Pietralla, 2022). The means are higher than in the present study (40.9 years; range 19-73), though there is no clear documentation of what the cut off age or criteria was to classify as ‘older’. Further, women were found to be less likely to use brain-computer interfaces than men in a report from Germany (Sattler & Pietralla, 2022). While this study was looking at both treatment and enhancement, the finding of an increase in men was not the case in the present study. It was the opposite with a larger proportion of women. This may be in part due to higher numbers of women experiencing MDD (Smith et al., 2013; Kessler & Bromet, 2013). An interesting factor that was identified in Sattler & Pietralla (2022) but wasn’t addressed the present study was religiosity which negatively correlated with moral acceptability but not with their willingness to use a device (Sattler & Pietralla, 2022). This would be an interesting intersection to review in the context of novelty and modern scientific perspectives.

There are some critiques to conducting an intervention online, an obvious point relates to technology and those who did not have access to technology could not take part, this might affect low socio-economic groups, in particular, those from ethnic minorities groups (Senecal et al., 2018). The observation may have seemed more apparent and intrusive for some participants as it was a 'strange' situation to be in, firstly to be connecting daily online (in the context of the pandemic), and to be 'watched' or observed, whilst having treatment may have been particularly uncomfortable for some participants, perhaps drawing on historical stereotypes of the medical model of looking at 'things' through a microscope.

To conclude, acceptability was achieved and the themes that arrived around the construct of acceptability were mainly positive. This study has provided one important highlight of giving space to participants to offer these viewpoints on a novel treatment. This is within a treatment group which has a challenging history which includes coercion, poor treatment outcomes and at times, a narrow view on the understanding of what acceptability means for the people who are ultimately engaging with the treatment. As the first qualitative acceptability study on tDCS in MDD, it has provided an overview of what some of the emerging themes are and leaves the door open for future studies to continue to engage with acceptability as a varied, qualitative construct.

Chapter 4: The neurocognitive assessment of depression following tDCS treatment using auditory verbal learning test (AVLT)

Chapter Overview

In this chapter, a literature review will be conducted to understand the definition of neuropsychology and the purposes of why and when a neuropsychological assessment might be conducted. The different aspects of cognition will be presented to recognize the neuropsychological profile of MDD such as attention, memory and learning, and executive function.

The introduction will determine the chosen aspects of assessment (in this thesis is memory, specifically verbal memory). The use of neuropsychological assessment in healthy and clinical population are also presented. Next, specific theory will be discussed to understand the combined neuropsychological and biological theoretical position of MDD around memory and learning and neurobiological aspects of neurocognition to inform the neuropsychological decision.

The chapter will address how MDD treatments can alter or affect the neuropsychological profile, this includes what is known about the antidepressant treatment paradigms and what is known about tDCS specifically as a treatment and the impact on memory assessment in MDD.

The rationale for the choice of assessment that will be used in this study: auditory verbal learning test (AVLT) is explained and to conclude the literature review, a rationale, aims and hypothesis for the study. The chapter concludes with a report on the: materials, methods, results and will end with a discussion of the findings.

4.0 Introduction

Neuropsychology as a new field was developed following investigations of cognitive functions within the field of neurology, with the main goal of identifying dysfunction (Casaletto & Heaton, 2017; Cipolotti & Warrington, 1995). The investigations of the relationship between the brain and cognitive functions were conducted initially using observation and since 20th century, standardised

neuropsychological assessments such as psychometric testing (IQ testing) and test batteries such as Lurian approaches (Luria, 1966) and flexible and fixed batteries (Lezak et al., 2004; Reitan & Davidson, 1974) and the Boston Process approach (Kaplan, 1988) (Casaletto & Heaton, 2017; Eling, 2019). As new assessment tools have been designed to specifically assess different domains of brain function, so too has the use of them expanded in both clinical and research settings, particularly considering new technological advances such as imaging (Casaletto & Heaton, 2017). To date, there are an extensive number of neuropsychological approaches and tests that can be conducted across various brains functions depending on the rationale of its' use (See Lezak et al., 2004).

In a professional clinical setting, neuropsychology is used to aid in the diagnostic process (Vakil, 2012). Another indication may be as part of differentiating between suspected diagnoses (Kulas & Naugle, 2003) or in the context of forensic assessment for litigation and compensation purposes (Vakil, 2012). Neuropsychology may form part of functional assessments for those with established impairment (Vakil, 2012). The neuropsychological assessment may assist in the creation of rehabilitation plans to locate, predict, and evaluate outcomes (Allanson et al., 2017; Vakil, 2012), as well as choosing and monitoring appropriate treatment strategies (Kulas & Naugle, 2003). Understanding the effect of treatment may then indicate an important rationale for the use of neuropsychological assessments within the research compass.

Cognition and impairments in MDD

Cognition is an area of interest when considering the diagnosis of MDD. Traditionally, MDD has been characterised by the expression of mood disturbance, being the core symptoms of an episode. Though, it has been long recognised MDD has a cognitive component, with decreased concentration and focus, part of the diagnostic criteria (APA, 2013). Cognitive disturbance and neurocognitive symptoms have been seen more as an epiphenomenon and explained as being "age-related", or "consequences of poor motivation or inattention" (Sandi & Richter-Levin, 2009). It is now

understood as part of the clinical presentation, an expressed symptom of a depressive illness, and frequently extends beyond decreased concentration and focus.

Cognition is a broad spectrum of subprocesses involved in the acquisition, storage, retrieval, and processing of information and has been defined in a variation of this dependent on discipline (Bayne et al., 2019). Cognition can be altered with MDD (Henry & Crawford 2005; Snyder, 2013) and can have the potential to remain altered to varying degrees with remission (Bora et al., 2013; Rock et al., 2014; Semkovska et al., 2019). Cognitive dysfunction can be mediated by specific areas of the brain meaning some aspects of the same cognitive domains can be impaired while others preserved (Vakil, 2012). Cognitive subprocesses investigated in MDD are attention, perceptual processing, executive functions and, learning and memory (Vakil, 2012) and there is evidence of broad cognitive deficits in MDD across the domains of processing speed, executive functioning and working memory (Chakrabarty, Hadijpavlou & Lam, 2016).

Attention deficits in MDD present themselves as patient-experienced sub-domains. Examples of these include impairments in selective attention (increased distractibility), sustained attention (inability to sustain focus) or divided attention (an inability to simultaneously monitor multiple channels of information) (Keller et al., 2019). Top-down attention serves executive function/cognitive control (encompasses sub-functions, such as the selection and updating of goal representations, response selection and suppression, and performance monitoring) and has a critical role in sensory perception and decision making (Keller et al., 2019). Mood states also influence how attention is allocated, with mixed theories that attention can increase and decrease with positive mood states (Vanlessen et al., 2016)

Divergent perceptual processing can be expressed as altered processing of emotion, such as facial emotion processing and emotion recognition, as well as reduction in the speed of processing. Happy faces are often evaluated as less happy or sad by those experiencing MDD. Increased vigilance towards negatively valenced faces and selective attention towards sad faces has been identified

(Bourke, Douglas & Porter, 2010). Emotional recognition across all emotions except sadness is reported in depressed groups (Dalili et al., 2015). Emotion recognition deficits are not limited to depression and have been found in adults with anxiety disorders (Demensecu et al., 2010).

Executive function and cognitive control are termed to describe the regulation of processes to guide behaviour towards a goal, particularly in novel scenarios (Banich, 2009). Broadly speaking, executive function and cognitive control involve shifting attention, updating working memory and inhibiting dominant responses (Miyake & Friedman, 2012).

Processing speed can be examined across all domains and is known to be reduced in MDD. Within in executive function, it may not be enough to explain beyond simple neuropsychological tasks (Stroop and trail making test [TMT]) when assessing executive function, a bidirectional relationship between processing speed and cognitive effort (Nuño et al., 2021). In addition to considerably heterogeneity within MDD groups relating to age, severity, and medications (Nuño et al., 2021).

Verbal and non-verbal learning and memory is a well-established deficit in MDD. Memory is not a unitary system and distinctions can be made between working memory (short-term storage and temporary maintenance of information) and long-term memory (consolidation and storage of information over hours to years) (Porter, Bourke & Gallagher, 2007). Memory can be further delineated to declarative (cognitive learning) and non-declarative (habitual learning, skills, procedures) (Porter, Bourke & Gallagher, 2007). Assessment of deficits are typically conducted around the process of acquisition, retention, and retrieval in different modalities (verbal or non-verbal- auditory learning skills) and time frames (working memory, long term memory) and compile of different retrieval conditions: free and cued recall, and recognition (Vakil, 2012).

These cognitive deficits of attention, perceptual processing, executive function, learning and memory can be positioned under two interacting systems of ‘hot and ‘cold’ cognition. ‘Hot’ cognition refers to the emotional processing and emotionally valenced cognitive tests are used to assess this. Rather, ‘cold’ cognition relates to any information processed, that is not emotionally

influenced. In that, information is both neutral, and independent of the emotional state (Roiser & Sahakian, 2013). Both hot and cold cognition can be affected in MDD (Miskowiak & Carvalho, 2014). Furthermore, a depressed mood is exacerbated and sustained by cognitive deficits and these deficits are more likely to occur during an active depressive phase than in remission (LeMoult & Gotlib, 2019).

Ahern et al., (2019) discusses a neuropsychological framework using a hot-cold cognitive model to explain MDD. It describes hot and cold processes as complimentary processes to each other during the activation and maintenance of negative schema. Both processes are required to disrupt the negative cycle (Ahern, Bockting & Semkovska, 2019). However, cold cognition has been an area of interest in MDD research as unresolved cognition impedes recovery (Groves, Douglas & Porter, 2018) and has been shown to predict poor response to treatment (Allott et al., 2016). Later, in this chapter, I will discuss cold cognition in relation to treatment response.

Neurobiology of cognition in MDD

Given neuropsychological characteristics do not work in isolation, it is not unexpected to have multiple regions across the brain involved in the neurobiology of cognition in MDD. Understanding the function of each brain region and how this relates to neuropsychological activity may assist in the identification of treatment targets.

The main regions where dysfunction occurs with MDD are prefrontal cortex, parietal and basal ganglia regions and the limbic system (thalamus, hippocampus, and amygdala) (Millan et al., 2012). Often hypoconnectivity causes disruption, such as in the frontoparietal regions which are involved in attentional control and emotion regulation is characterised in MDD. There is also hypoconnectivity between frontoparietal regions and parietal regions of dorsal attention network, which governs attention to external environment. That said, hyperconnectivity, increased connections, within the

default network, are believed to be related to self-referential thought. Between the frontoparietal regions and default network may reflect the negative biases (Kaiser et al., 2015) and may impact the altered cognitive functioning seen within MDD. Suggestions that there is widespread dysfunction across brains regions occurs through an interaction of these respective brain regions, for example executive functioning deficits may underlie deficits found in attention, memory, and rumination (Nitschke et al., 2004; Whitmer & Gotlib, 2013).

Several regions report changes in MDD in temporal lobe particularly in grey matter (Bora et al., 2012). One of the most consistently reported regions in MDD lies in the limbic system. The hippocampus reduces in volume (Campbell et al., 2004; Videbech & Ravnkilde, 2004; Frodl et al., 2006). The hippocampus is a key structure for learning and memory and responsible for inputting context to the amygdala (Fadok et al., 2018). The amygdala has seen increased volume in depressed subjects compared with matched healthy controls, which may be related to the acuity of the illness or medication (Hamilton, Siemer & Gotlib, 2008; Hajek et al., 2009). HPA axis activation can lead to hippocampal atrophy and prevention of neurogenesis within hippocampal regions, though relationship with altered neuropsychological testing may be related to specific subtypes such as those with recurrent and/or more severe presentations (Raber, 1998; Porter, Bourke, and Gallagher, 2007).

Inflammation and cytokine activity has been extensively researched as a factor contributing to MDD (Rosenblat et al., 2014) and likely to play a role in the cognitive pathogenesis in MDD. Depressed patients often display higher levels of cortisol and C-reactive protein (CRP; Stetler & Miller, 2011; Haapakoski et al., 2015). There has been a strong correlation between plasma CRP and cerebrospinal fluid (CSF) CRP ($r=0.855$, $p<0.001$), and both plasma and CSF CRP significantly correlated with inflammatory markers (interleukin [IL]-6, tumour necrosis factor [TNF] and IL-1 beta; $p<0.05$) and their soluble receptors/antagonists (Felger et al., 2020). IL-6 has been positively associated with serial seven's test and high-sensitivity C-reactive protein (hsCRP) was inversely associated with trail

making and design fluency in baseline conditions in unmedicated depressed patients (Krogh et al., 2014). Raised CRP was both significantly associated to a reduced connection between ventral striatum and ventromedial prefrontal cortex (vmPFC; corrected p<0.05), correlated with increased anhedonia (*R*=−0.47, *P*=0.001) and predicted decreased connections between dorsal striatal to vmPFC regions and correlated to decreased motor speed (*R*=0.31 to 0.45, *P*<0.05) and increased psychomotor slowing (*R*=−0.35, *P*=0.015). CRP effects on connectivity to these brain regions significantly mediated the relationship between CRP, anhedonia and psychomotor slowing. Increased plasma IL-6, IL-1beta and IL-1 receptor antagonist has been associated with connectivity between striatum and ventra-medial PFC (*R*=−0.33 to −0.36, *P*<0.05) (Felger et al., 2015). In addition to well-established monoamine pathway abnormalities, leading to cell signalling and neurocircuit deficits (Stahl, 2010).

Cognitive theory

As it may appear in the above summaries of the different domains, each subprocess does not work in isolation. This commonality is seen when symptoms or cognitive deficits found within MDD are proposed under theoretical aspects. The brief overview provides the understanding of theory in the context of cognitive dysfunction as an integrated theory with theoretical, biological, and neuropsychological foundations in MDD.

In the introduction (Chapter 1), a precis of popular theories in MDD were introduced to the reader. Within cognitive theory fields, if the cognitive changes seen in MDD are understood as an intrinsic reflection of biological changes occurring in the brain (Austin, Mitchell & Goodwin, 2001), negative cognitions are essential in the aetiology and progression of MDD. Therefore, often MDD presents itself as negative cognitive biases. Sandi and Richter-Levin (2009) propose MDD develops from a position of high trait anxiety. Beginning with attentional biases and increased fear responses develop

increased amygdala activation and HPA-axis reactivity can lead to the increase in storage of fear associations via a classical conditioning and negatively valanced episodic memory storage (Sandi & Richter-Levin, 2009). Attentional biases and negative memories can be triggered to a mood-congruent bias following high levels of stress and the prior mentioned amygdala activity and glucocorticoid hyperactivity will lead impairments across the hippocampus and functional connections between prefrontal cortex-limbic activity, imposing deficits across the domains of attention, working memory and learning and concentration (Sandi & Richter-Levin, 2009).

The cognitive deficits described in the paragraph above reinforce a sense of cognitive ineffectiveness and are central to Seligman's (1972) learned helplessness theory (Seligman, 1972). Seligman (1972) adopted the stance that negative cognition creates a psychological environment where patients grow to accept their circumstances cannot be changed and thus, develop a sense of 'learned helplessness'. This leads to stifled and disrupted learning ability and depressed behaviour (Seligman, 1972).

However, persons without high trait anxiety prior to an episode can still develop a depressive episode. Beck's (1979) cognitive model of depression provides an insightful perspective to the development of MDD (Beck, 1979). Beck (1979) argues simply stressful events can be activating to previously learned negative schemata from early experience which led to a negative outlook on the self, the world, and the future. This creates a logic error which exacerbates low mood. The negative schema acts as a crucial mediator across multiple body systems including information processing, autonomic nervous and immune systems (Beck, 1979). As part of a natural, evolutionary mechanism, it was theorised by Beck & Bredemeier, the "depression program" is adaptive to allow for the conservation of energy resource (Beck & Bredemeier, 2016).

Beck's work has been developed by Bower (1981), a seminal work on the relationship between mood and memory. Bower demonstrated the powerful relationship between emotion and memory, suggesting there was mood congruent effect and an impact on memory ability. This interrelationship with cognition was suggested to be through a connection of nodes and activation of any of these nodes that results in the automatic activation of adjacent nodes (Bower, 1981). Theorists, Ingram (1984) and Teasdale (1988) further expand demonstrating biased processing of emotional information results in the onset, maintenance, and recurrence of MDD. The evidence for this can be found in mood-congruent biases (i.e., self-referential processing, attention, memory, and interpretation) (Ingram, 1984; Teasdale, 1988).

The neurocognitive profile of memory and learning in MDD

For this thesis, a focus will be placed on learning and memory as a focal investigation of cognitive dysfunction in MDD. Specifically, assessing the short-term storage and temporary maintenance of information, or in other words, verbal memory and the process of acquisition, retention, and retrieval of free and cued recall in an auditory-verbal modality (verbal learning skills). There is a large body of research that exists on memory encoding, retrieval, recall and recognition (James et al., 2021; Mendes et al., 2021; Nikolin et al., 2021). Declarative memory has demonstrated consistent deficits that remain in remitted MDD, generally as a consensus to a small-to-moderate effect (Bora et al., 2013; Rock et al., 2014; Semkovska et al., 2019). Though, large effect has been identified in a subset group (Bora et al., 2013). In the latter study, age of onset is identified as a moderating factor which can explain the disparity in results and in fact found the most severe deficit in verbal memory (d=1.10) within a late onset depressed group. This group is further statistically distinguished from early onset depressed group. The earliest onset group demonstrated a small deficit (d=0.21) in verbal memory (Bora et al., 2013). This may suggest the cognitive component of MDD may be a more evident as the disorder progresses or within an already 'vulnerable' (aging) brain.

The most profound moderating factor identified to affect performance outcome of cognitive tests are the number of previous episodes which was demonstrated in over half of a total of 75 investigated variables around cognition (Semkovska et al., 2019). Within those, verbal memory was included with the variables, word list total learning, delayed recall and recognition, logical memory immediate and delayed recall, and Rey-Osterrieth Complex Figure (ROCF) delayed recall (Semkovska et al., 2019). The higher the number of episodes a patient had experienced across the course of their depressive illness appeared to decrease the number of well performed tests within the remitted group (Semkovska et al., 2019). Performance worsens with each consecutive depressive episode, in comparison to healthy controls (Semkovska et al., 2019). This means the number of episodes in a lifetime is a potential moderator to cognitive effects of response on treatment.

There is a relationship between the severity of symptoms and cognitive deficits. Both recurrent episodes and longer episodes have been associated with worsening cognitive functioning (Kessing, Forman & Andersen, 2011; McDermott & Ebmeier, 2009). Notably, the more severe an episode, the more profound the measured objective deficit can be seen (Farrin et al., 2003). Difficulties with list learning and free recall, which require sustained effort are noted with depressed patients (Bartfai et al., 1991). Although, this is not seen within a remitted group (Semkovska et al., 2019).

Different aspects of memory functioning as measured by the California Verbal Learning Test (CVLT; Delis et al., 1987) were assessed against self-reported depression and anxiety scales using Minnesota Multiphasic Personality Inventory (MMPI; Hunsley, Hanson & Parker, 1988) ‘D’ and ‘Pt’ forms. Meta analysis found both demographic characteristics and ‘D’ were significant predictors of CVLT total words 1–5 raw score [$F(7,3943) = 157.84$, $P < .001$, $R = .401$]. They found depression (without

anxiety) had effects on immediate recall and amount of acquisition, but not retrieval or recognition (Kizilbash, Vanderploeg & Curtiss, 2002).

There is a relationship between attention, learning and memory deficits, and MDD. It is not clear on what mediators and mechanisms underlie cognitive impairment (McClintock et al., 2010). There has also been an accelerated decline in cognitive dysfunction as age increases across memory, attention, processing speed and executive function domains (Gualtieri & Johnson, 2008).

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a battery psychological test which can assess numerous aspects of cognitive function. Cognitive deficits in executive function, memory and attention were found at moderate levels in MDD when compared to healthy controls (Cohen's d effect sizes ranging from −0.34 to −0.65). Executive function and attention showed significant moderate deficits (Cohen's d ranging from −0.52 to −0.61). Memory demonstrated a non-significant small-to-moderate deficit (Cohen's d ranging from −0.22 to −0.54) persisting in remitted MDD. These results suggest cognitive impairments, including memory, is independent of depressive mood symptoms (Rock et al., 2014).

Age and gender have been identified as moderating factors for verbal memory domains (Semkovska et al., 2019). The higher the age of the participant, the lower the performance on testing, relative to controls. The higher number of females in the remitted group, the better the performance, notably on word list learning and delayed recall, and logical memory immediate and delayed recall (Semkovska et al., 2019). Conversely, no significant differences between moderators (Age, gender, education, severity, and treatment) have been identified in cognitive performance of MDD patients (Zaninotto et al., 2016). A small but significant difference was noted between melancholic and non-

melancholic patients experiencing cognitive impairments, including verbal memory. However, a moderate heterogeneity was also observed for this domain. The melancholic group were more severely depressed and older in age compared to the non-melancholic group (Zaninotto et al., 2016).

Social functioning is the outward connection an individual has with the outside world, such as social relationships, occupation, and home life (Bosc, 2000). Social functioning impairments are well established to occur in MDD (Kupferberg, Bicks & Hasler, 2016) and can persist long term after treatment (Kennedy et al., 2007). The relationship of social functioning abilities and QoL to neurocognitive dysfunction has been identified as clinically important and significantly related (Evans et al., 2014). Though there has been limited research to address what the relationship is between these distinct constructs. A broad understanding is an association with or predicting a functional outcome across memory domain, as well as other domains (attention, executive function, and processing speed) (Evans et al., 2014; Cambridge et al., 2018). Age and symptom severity appear to have an enhanced effect on the neurocognitive-psychosocial dysfunction (Cambridge et al., 2018). Increased age, increased symptomology and severity indeed play a significant role, but it is not understood how other illness influences (duration, episodes, other clinical presentation such as psychosis) impact the understanding of neurocognition-psychosocial dysfunction (Cambridge et al., 2018). Further, the lack of current meta-analysis to date have been unable to address the relationship or any limitations. One consideration is the wide range of assessment tools which include clinician rated performance scales and subjective measures of psychosocial function. One review publication comments of the scarcity of longitudinal research on the topic (Cambridge et al., 2018). As psychosocial functioning has been broadly associated with neurocognitive function in MDD, adding to the research base or conducting explorative analyses may assist in what and how this relationship is represented within MDD populations. Domain specific relationship with composite scores have shown the strongest predictor to remission is executive function (Knight, Air

& Baune, 2018) and due to the complex tasks involved in psychosocial function would make this an apparent result. Knight et al., (2018) mention memory may have been a stronger predictor; however, they made a distinction between immediate and delayed memory as individual domains whereas prior studies had classified 'learning and memory' as a singular construct (Knight, Air & Baune, 2018).

Both neuropsychological and psychosocial assessment tools can be both objective and subjective. Typical neuropsychological tools assessing the ability to memorise or retain information, divide, or shift attention, or follow an organised plan in relation to neutral, non-affective information are in objective form. There are more variations under psychosocial assessments to be both objective and subjective. Subjective assessment would include a self-report nature of symptoms or experiences (Austin et al., 1992; Chakrabarty, Hadijpavlou & Lam, 2016; Ahern, Bockting & Semkovska, 2019).

Implications of treatment neurocognitive symptoms

When making comparison across healthy versus psychiatric groups, improvements across working memory following tDCS have been observed in both healthy and neuropsychiatric subject groups (Hill, Fitzgerald & Hoy, 2016). Differences were seen depending on whether the task was conducted online (during tDCS) or offline (after tDCS). Significant improvement in reaction times following offline working memory tasks was observed in healthy groups, while response accuracy saw strong trends towards significance. The opposite was seen in psychiatric groups with online response accuracy, but not reaction times, improving significantly with tDCS (Hill, Fitzgerald & Hoy, 2016; Dedoncker et al., 2016). This suggests that there could be a difference in the function of these brain regions in neuropsychiatric groups compared with healthy groups and a dynamic that will impact treatments and subsequent cognition outcomes, as the brain 'baseline' function is altered.

Specifically addressing verbal memory across young, healthy group, tDCS appeared to have no significant effect over sham condition at F3 (EEG 10/20 positions on international system) and these results may be procedural such as enhancing recall but not recognition (Bartl et al., 2020; Leshikar et al., 2017). Examining these factors separately would be advantageous in a clinical group setting to establish if this differs significantly to healthy groups.

Neurocognitive effects of MDD have been found to be reversible with treatments (Neu et al., 2005). The effectiveness of remediation has been disputed, though, as even with optimal treatment and at the point of remission of a depressive episode, it has been found some dysfunctions in cognition remain into remission (Reppermund et al., 2007). The extent of any persisting dysfunction is unclear (Neu et al., 2005) and may differ in relation to treatment options. Poor resolution of neurocognitive symptoms can present as a barrier to resolving any presenting psychosocial dysfunction (Evans et al., 2014).

Antidepressants and neurocognition

Initial support for pharmacotherapy improving neurocognitive symptoms was found in a large meta-analysis including 43 studies included with a total of 4828 participants (Keefe et al., 2014). Weighted mean effect sizes favouring treatment over placebo were significantly larger, with a small effect for verbal memory (0.10, 0.091 to 0.117) for those receiving monotherapy, using versions of the AVLT (CVLT and Repeatable Battery for the Assessment of Neuropsychological Status [RBANS]) and visual memory (0.44, 0.436 to 0.452) showed the largest effect size for those with an augmented treatments using RBANS, visual recall and reproduction. The results from this meta-analysis also

suggest augmentation therapy may assist those who have symptoms that remain following a successful monotherapy treatment regime (Keefe et al., 2014).

Expanding on Keefe's results, a longitudinal meta-analysis was conducted to address both pre- and post- cognitive deficits in MDD across inpatient and outpatient settings (Bernhardt, Klauke & Schroder, 2019). Changes were compared against healthy controls for 16 studies with a total of 859 participants. There was a small improvement in all cognitive measures (g = 0.17–0.35). For the MDD intragroup changes, a significant and small effect (p=<0.001) was found in verbal memory (g=0.27, 0.14–0.40, SE= 0.07, Z= 3.97), nonverbal memory (g=0.19 0.09–0.30 SE=0.05, Z=3.69), verbal fluency (g=0.35, 0.19–0.52, SE= 0.08, Z= 4.20) and global cognition (g=0.27, 0.16–0.37, SE=0.05 Z=4.91) but none for the control group. For comparison effect for test-retest processing speed, nonverbal memory, verbal fluency, and global cognition, no significant differences were observed between the test-retest effect sizes, indicating that there was no significantly different improvement between controls and MDD patients. For verbal memory, the MDD patients improved significantly more than healthy controls. No difference was found between other measures. For verbal memory and nonverbal memory, no subgroup analyses could be conducted as only one inpatient and no study of outpatient treatment was present. For verbal memory, mean age was a significant moderator variable (B = −0.012, SE = 0.003, p = 0.000), with younger patients showing a significantly larger improvement in cognitive functioning in the domain of verbal memory than older patients. The percentage change in depression severity and time between assessments had no significant influence on the effect sizes (Bernhardt, Klauke & Schroder, 2019).

In a prospective case-control trial, participants were assessed following treatments of SSRI, SNRI and vortioxetine and other pharmacological treatment (not otherwise stated) (Çökmüş, et al., 2021). Participants were assessed from baseline every 2 weeks until week 8, then assessed at week 12, then responder group only at week 16. Despite remission being achieved, neurocognitive symptoms

continued to be present based on digit symbol test (DSST), assessment speed and sustained attention (Çökmüş et al., 2021).

Neurocognitive effects on novel treatment such as ketamine have been explored as a direct comparison to electro-convulsive therapy (Basso et al., 2020). Ketamine was found to have a large and significant effect on percentage scores across the assessed domains (attention, visual memory, and executive function), composite scores showed a small significant improvement of these neurocognitive domains. Whereas ketamine and ECT saw a small but significant decrease in verbal memory. This was expected for ECT as it is known to cause transient neurocognitive impairment (McClintock et al., 2014) but not ketamine and one explanation for this may be that the initial response to treatment sees a decline in verbal memory with a resolution or improvement post treatment (Basso et al., 2020).

Psychotherapy and neurocognition in MDD has been less researched. The extent to which different psychotherapies impact neuropsychological components is not known and would be an area for consideration for future research. There are some emerging promising results for CBT and other forms of therapy such as the longitudinal changes of MDD in an outpatient setting following CBT treatment, found small improvements on attention, figural memory, and processing speed (Bernhardt et al., 2021). Further, MDD with more severe neurocognitive profile have greater effect of remitting with CBT than non-remitters suggesting CBT to be effective for participants presenting with neurocognitive symptoms (Metts et al., 2018). The neurocognitive profile was considered as a complete battery and as such, unique composites were not examined so were unable to stipulate if a specific cognitive domain excelled (Metts et al., 2018).

Combination therapy has been explored in relation to neurocognitive effects. Interpersonal and social rhythm therapy (IPSRT), a form of interpersonal therapy, was compared with a hybrid version incorporating cognitive remediation (IPSRT-CR) (Douglas et al., 2022). There was no significant difference between groups on global cognition, the primary outcome of the study, however, there were some moderate effects observed in learning. Distractor list recall significantly improved at the end of treatment (12 months) in the IPSRT-CR group. At follow up (18 months), total learning. Though Douglas et al (2022) present these results cautiously due to the potential for a type 1 error in their design, which required a protocol change (Douglas et al., 2022). It does raise the potential for unique verbal learning changes posited by Basso et al (2020) that occur only post-treatment.

A comprehensive critical review of neurocognitive effect of neuromodulation (McClintock et al., 2020) provides a summary of the cognitive effects found in MDD. This review provides oversight of acute effects of affective bias, and acute nonaffective change in processing speed, and visual attention and potential mechanism of action underlying antidepressant effect of neuromodulation (McClintock et al., 2020).

Cognition and treatment action of tDCS

It is well understood there is a delay to the antidepressant response and this delay is explained by time required to develop implicit emotional processing positive bias and is probable that requiring a relearning of new associations to emotional stimuli (Harmer & Cowen, 2013; Godlewska, 2019).

Improving recognition in an emotional face recognition task, most notably for positive faces, was seen following anodal tDCS (Nitsche et al., 2012). This suggests stimulation of the left DLPFC could act as a possible method of antidepressant treatment. Previous results of left anodal tDCS

supported this notion in enhanced down-regulation of negative emotions both online (during tDCS; Peña-Gómez et al., 2011) and offline (after tDCS session was completed; Maeoka et al., 2012). Offering further insight of the concept, clinical depression trials have shown an increased accuracy but not in response time (RT) or speed on an affective go-no go task (Boggio et al., 2007). Differences in RTs were found in valenced words on an emotional Stroop task, with a significant effect on non-neutral vs. neutral and positive- vs. neutral-words and no effect for accuracy within MDD (Brunoni et al., 2014). It is possible there is a cascade with corrected attentional biases to emotional information (Wolkenstein & Plewnia, 2013), which lead to emotional processing improvements and an enhancement of working memory in both MDD and healthy controls (Fregni et al., 2005; Oliveira et al., 2013; Wolkenstein & Plewnia, 2013) with the use of a single tDCS session. The specific improvement in emotional working memory in patients and not healthy controls following a single session of DLPFC tDCS, further indicates a potential cognitive target for its antidepressant effects (Moreno et al., 2015). Furthermore, there are significant improvements on a battery of cognitive testing including Paired Associates Learning (PAL) and Spatial Recognition Memory (SRM) and Rapid Visual Information Processing (RVP) following multiple sessions of tDCS (Salehinejad et al., 2017). This would suggest that an underlying mechanism of bias in depression lies with cognitive control deficits (Salehinejad et al., 2017).

Emotional processing predates antidepressant response and may underpin to some degree the antidepressant action of tDCS (Godlewska, 2019). A neurocognitive model in MDD purports an exertion of control from the DLPFC of the immediate processing of emotional information (Plewnia et al., 2015), and on cognitive performance such as attention, cognitive control and working memory (Tortella et al., 2014; Ironside & Perlo, 2018). Stimulation of the dorsal network improves top-down control over ventral limbic regions (i.e., hippocampus and amygdala) (Spezia Adach et al., 2015).

The current underlying theory of treatment action and how this relates to potential neurocognitive effects are not fully understood. It appears that tDCS has the same action in relation to emotional processing but conceptualising under the existing cognitive neuropsychological (CNP) theory poses a challenge (Godlewska, 2019).

Several theories have been suggested to explain the quicker response in symptoms change. The first being the magnitude of effect is larger and in turn, the period required for interaction with the environment is shorter to see these effects to meet a clinical improvement (Godlewska & Harmer, 2021). The second is symptoms improvement happen earlier in neuromodulation and this facilitates social interactions and formation of positive biases (Godlewska & Harmer, 2021).

Novel treatments (ketamine) being experimented in rodent models around negative affective bias are providing insights into the understanding of the role of memory in antidepressant treatments. It was found that traditional antidepressant treatment affects positive bias acquisition but do not affect prior acquired negative memory associations and the retrieval process within bias networks. Conversely, this model found ketamine didn't affect positive bias learning but does remove negative associations within the memory network which had been paired with psychosocial stress or administration of an anxiolytic through medial prefrontal cortex regions (Stuart et al., 2015). This suggests novel rapid-acting drugs may be able to impact established negative memories as they are less dependent on the environment and glutamate may give a fascinating insight to form part of the hypothesis into understanding the role further (Harmer, Duman & Cowen, 2017).

The domains of cold cognition are dissociable and distinct both psychologically and anatomically (Park et al., 2018). The action of tDCS in the cold cognition domains could be feasibly different than how we understand antidepressants action and therefore further research is warranted, with the view of potentially looking at predicters of treatment response (Park et al., 2018).

An examination of key cognitive domains (global cognitive functioning, verbal memory, executive functioning, attention and working memory) on the effect of tDCS mood-independent cognitive enhancement suggest no beneficial effect following a course of tDCS for patients with MDD (Martin et al., 2018). Although improvements are seen in these areas after one session (Martin et al., 2018). Taken together, these results would suggest there are no cumulative, or lasting cognitive effect (Martin et al., 2018).

Not included in the recent meta-analysis by Martin et al., (2018) and in direct contrast to the results presented, an international study using a sample including both MDD patients and bipolar patients used tDCS in 2 doses (2.5 mA for 30 min) or low dose (0.034 mA), for 30 min for a total of 20 sessions across 4 weeks (McClintock et al., 2020). Significant improvements were seen across patients, time and in multiple cognitive domains including in verbal learning and memory, selective visual attention, auditory attention, and information processing speed irrespective of dose (high or low dose tDCS; McClintock et al., 2020).

More studies are required which address a design which are seen across drug studies with a participant baseline assessment after short term or acute treatment and at the point clinical response is seen (Godlewska, 2019).

4.1 Auditory Verbal Leaning Test

The AVLT (Rey, 1964) was created as a measure of rote verbal memory where a participant is asked to repeat facts or figures to memorise them (Lezak et al., 2004). The AVLT can assess different domains in memory (immediate memory, new learning, retroactive and proactive interference, and recognition) (Rey, 1964; Lezak et al., 2004). There is also an affective word list version which include

positively and negatively valenced words (Snyder & Harrison, 1997). This would be conducted in the same way to understand affective learning.

The test consists of 5 practice trials of a neutral (non-affective) word list (Lezak, et al., 2004). Each list requires attention and short-term memory, as these are required through the whole trial. Attention and short-term memory are particularly required for trial I and VI. Trials I-V assess verbal learning and memory through the learning curve across these trials, the total acquisition. A distractor list (i.e., List B) is then administered with different, unrelated neutral (non-affective) words. Trial VI assesses the immediate recall after a distractor list. Delayed recall and recognition are assessed after 30mins or more in trial VII and VIII (Correia & Osorio, 2014; Lezak, et al., 2004).

In addition to the assessment of immediate and delayed recall, and recognition, errors and specific faults can form another source of information that can infer attention, memory, and learning performance (Lezak, et al., 2004). An example of this can be repeated words or recall, which can be used as an index of inattention, difficulty with spontaneous recall or inappropriate use of the environmental feedback. Alternatively, intrusion words that were not on the list might be considered false memory or confabulation (Corriea & Osorio, 2014). Difficulties in monitoring might be suggested with repetition of these intrusions. Monitoring difficulties may also be seen, following the repetition of question words, though individually, this might be a display of insecurity. Measuring proactive and retroactive intrusions through List A (trial VI) and List B (trial VII) can be considered an example of interference (Corriea & Osorio, 2014; Lezak, et al., 2004).

The AVLT is sensitive to numerous neurological and psychiatric disorders, such as AD, epilepsy, and depression (Spreen et al., 2006). Age, gender, education, and IQ can be moderating factors to AVLT

(Uchiyama et al., 1995; Van der Elst et al., 2005), with age being the strongest predicter on performance (Van der Elst et al., 2005). Education has been cited as a moderating factor (Uchiyama et al., 1995). Age and education negatively and positively correlate respectively, with performance scores (Mitrushina et al., 2005; Spreen et al., 2006), though appears to be specific to the subgroup of males and an inpatient status (Uchiyama et al., 1995).

Repeat assessments over time can detect changes over the period of treatment or post-treatment. Repeated use of the same form or test in this manner could confound the assessment due to practice effects (Hawkins & Sayward, 1994), particularly if the same form is used for each task. To allow for retest ability within short time frames, multiple alternative forms have been developed. Up to 6 alternatives to Rey's (1964) original are available (Crawford, Stewart, & Moore, 1989; Geffen, Butterworth, & Geffen, 1994; Madjan, Sziklas & Jones-Gotman, 1996) and they do not differ in terms of difficulty. Though, each make a direct comparison is made with Rey's AVLT (1964) and are equal to Rey (1964) but not necessarily equal to each of the other retest forms (Hawkins, Dean & Pearlson, 2004). Considerations should be made to the limited studies making comparisons between the alternative forms and the limited overlap in terms of relative scoring and statistical findings of alternative forms. The data currently available would suggest any of these differences are minimal (Hawkins, Dean & Pearlson, 2004).

4.2 Rationale for this study

Using tDCS treatment as an at-home treatment is a relatively new concept and there have been limited studies looking at whether there has been any effect or difference in effect across the cognitive spectrum in clinically depressed patients. This study would aim to add knowledge to this limited base within a feasibility study design and using the current knowledge base of clinically based neuropsychological assessment.

4.3 Aims and Hypothesis

Aim

The aim will be to assess three outcome areas from AVLT (Rey, 1964): total learning, learning over trials, short-term percentage retention, to see if these aspects are affected by tDCS treatment over 4 timepoints (baseline - classed as V1, post V1, V10 and V21 - end of treatment). Covariates of the change in HAMD and SDS over time will be addressed in a repeated measures analysis of covariance (ANCOVA).

Research Question

Question: Does verbal learning improve over time following tDCS treatment for MDD?

Hypothesis

It is expected those who have had a response to treatment will also improve across two areas of total learning and learning over trials. An exploratory review of short-term percentage retention (STPR) which would follow the line of the earlier area: i.e., if total learning and learning over trials, this may allow to posit an improvement of STPR.

4.4 Methodology

Overview

The study design is described to include how the assessment was conducted in the context of the feasibility study and collection of the data is defined. This section will describe the participants and enrolment to take part in AVLT (Rey, 1964) as part of a feasibility study. The tDCS montage and parameters are provided here as a protocol for the treatment of MDD.

Study design

A within-subjects design was adopted for this study. The independent variable was time for each outcome measure. Tasks were completed offline within 30 mins of the stimulation ending. The stimulation sessions were part of a treatment protocol consisting of 30 mins sessions completed at roughly the same time for each participant. The first 3 weeks were 5 tDCS sessions per week, with a couple of participants completing 4 tDCS sessions on week 1 due to restrictions within the Flow Neuroscience app. The study then reduced sessions to 2 tDCS sessions per week for 3 weeks.

The total time of stimulation and current intensity (2mA) was within the safety recommendations and standard experimental protocols (Nitsche et al., 2003). All reported adverse effects of tDCS were mild and expected (Brunoni et al., 2011).

Participants

All participants were enrolled in at-home tDCS acceptability and feasibility study and were enrolled through this study. The demographics of participants who agreed to complete this assessment are described below (n=21). All participants were aged 18 or older. All participants were assessed to be experiencing a current depressive episode (17-item HAMD ≥ 16) using MINI and were engaged in some form of treatment, either taking a stable dose of anti-depressant or psychotherapy (either

face-to-face or online CBT). The assessments and clinical history were reviewed with a consultant psychiatrist. No participants were classed as treatment resistant (defined by having ≥ 2 or more antidepressants). The full eligibility criteria can be found on p. 49.

tDCS Montage and Parameters

All participants included in the AVLT analysis used the same tDCS device (Flow Neuroscience). The tDCS device used 2 sponge electrodes with a surface area of 35cm² which were sealed and pre-soaked in saline by Flow Neuroscience. The electrodes were opened and placed in the device by the participant and the device moved on the head to be positioned at F3, F4 (EEG 10/20 positions on international system). Most sessions required additional saline to be added by the participant to reduce redness and dry skin as a side effect and increase contact to reduce burning sensation as a side effect.

The return electrode refers to the electrode which is not stimulating the site of interest (in this study, the return electrode is the right DLPFC to represent the current flow being directional from the stimulating electrode (positioned at the left DLPFC) to the return (the right DLPFC) and eliminates the assumption of a unidirectional flow of current (Antal et al., 2017; Bikson et al., 2010; Woods et al, 2016). The stimulation ran for a constant 30 minutes and was powered and controlled by the participant. The participants were aware they could stop the session at any time and would inform the researchers if this was their choice. No sessions prior to assessment were stopped before the end of the 30 minutes.

4.5 Materials and Methods

Overview

This section will summarise the assessments used with an example list of words for practice and distractors, and the outcome measures for the study are outlined. All assessments were either clinician-rated pen and paper tasks or verbally completed by participant.

Assessment

A clinical assessment was conducted which included demographics and health and treatment history were completed by a researcher under supervision by a consultant psychiatrist at baseline during a 2-hour session. Ammons Quick Test was used to measure IQ scores (Ammons & Ammons, 1962) on the first session. The AVLT was administered at over the 4 timepoints baseline (classed as V1 prior to treatment), immediately after V1, V10 and V21 (Rey, 1964) and administration details are detailed under data collection. Participants were given the tests in a random order for administration over the 4 time points.

Mood scales and side effect screening were conducted as part of the clinical trial. These included HAMD-17 (Hamilton, 1960) and SDS, administered at V1 (baseline), V10 and V21 (Sheehan & Sheehan, 2008). Some were conducted as part of the trial but not included in this analysis (HAMA, Hamilton 1959; PHQ-9, Kroenke, Spitzer & Williams, 2001; and AEQ; Brunoni et al., 2011)).

A final visit was offered for participants who did not complete the successive visits. Further, at each visit, the following assessments were performed: 17-item HAMD (Hamilton, 1960), and the SDS was administered at this time (Sheehan & Sheehan, 2008).

To assess memory and verbal learning, the Rey AVLT (Rey, 1964) was used to assess these aspects of neuropsychological functioning. To attempt to reduce practice effects, different forms of AVLT were used at each different testing occasion (Crawford, Stewart, & Moore, 1989; Geffen, Butterworth & Geffen, 1994; Madjan, Sziklas & Jones-Gotman, 1996) and were counterbalanced using pre-identified excel sheet in a random order, created by a researcher (RR).

Figure 7. *Example List (Geffen, Butterworth & Geffen, 1994).*

List A	List B
Pipe	Bench
Wall	Officer
Alarm	Cage
Sugar	Sock
Student	Fridge
Mother	Cliff
Star	Bottle
Painting	Soap
Bag	Sky
Wheat	Ship
Mouth	Goat
Chicken	Bullet
Sound	Paper
Door	Chapel
Stream	Crab

Outcome measures

The outcome measures from the AVLT were:

1. Total learning (the total number of words learned over the first 5 trials)
2. Learning over trials (LOT) = The sum of words remembered across Trials 1–5, corrected for immediate word span (Trial 1):

LOT= (Sum of Trials 1-5) – (5 x Trial 1 score)

3. Short-term percentage retention (STPR) =Trial 6 recall expressed as a proportion of Trial 5 recall:

$$STPR = 100 \times (\text{Trial 6 recall}/\text{Trial 5 recall})$$

The 17-item HAMD (Hamilton, 1960):

Response to treatment was defined as a minimum of 50% reduction from the week 0 (baseline) 17-item HAMD, total score. Remission was defined as an endpoint 17-item HAMD total score of ≤ 7 (Hamilton, 1960).

Sheehan Disability Scale (Sheehan & Sheehan, 2008)

The SDS scored a brief, patient rated measure of disability and impairment on three Likert scales from 0-10 (work/school, social life, family life/home responsibilities) (Sheehan & Sheehan, 2008) and was assessed at the same time as AVLT (Rey, 1964). The scores were given using a visual analogue scale: 0 (no impairment), 1–3 (mild), 4–6 (moderate), 7–9 (marked) and 10 (extreme) disability. The maximum total score is 30 and the higher the score, the more impairment has been perceived by the participant.

Data collection

Two researchers (RW and RR), trained in the use and administration of AVLT (Rey, 1964), completed the assessments with participants, via an online video call. Participants were rated by the same researcher in the study, i.e., the rater completed both treatment sessions and completed the assessments at all timepoints. Data were collected 4 timepoints of assessment. Participants who finished early (n=1) had their LOCF. 21 of 26 participants completed all assessment points.

Participants were asked to complete the test in the same environment (i.e., at the same desk space, in the same room) for each of their assessments and to allocate space and time where they would not be distracted for the duration of the test. The assessment was completed at roughly the same time for each participant. Participants were informed of the instructions whilst online by researchers reading to the participants each time the assessment was completed. The word list was then read to the participants, and responses noted. In line with the guidelines of the test, this same list was repeated 5 times, then a distraction list was read, and a final free recall of the practice list was requested from the participants. The delayed recall (post 30 mins) was not completed due to the confines of the study.

Statistical analyses

Data were compared using a range of statistical tests. A LOCF method was used for patients who completed the study before the full 6 weeks of treatment. In point (i) age, gender, IQ and years of education were compared using Chi-square analyses, ii) AVLT (Rey, 1964) and iii) change scores at V21 for depression and SDS were used. The analysis for (ii) and (iii) were completed at V1 (baseline), post V1 (immediately post intervention), V10 and V21 and change score from V1 (baseline) to V21 respectively.

To examine the effect of time on AVLT (Rey, 1964), a series of repeated measures analysis of covariance (rmANCOVA) were conducted. Time was used as the repeated measure independent variable (i.e., V1 (baseline), post V1 (post intervention), V10 and V21) and AVLT total learning, LOT and STPR as the dependent variable (DV). The covariates included were baseline scores for HAMD and SDS. Age, gender, education, and IQ were also included as covariates. Exploratory correlation analysis was conducted using Pearson's *r* to see if association between baseline scores of 17-item HAMD and SDS were correlated to AVLT scores.

Statistical analyses were carried out with SPSS 26.0 (IBM, 2019). The results will report exact p values, the alpha level used as a significance criterion was set at *P*=<.05

4.6 Results

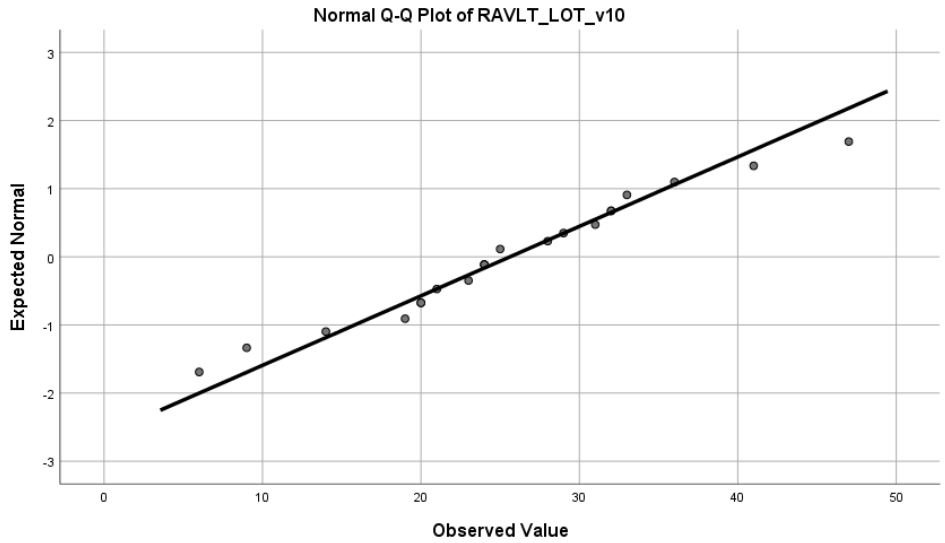
Descriptive results

This study included 21 of 26 participants from the feasibility study. The majority were female (n= 16). The age ranged from 19-73 (mean 39.90, standard deviation (sd) 14.233). The years of education ranged from 12-18 years (mean 15.48, sd 2.294). IQ, as measured by Ammons (Ammons & Ammons, 1962), ranged from 83-110 (mean 101.10, sd 7.873). Ethnicity was reported as n=13 as White British, n=3 as Mixed heritage (Black and White), n=2 as Black British, n= 1 as Chinese, n=1 as Pakistani and n= 1 as Sephardi Jewish.

21 participants completed 4 timepoints and 20 participants completed them at the allocated timepoints. One participant completed earlier by a few sessions due to a fault in the device and this assessment was included using LOCF.

For all analyses that follow assumptions were checked during analysis, no assumptions were violated unless otherwise stated. The data was normally distributed as shown in QQ plots (examples in Figure. 8). Equal variance was examined in the ANOVA. There were no significant interactions between age, gender, IQ and years of education.

Figure 8. *Example of Q-Q Plot – LOT v10*



ANCOVA analysis

Prior to running the ANCOVA analysis, a one-way ANOVA was conducted, and the results are below in Table 7. An exploratory correlational analysis with the prospective covariates.

Table 7 show the mean and standard deviation of AVLT total learning, LOT, and STPR.

Table 7. *Means and standard deviation of AVLT*

Measure	Baseline		Post-session 1		Post-session 10		Post-session 21	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AVLT (n=21) Total learning	64.57	14.07	61.00	13.81	62.05	12.27	58.62	13.83
Learning over trials	30.05	13.55	28.86	9.275	25.62	9.81	22.90	8.79
Short-term percentage retention	87.86	17.55	79.21	13.87	85.50	18.54	82.10	21.56

Table 8 shows there was no effect of time and no effect of the interactions with chosen covariates (17-item HAMD percentage change at visit 21) and time.

Table 8. *ANOVA and ANCOVA for total learning, learning over trials and short-term percentage retention*

Measure	Time (ANOVA)			Time (ANCOVA)		
	Df	**F**	***P***	***Df***	***F***	***P***
AVLT (n=21) Total learning	3,54	.696	.559	3,45	.681	.568
Learning over trials	3,54	.808	.495	3,45	.735	.537
Short-term percentage retention	3,54	.246	.864	3,45	.357	.784

(ANOVA, analysis of variance; ANCOVA analysis of covariance which include age, years of education, IQ, and baseline 17-item HAMD and SDS at V1, significance set at p=<0.5)

There was no main effect of time in the ANOVA or ANCOVA. All interactions with covariates (Age, years of education, IQ, 17-item HAMD V1, SDS V1) were not significant. There was an observed trend towards significance in the total learning (time) and years of education interaction (F (df)= 2.703 (3, 45), p= 0.057). There was an observed trend towards significance in LOT (time) and age interaction (F (df)= 2.685(3, 45), p=0.058). No trends were observed in STPR.

Correlations

There were some significant positive correlations total learning baseline and the baseline (r=.638, n=21, p= .002) and post V1 (r=.603, n=21, p= .004) and visit 21 (r=.517, n= 21, p=.016) LOT. There was an observed significant positive correlation between total learning and LOT at visit 10 (r=.556, n=21, p=.009) and visit 21 (r=.659, n=21, p=.001).

SDS visit 1 scores positively and significantly correlated with LOT at visit 10 (r=.515, n=21, p=.017).

SDS visit 10 significantly correlated in a positive fashion with the baseline total learning (r=.437, n=21, p=.048), as well as post visit 1 (r=.600, n=21, p=.004) and visit 10 (r=.451, n=21, p=.040) but not visit 21. SDS visit 10 was correlated to LOT post visit 1 (r=.444, n=21, p=.044).

SDS visit 21 was significantly positively correlated with post visit 1 (r=.450, n=21, p=.041) and post 10 (r=.459, n=21, p=.036) total learning scores.

Only one correlation was established between AVLT measures and HAMD scores from visit 1, visit 10, and visit 21. This was a significant and positive correlation between visit 10 HAMD scores and the LOT post visit 1 (r=.439, n=21, p=.047). All correlational results included in the appendices.

There was no interaction between change of HAMD, but there were interactions between AVLT timepoint and with change of SDS.

4.7 Discussion

The AVLT (Rey, 1964) was performed to assess total learning, LOT, and STPR across 4 timepoints. The assessment was completed as part of a 6-week study of active tDCS treatment for MDD. A repeated measures ANCOVA was performed for each outcome measure and there was no significant effect of time or significant covariate effect of HAMD and SDS for any of the investigated areas of interest (total learning, LOT, or STPR). A trend was observed between total learning (time) and years of education interaction and an observed trend towards significance in LOT (time) and age interaction. No regression analysis was undertaken as this is effectively incorporated into the ANCOVA analysis, through the assumption of the homogeneity of regression slopes. Exploratory correlations showed multiple relationships between total learning and LOT. There was also a positive between SDS and total learning and LOT.

Martin et al (2018) found there were no overall cognitive benefits of multiple sessions of tDCS as measured by AVLT (Rey, 1964). These results contrast with McClintock et al., (2020), who found a significant difference verbal memory (an AVLT measurement) and specific genes (*BDNF* Val66Met and *COMT* Val158Met polymorphisms) interacted with verbal memory and verbal fluency outcomes. Genetic testing was beyond the scope of this study but could offer on explanation as to why we found some differences. There is some discussion around the age of onset in depression consisting of a larger factor to overall cognitive deficits as part of this presentation (Bora et al., 2014). While the average age across both groups (high dose and low dose) in McClintock's study (2020) were higher than seen in this study, the age of onset is typically unreported outside of LLD. Another exploration may be the severity of cognitive deficit at baseline, this is not commented on. Further, McClintock's study includes participants that might be considered as treatment resistant and as such, it is possible these participants have more persistent cognitive effects.

The results found in this study may suggest tDCS does not remediate verbal memory cognitive effects at the earlier point of response or remission. It has been noted the stability and course of cognitive effects found in MDD can last into remission (Gruber et al., 2007). With this, it might be a consideration to continue neuropsychological testing at post 1 month, 3 months and 6 months, to assess a more longitudinal time frame.

The trends of total learning (time) and years of education interaction and LOT (time) and age interaction are unsurprising. It may be logical to consider that higher years of education may impact the total learning. This may be due to other factors other than tDCS such as improved learning skills or higher cognitive reserve ability. Age is recognised as a moderating factor to both cognition and social functioning relationship (Cambridge et al., 2018; Semkovska et al., 2019). As age increases, cognitive ability can become more impaired. In the feasibility study included in this thesis, there was no global cognitive exam to control for global cognitive changes. LOT was originally introduced to act as a more accurate assessment of learning as it considers all 5 learning trials. It may be that verbal memory and in particular, LOT, a focus of increased learning is an aspect affected by tDCS (Can et al., 2015). Alternatively, given the results are taken from a pilot feasibility study and not adequately powered, it may be learning is one of the early effects of tDCS treatment in MDD and could be an area of future interest.

There are also differences reported in relation to monotherapy or augmentation (Keefe et al., 2014). This group were all engaged in a first line treatment, either antidepressant or therapy and commenced tDCS as well. It was suggested that augmentation may assist in remediating any persistent cognitive alteration. This was not observed within this group. This could have been for multiple reasons, the timeframe for mood effects and cognitive effects may be different. tDCS seems to have a quicker response time on classical mood symptoms and given that some cognitive deficits

remain even in remission, it is reasonable to conclude that there is a cognitive 'lag' that remains following tDCS also.

This analysis also did not explore any group difference within MDD such as melancholic vs non-melancholic. Melancholic typically were more depressed (Zaninotto et al., 2016) and it has been identified depression (without anxiety) influences immediate recall, which is what has been assessed in this analysis (Kizilbash et al., 2002). Further, this research does not have a control group to compare so there is limited comparison statement that can be made. This would be a consideration for future research looking at this type of sample of participants.

More global cognitive improvements have been noted to have a significant change (Rock et al 2014) as well with SDMT (Smith, 1991) which investigates processing speed (McClintock et al., 2020). Other factors such as age, severity show a persistence of cognitive disturbance or non-improvement (Semkovska et al., 2019). Without a control group, it is difficult to make a distinction between these factors.

It is possible other factors that were not assessed may have been significant such as the delayed recognition. This was found to uniquely predict response of treatment for 'CBT only' in MDD in contrast to a combination treatment of CBT and anti-depressants (Kundermann et al., 2015). This supports how treatment the participants received may affect neuropsychological outcomes. The group was split in terms of treatment (57% medication, 43% CBT). There is limited research that tDCS has been shown to increase performance accuracy in delayed recognition both health control and depressed patients (Giglia et al.,2014; Salehinejad et al., 2015). Looking at more comprehensive

neuropsychological assessments, combined with untangling the group differences and treatment to gain greater understanding.

There is also potential for participants to be fatigued by the test, which could act as a limitation. Though, effort was a consideration for researchers and discussed throughout the study, there can be a negativity bias effect based on the participant perception of how they are performing in the test which can inform the results (An et al., 2017; Boone, 2009). Another potential confounding factor within the design of the study is having an assessor as the researcher who gave the tDCS treatment. As was the case for the clinical trial in this thesis. This could also lead to a bias depending on the therapeutic relationship the researcher has with the participant and may impact on the empirical nature of the data collection.

Future directions could look at different aspects of AVLT such as distractors and intrusions. Distractors is the list B of words used in between learning the trials and initial recall of words. Intrusions are words not on the list being practiced or recalled. These are examined under a different process and can provide meaningful data in the effects of tDCS (Can et al., 2015). Another consideration could be to look at affective vs non-affective AVLT word lists. There is an established evidence base for affective changes in tDCS in both healthy and MDD groups (Boggio et al., 2007; Fregni et al., 2005; Nitsche et al., 2012; Peña-Gómez et al., 2011; Oliveira et al., 2013; Wolkenstein & Plewnia, 2013). Using these together could allow for a direct comparison between hot version cold verbal memory skills to investigate any changes over time.

A more complete battery of neuropsychological assessment may also help to explain these results. It has been common to see a reduced response in verbal memory at the point of remission because of

antidepressant treatment (Bernhardt, Klauke and Schroder, 2019) and tDCS treatment (McClintock et al, 2020) and to further explore age, severity and treatments as moderators.

The SDS compiles of 3 scores for social, home and work life. Each of these could be individually affected by MDD and equally respond in different ways to treatment. Being able to assess early responding symptoms across social functioning could be supportive and complimentary to future treatment regime. Future research could consider assessing each score on the SDS in an individual manner.

Chapter 5: Overview of Thesis Research Findings

Chapter Overview

This thesis has sought to bring together three key areas of research that add to this relatively new research topic. This chapter serves as a complete overview of the research programme I have undertaken. The chapter will include a brief overview of what at-home tDCS is, the clinical trial underpinning these projects and each project undertaken for this thesis. The discussion will be positioned with at-home tDCS as the novel procedure against the more typical clinically based tDCS. It will demonstrate the use of both quantitative and qualitative research methods to answer questions raised from the gaps in the literature for this research. Both results and findings will be discussed in relation the methodological approach and decisions. It will also include the unique position the COVID-19 pandemic has played in the research and how this could impact how we deliver this treatment and care in general for people who are depressed.

5.0 A meta-analysis of randomised controlled trials of tDCS in late-life depression

TDCS is a potential novel treatment that could be offered as an alternative first line treatment within the primary care setting. The question of whether there is efficacy and acceptability of tDCS in LLD has been addressed in Chapter 2 through Bayesian meta-analytic techniques. The effect on efficacy and acceptability in LLD remains unclear.

Anodal left DLPFC stimulation was predicted to improve symptoms associated with LLD, when compared to sham and considered acceptable in LLD. The continuous outcome measures was depression improvement expressed as a z-score and categorical measures of response and remission. For acceptability, dropout rates were calculated and expressed in percentage, and association measured as odds ratio. To assess the efficacy and acceptability, one eligibility criteria

were active vs sham tDCS randomised control trials. This posed a challenge as no tDCS RCTs specifically for LLD have been completed. The individual participant data were taken from existing trials of a wider age range (18+) which included unipolar and bipolar depression.

Using Bayesian multilevel modelling for IPD meta-analysis, treatment with tDCS was associated with a reduction of SMD = -0.14 (95% credible interval [-0.44; 0.15]) in depression scores, relative to sham tDCS, which was not statistically significant. An average effect of tDCS across studies showed 82% probability that tDCS treatment has at least a small effect (change in symptoms score < 0) in improving depressive symptoms in LLD, based on estimated posterior distribution. There was no evidence of significant main effects of age or their interactions with treatment, though samples sizes were small. There was also no significant main effect of treatment resistance or illness duration. Sensitivity analysis using a two-step IPD frequentist meta-analysis with LOCF showed similar results, with tDCS treatment associated with a reduction of -0.12 (95% confidence interval [-0.34; 0.12]).

The Bayesian analysis showed a high probability of a small reduction in the mean depression scores. The potential for an effect in reducing SMD of mood scores provide some hope tDCS could be an alternative treatment for LLD. As discussed in Chapter 2, the currently available treatments for LLD only offer a limited relief for those experiencing a depressive episode and due to limited treatments.

Results show there is potential for some effect and the full extent would not be known until a focused study is conducted using typical tDCS parameters for a specified treatment group (i.e., LLD with treatment resistance). Areas of interest to include in an RCT might be taking detailed history around participant age of onset (Van den Berg et al., 2001), current episode length (Tunvirachaisakul et al., 2018), treatment and treatment history (i.e., refractoriness of episodes, Brown et al., 2020), co-morbid physical illness (Tunvirachaisakul et al., 2018), co-morbid treatments, cerebrovascular activity (i.e. WMH) (Kim & Han, 2021), history of childhood abuse (Wielaard et al., 2018), current and

prospective cognitive profile assessment (Kumar et al., 2020), as well as other demographic information such as ethnicity (Vyas et al., 2020), social support (Werner-Seidler et al., 2017). Using a similar feasibility study to the one included in this thesis may be of benefit to focus and establish the potential to recruit an older population into a tDCS trial and look at aspects of a randomised control trial such as efficacy, side effects and acceptability assessments.

There is limited data available to fully understand efficacy of tDCS in LLD. However, use of tDCS as a clinical intervention has been successfully trialled in the older adult population for multiple different disorders such as AD and MCI (Wang et al., 2021), amyotrophic lateral sclerosis (Sivaramakrishnan et al. 2019) osteoarthritis (Ahn et al., 2018) and falls risk (Yosephi et al., 2018), in addition to a large body of research developing in healthy older adults (Indahlastari et al., 2021; Huo et al., 2021; Summers et al., 2016). This body of evidence supports the acceptability of tDCS within this late-life age group.

The efficacy and safety of different neuro-modulatory techniques have been established as a treatment approach for LLD. Particularly, TMS and ECT, among others, were found to be as promising novel treatment for treatment resistant LLD (Van Rooij, Riva-Posse & McDonald, 2020). With the limited availability of data from tDCS that is currently available, TMS research might provide some insight into the potential of tDCS.

The use of TMS as a treatment for LLD in RCTs have established suboptimal results which have been found in open label rTMS studies focused on older adults, with 31.6% reduction in depressive symptoms and 30% rate of response (Abraham et al., 2007), and 24.7% reduction of depressive symptoms and 18.6% response rate (Milev et al., 2009). It has been recognised these studies did use parameters that would be considered inferior to current guidelines (NICE 2022).

More recent RCTs have been trialling higher doses to find the most efficacious parameters, for example for 5 days per week for 4 weeks, an H1 coil was used at 18 Hz, 120% of resting motor threshold, (6012 pulses), over dorsolateral and ventrolateral prefrontal cortex regions and found this was safe to use and both tolerated well and efficacious for LLD (Kaster et al., 2018). A higher report of pain was found in the active group (16%) compared with sham (Kaster et al., 2018) and is comparable to reports of adverse events across other trials (12.4%) (Overvliet et al., 2021).

Higher doses may increase the effectiveness of tDCS. As brain atrophy is associated with the normal aging process, decreasing amounts of the tDCS current reach the brain surface due to greater brain atrophy. Suggestions of dose alterations to match the degree of atrophy may be required to achieve results that are similarly found in non-atrophied brains (Indahlastari et al., 2020). WMH increases seen in aging and later life also present an increased risk of the development of depression. Finite element methods (FEM) were employed to assess how vascular change such as WMH lesions affect the current being delivered from tDCS. What was found is both current density and percentage change between current density values generated within lesion and non-lesion areas of the brain demonstrated less current was delivered to brain tissues outside the lesion regions and this was caused by WMH (Indahlastari et al., 2021). This means both those later in life, and those with vascular risks are likely to require adjusted tDCS parameters such as future dose customisation to improve efficacy of the tDCS. It is currently unclear what the specific adjustments might be as more research is needed.

tDCS has been investigated to measure the effects of neuronal correlates in aging which may provide some insights into developing a tailored tDCS protocol specific to later life. A significant reduction in GABA level was observed following anodal tDCS (atDCS) when compared with sham tDCS, which reflects the preserved neuro-modulatory effect of atDCS in later life. In addition, resting-state functional coupling was decreased during atDCS compared with stDCS, most likely indicating

augmented efficiency in brain network functioning (Antonenko et al., 2017). As seen in working age population, interhemispheric functional coupling reduced with tDCS. In addition, unique to later life groups, it was found that an increased age correlated with higher interhemispheric connectivity. This suggests functional decoupling induced by stimulation. A further finding relates to neuroplasticity in later life, the magnitude of local plasticity induced by atDCS relates to the strength of the functional network at their baseline (Antonenko et al., 2017). More research looking at neural correlates in LLD may also be of benefit to aid the specified treatment protocols.

In addition to the portability and cost effectiveness (Priori, Hallett & Rothwell, 2009; Sauvaget et al., 2019), there is a benefit of using at-home tDCS particularly in late-life. TDCS is tolerable and has a favourable, well established safety profile (Bikson et al., 2016; Matsumoto & Ugawa, 2017) and has particularly been explored in a late-life population. It was found peak electrical fields do not differ significantly to those of younger age groups when using the established 'dose' of 1-2 mA, however the sample was small and was not powered to make any speculations of whether this dose might be effective (Thomas, Datta & Woods, 2017). It is well known in LLD, there is a preference for services via GP (Unützer et al., 2003) and if a treatment can be applied at home, it is likely to have a high acceptability rate. Taking these together, will improve the treatment adherence which can be problematic at times within psychiatry (Semahegn et al., 2020). With the increase of open label studies (Bares et al., 2019; Kurzeck et al., 2021; Martin et al., 2011) which allows for the extension or continued prescribing of the treatment (Taylor & Wainwright, 2005), the potential for a long term tDCS would be more accessible for this age group with an at-home device.

With even slight improvements in cognition impacting daily functioning (Begemann et al., 2020), it is understandable why cognition may be an interesting target area for clinical groups. Different brain functions have been examined and highlighted as potential target areas including working memory,

episodic memory, attention, and executive function (Bora et al., 2013; Rock et al., 2014; Semkovska et al., 2019).

tDCS intervention in cognitive aging has been focused on a seemingly apparent concern: remediation of cognitive decline and the findings are promising. A proposition that tDCS could indeed have remediating effects on cognition (Indahlastari et al., 2021b). Inter-individual variability on dose response and larger cohorts within studies are two main areas that may enhance cognitive remediation. An area that modulates dose response inter-individual variability is both genetic polymorphism and aging (Wiegand et al., 2016). Those with a catechol-*O*-methyltransferase (COMT) gene variation, a gene involved in cognitive process and a potential modifier in stimulation, were more responsive to tDCS, specifically COMT-val carriers (compared with COMT met/met carriers) (Hayek et al., 2021). It has been found that higher tDCS intensity does not always lead to cognitive gains and genetic polymorphisms also play a modulating role in working memory. After one session, COMT val158met genetic polymorphism predicted significant difference in working memory performance. After one month using tDCS paired with a working memory training, there was a significant interaction between the intensity of tDCS, COMT genotype and working memory task (Stephens, Jones & Berryhill, 2017).

The main limitation to the meta-analysis is the small sample of IPD that was available and then included into the analysis. Small samples can lead to a low power and jeopardise the validity and generalisability of the effectiveness. Earlier in the previous chapter, it was reported small samples can most commonly create a sampling error, leading to bias across all the reportable effect sizes with varying extent, though the mean difference was unaffected (Lin, 2018). There are other concerns with a small sample such as measurement error, range variation, imperfect construct validity of measures, artificial dichotomization of continuous measures, and others (Schmidt & Hunter, 2015). In addition, publication bias may interfere with the validity of the results. Typically,

effect size and sample size are independent from each other. However, it has been established there is a negative correlation (r = −.45 [95% CI: −.53; −.35]) between effect size and sample size which suggests a publication bias that appears to be pervasive across psychology with an inordinately high number of p values only just reaching significance (Kühberger, Fritz & Scherndl, 2014).

Lack of data within the small sample did not allow for moderator analysis in this thesis meta-analysis. In structural equation models such as Bayesian approaches, small samples can lead to estimation convergence failure, inaccurate parameter estimates and model fit statistics (Wang & Wang, 2012). There are challenges with accurate model or group comparisons, having enough flexibility to allow for examining complex associations (McCallum et al., 1999; Wolf et al., 2013). Randomisation ceases to be effective in a small sample (Schmidt & Oh, 2016). Bayesian methods have been established to well handle small sample sizes but are highly sensitive to prior distribution specifications to the extent if not well heeded, Bayesian estimates can be more biased than frequentist approaches (McNeish, 2016).

Future Directions

Undoubtedly, there is a need for more data. This means larger samples of older adults within all age randomised control trials. Being more inclusive may mean increased trial promotion within spaces this clinical group can be found, such as older adult mental health teams, increased education across primary care to provide more opportunities for people with LLD to take part in the research.

There is beginning to be dedicated RCTs to investigate tDCS within the clinically depressed population such as using high definition tDCS (HD-tDCS) and is a novel approach for this age group (Wong et al., 2019), mentioned in the earlier chapter. An importance placed on identifying key moderating factors such as age of onset, concurrent treatments, and wider subgroups such as levels of severity, might the areas to begin focus. Secondary to this, would be addressing the impact of

physical and cognitive impairments as well as functional abilities. Finally, investigation into neural and neuropsychological correlates using latest technology such as concurrent imaging techniques.

Subgroups can be considered such as treatment resistant LLD, as well patients with remitted LLD. This group can expand the current knowledge base on the longevity of the treatment as well as recovery pathway on symptomology, and neurocognitive processes.

One aspect to consider on reporting future trials would be using CONSORT or other standardised methods of reporting should be encouraged, as this will ensure a good standard of reporting practice.

5.1 Investigating the feasibility and acceptability of at-home tDCS, using a new paradigm for qualitative analysis of acceptability

A working definition of acceptability has been proposed to understand this complex construct, "*a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention*" (Sekhon, Cartwright & Francis, 2017, p. 4).

Qualitative research involves the investigation in a methodical process to acquire new knowledge, to understand people's experiences, seek to make meaning or access meaning of those experiences, (Curry, Nembhard & Bradley, 2009; Hibbett et al., 2014; Willig, 2019). Qualitative approaches are expanded on in Chapter 3.

tDCS is highly acceptable as a treatment for MDD within clinical settings (Moffa et al., 2020) and can be conducted by the participant at home which is known as at-home tDCS (Alonzo et al., 2019). Until now, the acceptability of tDCS within depressed clinical groups has been understood in the context of quantitative measures such as drop out, all-cause drop out and discontinuation measures (Moffa et al., 2020; Mutz et al., 2018, 2019; Razza et al., 2020; Zhang et al., 2021). It is suggested with low dropout rates, as found with tDCS in this group, this would imply a high rate of acceptability.

There has not been any qualitative research to understand the patient perspective of acceptability on the use of at-home tDCS in depression. The research conducted in this thesis used the following question in a series of pre-defined categories related to this topic: *How do patients with depression describe the acceptability of using a novel treatment, at-home tDCS?*

The pre-defined categories will include acceptability as an overall concept, helpfulness, side effects, effort and burden, ethicality, self-efficacy and recommendation, and design (Sekhon, Cartwright & Francis, 2017). The qualitative analysis provides a thematic review of Sekhon's (2017) pre-identified categories through a standardised set of questions, conducted as semi-structured interviews, and allowed to draw some nuances around the treatment, which will be discussed in more detail below.

Four overarching themes were identified: (**1)** Side effects, **(2)** Effectiveness **(3)** Time commitment **(4)** Support, feeling held, contained.

The subthemes were 1.1. Physical sensation of the treatment and 1.2 side effects from the treatment, 2.1 Expectation of tDCS as a treatment, 2.2 Recovery & enhancement: the extent of the effectiveness, 2.3 Un/certainty and novelty. Following theme 3 and 4 were the following subthemes: 3.1 An everyday commitment, 3.2 the convenience of having sessions at home, improving acceptability (gaining time), 4.1 Feeling connected by daily visits by the same person 4.2 Being observed feels safe versus anxiety provoking.

In atypical enquiry of acceptability quantitative binary data has been taken which informs if a participant drops out of the study. If feedback is provided, this can give some information around acceptability and tolerability. Otherwise, it is assumed as an all cause non-acceptable/tolerable intervention. In relation to the first theme (side effects), we were able to identify a nuance between typical side effects and a new physical experience. This may be an important alignment to tease out to prevent the over-reporting of side effects and also to classify the reported side effects for example short lived side effects due to it being a new physical experience and side effects due to application, conduction and diffusion of the electrical current. The former is a very subjective experience and did differ from participant to participant, whereas a more practical side effect of redness seemed to relate more to ensuring the application of the apparatus was completed correctly

and could potentially resolve this side effect. In that when the user or applicator of the device has enough saline, careful attention is paid to the condition of the skin, the device is being applied to and is positioned in the correct space on the head, this side effect is fully minimised or eradicated. Having the differential experiences of side effects could also feed into a more qualitative approach to assessing and documenting 'side-effects' for tDCS and other novel non-invasive brain stimulations.

The second overarching theme found in the analysis was 'Effectiveness' with 3 subthemes: 2.1 Expectation of tDCS as a treatment, 2.2 Recovery & enhancement: the extent of the effectiveness, 2.3 Un/certainty and novelty.

Effectiveness is an important aspect of all treatments, with improving affective attitude and a perceived effectiveness can improve adherence to a treatment protocol (Lin et al., 2003). In an obvious sense, someone may not wish to take medication without it being effective in some form. The expectation of a treatment may have an enhancing or additive effect on the treatment (Bystad, Bystad & Wynn, 2015). Whilst the feasibility trial included in this thesis did not include a 'placebo' condition/group (which the equivalent is sham tDCS), the outcomes could be positioned for conditioning responses (Boehm et al., 2017). An implicit assumption of conditioning responses because clinical trials use effectiveness as the difference between response and placebo (or sham in this case), additivity is implied (Kirsch, 2000). Within the feasibility trial included in this thesis, there are conditions that may be considered as an additive factor which could have impacted on effectiveness. Firstly, there were concurrent treatment of antidepressants or psychotherapy. It is not clear whether concurrent treatment may have a cumulative effect and what effects these are (Alonzo et al., 2012; Loo et al., 2012; Pazdur, 2008). Further, the study was conducted with real-time supervision, which means a researcher was present for each study visit to answer questions about application of the study and study protocol, experienced side effects and any other queries

participants had related to the study. The real-time supervision allowed for real-time practical, problem solving, direct clinical supervision and regular mood monitoring as part of the safety protocol. The extent a researcher interacts with study participants depends on the trial design, and trial design can impact on the additive model in that with a standard two group study, the placebo effect is not measured directly, those with a comparison to baseline inaccurate values of the effect can be given (Boehm et al., 2017). tDCS as a treatment has, at times, shown to be difficult to replicate results, and it would be important to regularly review the perceived effectiveness alongside any clinical outcomes as well as quantitative acceptability measures. Not least because of the practical factors in with conducting tDCS which can affect results (current, electrode size and placement and duration of stimulation). There are also relevant differences such as participant individual differences such as age, anatomy and neural states and expectations have been identified as a potential for inducing inter-individual differences to responsiveness to treatment (Li, Uehara & Hanakawa, 2015).

The third overarching theme is associated with time commitment, mainly related to physically taking part in the tDCS sessions. The subthemes 3.1 An everyday commitment, 3.2 the convenience of having sessions at home, improving acceptability (gaining time). An element of the study requires allocating time for required daily sessions which are 5 x weekly, this then drops to 2x weekly, though it is comparable to currently available treatments. The study also required an overall commitment of 6 weeks. The second subtheme of the main theme: time commitment relates to the convenience of having sessions at home. This was a positive aspect of improving acceptability as there was a perspective of gaining time either by not having to go out to the GP to get a prescription, then to a pharmacy or waiting for home delivery. With conventional therapy, patients would be required to attend a therapy clinic and sessions are typically 1-hour sessions, which are longer than tDCS for depression, at 30 mins. Both options entails waiting for GP services at some point either for

prescription or referral, and currently it is not clear the waiting times to access a GP, but it can be up to 3 weeks in the UK (Thorlby, Gardner & Turton, 2019). For therapies, a waiting list that can be as long as 18 months (NHS England, 2015). Following the COVID-19 pandemic, eHealth interventions were promoted to address both old and new concerns with access and wait times to therapy (Bennett et al., 2020). An eHealth approach has been taken in the feasibility trial to conduct at-home tDCS remotely which may also increase the sense of added time as prior to the COVID-19 pandemic, the feasibility trial had a protocol in place for a researcher to be present at the participant home, which is unknown on how this may have impacted time commitment.

The fourth overarching theme was "Support, feeling held and contained". Three subthemes were developed. The first relates to 'Feeling connected by daily visits by the same person'. The latter two subthemes describe a dichotomous experience of being observed: 4.21 for most was positive, felt safe and 4.22 for some was anxiety provoking. This describes the polarities of having someone available on a one-to-one level via teleconferencing can be incredibly reassuring as it is intrusive. The uniqueness of this study is patients had real-time supervision with a professional/researcher. Not only is this uncommon in this type of research, but it was also offering a secondary therapeutic environment for which participants can request support in real time. With perceived need and utilisation of available services having a strong association (Roberts et al., 2018), it is also a variable that is not well controlled for, given each participant may require different levels of support. Support was also not limited to resolving technical or practical issues with the device, it extended to practical health advice, sleep hygiene, anxiety management and other generic queries, which were presented and reviewed with the chief investigator. In addition, a summary was provided to the GP, to which the GP also followed up on certain queries with the participants. To that end, it was difficult to extrapolate that acceptability is merely from having the device as a treatment, given the design involved a tailored and multifactorial approach to treating the participants. Though, effectiveness was another theme that was clear in the analysis and is closely tied to acceptability as a concept. The

sense of symptoms dissipating was not the only theme under effectiveness that was under consideration for participants. With the device being novel, there came a level of expectation that all experienced symptoms would be managed by this device within the treatment time (of 6 weeks). Or in the converse, an uncertainty of its' effect. On their own, the themes bring a new insight into the understanding of acceptability within this patient group, largely who were classed as remitted at the time of interviewing (V21, classed as end of treatment and at V23, 6 months after treatment).

Placing these themes in the context of a new acceptability framework by Sekhon et al., (2017) has helped to highlight what aspects might be prioritised by patients. In this study, there was not a healthy control group, but this would also add another dimension, as would acceptability of the health care professionals facilitating the device.

The first limitation is the lack of a prospective and concurrent interview, as proposed by Sekhon et al. (2017). The participants were given an opportunity to offer some thoughts on the expectation of the study prior to commencing treatment in form of a survey. However, an interview may have been able to tease out some of the more nuanced points around the participant perceived expectations. A concurrent acceptability review would have allowed for real time alterations to maximise the potential learning around acceptability of this novel treatment.

The was no formal debrief following the completion of the data collection. This may have assisted in the development of themes and given an opportunity to clarify and follow up with more questions on areas that might be considered unclear by the research team. Whilst an informal discussion was completed initially after the interviews and within the team discussion of theme development, a formal system of 'interviewing the investigator' may have supported, evaluate and verify initial hunches and address any authenticity biases (Frels & Onwuegbuzie, 2012) Having a formal debrief system can also help to address any unanticipated emotions that may arise (Scott, 1997).

Data in written form was not included in this analysis. This may have enhanced the knowledge and maximised the data provided by the participants. It is conceivable that new or other's themes could have emerged from this data, especially given the written feedback was not in the presence of a researcher. A claim of enhanced validity is made when combining data in this way, though some critical issues are raised such as the clarity in the purpose, basis and focus of the study methods, maintaining an awareness for the limitations of the methodologies, possible variations in error measures and generalisation (Bazeley, 2004).

The researcher who completed the intervention also completed the semi-structured interview. This has the potential for bias. Participants may not feel comfortable to disclose what might have made them unhappy about the study or withheld information for not wanting to disrupt the 'therapeutic relationship' they have with researcher. Appropriately applying the debrief method could aid to address any potential biases that may be present with the researcher and may reduce any unforeseen challenges the researcher might develop with instrumentation of the interviews (Chenail, 2011).

Incorporating prospective interviewing and concurrent review through a questionnaire and/or interview will provide critical real time information to allow for a study to confidently report the success of its' process around acceptability. It may further impact the overall attrition rate both positively and negatively depending on the outcomes and would require careful consideration of the benefits and drawbacks at study level. Consider a formal debrief process to be in place prior to the commencement of the study. This will allow for the researcher to appropriately develop their skills, especially for novices and address any biases that may be present. Consider if and how to maximise the data collected. If it is not feasible to combine methods, consider completing separate analyses.

5.2 The neurocognitive assessment of depression following tDCS treatment using auditory verbal learning test

It is well recognised MDD has a cognitive component, with decreased concentration and focus part of the diagnostic criteria (APA, 2013). Cold cognition, information processed that is not emotionally influenced, has been an area of interest in depression research as it has been shown to predict poor response to treatment (Allott et al., 2016) and unresolved cognition impedes recovery (Groves, Douglas & Porter, 2018). AVLT (Rey, 1964) was used to assess measures of verbal learning in MDD at baseline (classed as V1 prior to tDCS), and then over 3 further timepoints (post tDCS on V1, V10 and V21 - end of treatment). It was hypothesised AVLT total learning and LOT would improve over time. Age, gender, education, and IQ, the change in 17-item HAMD (Hamilton, 1960) and SDS (Sheehan and Sheehan, 2008) were included as co-variates in a repeated measures ANCOVA. An exploratory review of STPR will follow earlier hypotheses (i.e., if total learning improves, STPR will improve).

There were no significant effects found of time on total learning (df= 3,54, F= .186, p= .905), LOT, (df= 3,54, F= 1.355, p= .266) and STPR (df= 3,54, F= .673, p= .573). The co-variates of age, gender, education, IQ, percentage change of HAMD and SDS were not significant in moderating the results. The results did not meet the hypothesis and contrasts what was expected in previous studies (McClintock et al., 2020). They are in line with some previous non-significant changes over time following tDCS (Martin et al., 2018). There have been mixed results found regarding the effect of tDCS on cognition. Cognitive function is not enhanced with tDCS within the working age depressed population (Martin et al., 2018). In assessing key cognitive domains, including global cognition, executive function, verbal memory, attention, and working memory, individual participant data was analysed to show no beneficial effect of tDCS. An unexpected reduction in performance gains were found in SDMT (Smith, 1991) and DSST (Wechsler, 1955) following a course of tDCS. This was most prominent in subgroups, such as women and MDD, where effects were predicted to be greater. A lower cognitive global baseline also saw a greater effect. There was an overall improvement in both

groups (MDD and control), which may be explained by practice effect over performance reduction (Martin et al., 2018). This may suggest using different tests or a battery of cognitive assessments aid in highlighting what changes over time occur. One difference which could explain the difference found in larger RCT study (McClintock et al., 2020) which were not included in larger IPD data, was this sample included treatment resistant patients. Potentially, there is a different profile and recovery marker in cognitive change in this group.

Processing speed improvement across groups were also seen in Moreno et al (2020). In contrast to Martin et al (2018) IPD analysis, an increased performance was seen in verbal fluency, when compared to placebo, but no difference when compared with escitalopram. Specifically in the responder subgroup, a moderate effect was seen in both tDCS and escitalopram, outperforming placebo in verbal fluency (Moreno et al., 2020). This may suggest antidepressant treatment regardless of which treatment it is, successfully improves processing speed compared to placebo groups. Processing speed may also be one of the first changes that is seen in depression response and recovery.

This chapter reviews the short-term memory aspects of the AVLT and did not include long term recall of verbal fluency. It has been identified young adult's long-term recall significantly increases with multi session tDCS and older adults found an overall increased recall performance. Lower baseline learning ability was also suggestive of a countenance of memory impairment (Perceval et al., 2020). These effects held after one week and after three months, which means this is not only explained by 1 session overnight consolidation (Perceval et al., 2020).

In contrast to selective findings, a recent study by McClintock et al., (2020) found global cognitive tDCS-induced changes following both low dose and high tDCS. Initially, there seemed to be verbal learning and processing speed improvements across high and low doses with bipolar patients. However, in sub analyses, it was found that a specific genotype: BDNF Val66met Val/Val, carriers of this gene found to have a higher improvement (McClintock et al 2020).

A recent umbrella review of meta-analyses investigating neurocognitive measures following tDCS (Farhat et al., 2022). Umbrella reviews have wide eligibility criteria to incorporate the maximum number of meta-analyses including sham-controlled trials. As such, it found a wide range across age, multiple patient groups, included studies that were both anodal and cathodal based stimulation (Farhat et al., 2022). This review found 11 of the included meta-analyses had low (n=2) or critically low (n=9) quality. This indicates the need to review in the way meta-analyses are conducted and consideration for separate analyses for conditions grouped under neuropsychiatric conditions (i.e., depression, separated from schizophrenia) and to extend this further to Research Domain Criteria (RDoC) framework such as Bartl et al., (2020) has (Farhat et al., 2022).

The strength in the design of the study was to conduct the neuropsychology online using video conferencing software. Every effort went to ensuring good connections, that the researcher was well heard, and participants understood A meta-analysis assessing the effect of video conferencing on the assessment scores of a wide range of test and within multiple groups including healthy and clinical groups found some test score were 1/ 10^{th} lower when performed on video conferencing compared to in person (Brearly et al., 2017). Although, digit span, verbal fluency and list learning did not differ assessments as they are verbally mediated, and overall, only one test showed significant effect to the use of videoconferencing which involved word retrieval did see this deficit (Brearly et al., 2017). Further, disruption to the tests due to technology (connection issues) was not a source of variability in scoring (Brearly et al., 2017).

A main consideration when using teleconferencing to conduct neuropsychological assessment was due to the on-going COVID-19 pandemic during the collection of data in the feasibility trial. This led to a paradigm shift and the expansion of these methods across research and clinical settings (Hewitt & Loring, 2020; Parsons & Duffield, 2020). Further considerations of the patient population needs, and diagnostic differences were required (Hewitt et al., 2020).

Benefits of teleconferencing include a reduction of commute times or disrupted routines and allows for flexibility to conduct other assessments which ultimately reduces assessment fatigue (York et al., 2021). It allowed for assessments to continue without the need for interruption due to stay-at-home orders or 2 metre social distancing (Hewitt et al., 2020).

In this study, 2 different researchers conducted the assessment using teleconferencing. Extending the use of technology in cognitive and neuropsychological assessment may have comparable validity and reliability. Increased standardisation and a reduction in errors and interpretation may be another benefit (Parsey & Schmitter-Edgecombe, 2013).

There is some discussion around the age of onset in depression consisting of a larger factor to overall cognitive deficits as part of this presentation (Bora et al., 2014). Other factors such as age, severity show a persistence of cognitive disturbance or non-improvement (Semkovska et al., 2019).

The sample did not explore subgroups such as of cognitively impaired and not impaired and was assessed at the earliest point in remission post treatment. A delay in neuropsychological remediation may be possible and a follow up assessment may be of benefit. The current analysis provides an immediate response on neuropsychological markers in AVLT following a course of tDCS. However, neurocognitive deficits have been present in as much of 52% (Gu et al., 2016) of MDD

patients and continued to be present as long as 2 years after remission (Jaeger et al., 2006). Group differences in tDCS response may have impacted on the significance of the results. A systematic review and analysis show, compared to healthy controls, remitted patients had significantly worse scores across neuropsychological domains of attention, learning and memory, working memory. Partially remitted patients were found to perform significantly worse than remitted patients (Grützner et al., 2019). A small cluster of patients included in the analysis may be classed as partially remitted, as measured by HAMD scores. This could have influenced the overall analysis.
In terms of clinical subgroups, verbal fluency and psychomotor speed differentiate melancholic with atypical patients, with melancholic patients performing worse (Bosaipo et al., 2016). When compared with healthy controls both subgroups were impaired across several domains, and melancholic patients had greater and more extensive neurocognitive impairments (Bosaipo et al., 2016).

The analysis was exploratory and as such, the results are not generalisable. Under the feasibility clinical trial, neuropsychological testing was an exploratory outcome, the analysis was not powered for neurocognitive analysis and did not include healthy controls. All these factors will act as limitations to the results.

The AVLT (Rey, 1964) assessment presented in this thesis was one example of neurocognitive assessment. There are a wide range of assessment that assess memory, attention, executive functioning (Lezak et al., 2004) and often it is demonstrated in the literature that a battery of assessments is conducted alongside the tDCS treatment (Brunoni et al., 2016b; Moreno et al., 2020).

Completing RCTs with healthy controls are included for at-home tDCS treatment and neuropsychological assessment for comparison. Further, overall survival and time to progression can be conducted under RCT (Pazdur, 2008). The consideration of included multiple arms to the

study which includes a tDCS only arm as all participants were engaged in some form of treatment (either antidepressants or psychotherapy) as concurrent treatments can be a confounder to survival analysis (Pazdur, 2008). Furthermore, to assess if concurrent treatments have any impact on cognitive results. Combine this with severity and length of illness may provide critical insight into the understanding of the neurocognitive processes in MDD and to what, if any extent tDCS can remediate that in specific subsets of this clinical group. Benefits of understanding cognitive remediation following tDCS treatment could impact cost analysis and effectiveness (Glen et al., 2020). This would also support acceptability under Sekhon et al., (2017) acceptability framework under opportunity cost.

5.3 COVID-19 and major depressive disorder

One consideration throughout the feasibility study was the presence or prior experience of COVID-19 among our participants. At the time of writing this thesis, COVID-19 is well understood and clinically known as SARS-Cov-2. COVID-19 is a serious acute respiratory syndrome caused by a novel coronavirus, which led to a pandemic. COVID-19 appears to activate antiviral and pro-inflammatory response that is uncontrolled through cytokine release (Yang et al., 2020). Due to the ferocity of the spread of this contagion, governments around the world called for national mandated lockdowns, the introduction of personal protective equipment such as masks to limit the spread. One obvious repercussion from these measures were an increase in social isolation and loneliness which can have a direct relationship with the risk of developing MDD or exacerbating a current episode (Elmer, Mepham & Stadtfeld, 2020; Sommerlad et al., 2021), through a cycle of stress, anxiety, and other psychological concerns (Röhr et al., 2020).

Over the 2 years of the pandemic so far, the relationship between neuropsychiatric illness and COVID-19 has been investigated. With prevalence rates of MDD in patient with a COVID-19 infection

at 38% and insomnia a precursor symptom to depression at 48%, this risk is considerable (Lui et al., 2021). Some research suggests that the development of MDD as a direct resultant from COVID-19 may be limited to no or a mild risk but has an overall effect of worsening an established diagnosis is present (Bourmistrova et al., 2022). The severity of the COVID-19 factors where an activation of the immune system has occurred and the presence of a 'cytokine storm' induces indoleamine 2,3-dioxygenase significant activity (Boucas, Rheinheimer & Lagopoulos, 2022). This in turn increase kynurenine which metabolises in the brain causing chemokine production and long-term impairment in the brain (Boucas, Rheinheimer & Lagopoulos, 2022). The process has been posited to increase the risk of developing depression (Boucas, Rheinheimer & Lagopoulos, 2022). Further, systemic inflammation may play a role in the elevated cytokine levels and inflammation is also a convergence point for cognitive decline and MDD (e Silva et al., 2022).

Other influences have been theorised suggest as hippocampal involvement. Previous studies have suggested negative effect on spatial memory and learning due to respiratory illness such as influenza as this causes CA1 and CA3 neuronal reduction (Ritchie, Chan & Watermeyer, 2020). Though COVID-19 does rapidly invade the central nervous system it appears to be more focal in temporal regions (Morgello, 2020). If brain regions are compromised having a depression following COVID-19, this may exacerbate the presenting damage (Mohammadkhanizadeh & Nikbakht, 2021).

With this information, it may be that there is a higher presence of MDD following the recent pandemic, making novel treatments that are also accessible to patients even more important. Non-invasive neuro-modulatory techniques may lend themselves well to assist with neuroimmune modulation and therefore may be a target treatment option for any subsequent neuropsychiatric illness (Baptista et al., 2020).

Some predictors for the development of neuropsychiatric illness have been identified which may aid in research purposes when considering COVID-19 and its' overall effects in novel treatment studies. The predictors include being female (Mazza et al., 2020). Gender is particularly important because whereas females are likely to have increased risk to long term complications of a COVID-19 infection, they are less likely to have severe short term COVID-19 complications (Bucciarelli et al., 2022). Thus, less likely to experience a severe cytokine storm due to the protective properties of oestrogen (Bucciarelli et al., 2022). A previous positive diagnosis (of MDD), with outpatients showing increased anxiety and sleep symptoms (Mazza et al., 2020). Both of have a bidirectional relationship with MDD (Alvaro, Roberts & Harris, 2013). There is also an inverse correlation with hospitalisation and MDD symptomology (Mazza et al., 2020). Age was also factor with younger patients reporting higher levels of depressive symptoms (Mazza et al., 2020). Research continues to understand the phenomena of neuropsychiatric illness following COVID-19 and treatment that may best suit it. tDCS may have some strengths as a neuro-modulatory treatment (Baptista et al., 2020). It has shown early efficacy in successfully treating neuropsychiatric symptoms post COVID-19 (Shinjo et al., 2020; Gòmez et al., 2021). It can be provided at home and will supersede any clinic-based treatment in an active phase of the pandemic (Caulfield & George, 2020).

References:

Abraham, G., Milev, R., Lazowski, L., Jokic, R., du Toit, R., & Lowe, A. (2007). Repetitive transcranial magnetic stimulation for treatment of elderly patients with depression–an open label trial. *Neuropsychiatric Disease and Treatment*, *3*(6), 919. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656335/

Abramson, L. Y., Seligman, M. E., & Teasdale, J. D. (1978). Learned helplessness in humans: critique and reformulation. *Journal of Psychopathology and Clinical Science*, *87*(1). https://doi.org/10.1037/0021-843X.87.1.49

Ahern, E., Bockting, C. L., & Semkovska, M. (2019). A hot-cold cognitive model of depression: integrating the neuropsychological approach into the cognitive theory framework. *Clinical Psychology in Europe*, *1*(3), 1-35. https://doi.org/10.32872/cpe.v1i3.34396

Ahn, H., Suchting, R., Woods, A. J., Miao, H., Green, C., Cho, R. Y., ... & Fillingim, R. B. (2018). Bayesian analysis of the effect of transcranial direct current stimulation on experimental pain sensitivity in older adults with knee osteoarthritis: randomized sham-controlled pilot clinical study. *Journal of Pain Research*, *11*, 2071. https://doi.org/10.2147/JPR.S173080

Ahonen, M. (2019). Ancient philosophers on mental illness. *History of psychiatry*, *30*(1), 3-18. https://doi.org/10.1177/0957154X18803508

Aizenstein, H. J., Butters, M. A., Wu, M., Mazurkewicz, L. M., Stenger, V. A., Gianaros, P. J., ... & Carter, C. S. (2009). Altered functioning of the executive control circuit in late-life depression: episodic and persistent phenomena. *The American Journal of Geriatric Psychiatry*, *17*(1), 30-42. https://doi.org/10.1097/JGP.0b013e31817b60af

Albert, P. R. (2015). Why is depression more prevalent in women?. *Journal of Psychiatry & Neuroscience: JPN*, *40*(4), 219. https://doi.org/10.1503/jpn.150205

Alexopoulos, G. S. (2001). "The Depression–Executive Dysfunction Syndrome of Late Life": A Specific Target for D3 Agonists?. *The American Journal of Geriatric Psychiatry*, *9*(1), 22-29. https://doi.org/10.1176/appi.ajgp.9.1.22

Alexopoulos, G. S. (2011). Pharmacotherapy for late-life depression. *The Journal of Clinical Psychiatry*, *72*(1), e04.https://doi.org/10.4088/JCP.7085tx2cj

Alexopoulos, G. S. (2019). Mechanisms and treatment of late-life depression. *Translational Psychiatry*, *9*(1), 1-16. https://doi.org/10.1038/s41398-019-0514-6

Alexopoulos, G. S., Hoptman, M. J., Kanellopoulos, D., Murphy, C. F., Lim, K. O., & Gunning, F. M. (2012). Functional connectivity in the cognitive control network and the default mode network in late-life depression. *Journal of Affective Disorders*, *139*(1), 56-65. https://doi.org/10.1016/j.jad.2011.12.002

Alexopoulos, G. S., & Morimoto, S. S. (2011). The inflammation hypothesis in geriatric depression. *International Journal of Geriatric Psychiatry*, *26*(11), 1109-1118. https://doi.org/10.1002/gps.2672

Alexopoulos, G. S., Kiosses, D. N., Klimstra, S., Kalayam, B., & Bruce, M. L. (2002). Clinical presentation of the "depression–executive dysfunction syndrome" of late life. *The American Journal of Geriatric Psychiatry*, *10*(1), 98-106. https://doi.org/10.1097/00019442-200201000-00012

Alexopoulos, G. S., Meyers, B. S., Young, R. C., Campbell, S., Silbersweig, D., & Charlson, M. (1997). 'Vascular depression' hypothesis. *Archives of General Psychiatry*, *54*(10), 915-922. https://doi.org/10.1001/archpsyc.1997.01830220033006

Alhojailan, M. I. (2012). Thematic analysis: A critical review of its process and evaluation. *West East Journal of Social Sciences*, *1*(1), 39-47.

Allanson, F., Pestell, C., Gignac, G. E., Yeo, Y. X., & Weinborn, M. (2017). Neuropsychological predictors of outcome following traumatic brain injury in adults: a meta-analysis. *Neuropsychology review*, *27*(3), 187-201. https://doi.org/10.1007/s11065-017-9353-5

Allott, K., Fisher, C. A., Amminger, G. P., Goodall, J., & Hetrick, S. (2016). Characterizing neurocognitive impairment in young people with major depression: state, trait, or scar?. *Brain and behavior*, *6*(10), e00527. https://doi.org/10.1002/brb3.527

Alloy, L. B., Abramson, L. Y., Metalsky, G. I., & Hartlage, S. (1988). The hopelessness theory of depression: Attributional aspects. *British Journal of Clinical Psychology*, *27*(1), 5-21. https://doi.org/10.1111/j.2044-8260.1988.tb00749.x

Almathami, H. K. Y., Win, K. T., & Vlahu-Gjorgievska, E. (2020). Barriers and facilitators that influence telemedicine-based, real-time, online consultation at patients' homes: systematic literature review. *Journal of medical Internet research*, *22*(2), e16407.

Almeida, D. M., & Kessler, R. C. (1998). Everyday stressors and gender differences in daily distress. *Journal of personality and social psychology*, *75*(3), 670. https://doi.org/10.1037/0022-3514.75.3.670

Alonzo, A., Fong, J., Ball, N., Martin, D., Chand, N., & Loo, C. (2019). Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. *Journal of Affective Disorders*, *252*, 475-483. https://doi.org/10.1016/j.jad.2019.04.041

Altamura, A. C., Dell'Osso, B., Vismara, S., & Mundo, E. (2008). May duration of untreated illness influence the long-term course of major depressive disorder?. *European Psychiatry*, *23*(2), 92-96. https://doi.org/10.1016/j.eurpsy.2007.11.004

Alvaro, P. K., Roberts, R. M., & Harris, J. K. (2013). A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. *Sleep*, *36*(7), 1059-1068. https://doi.org/10.5665/sleep.2810

American Psychiatric Association, D. S., & American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5). Washington, DC: American psychiatric association. Accessed at https://doi.org/10.1176/appi.books.9780890425596

Ammons, R. B., & Ammons, C. H. (1962). The quick test (QT): provisional manual. *Psychological Reports*, *11*(1), 111-161. https://doi.org/10.1177/003329416201100106

Amr, S. S., & Tbakhi, A. (2007). Ibn Sina (Avicenna): the prince of physicians. *Annals of Saudi medicine*, *27*(2), 134-135. https://doi.org/10.5144/0256-4947.2007.134

An, K. Y., Kaploun, K., Erdodi, L. A., & Abeare, C. A. (2017). Performance validity in undergraduate research participants: A comparison of failure rates across tests and cutoffs. *The Clinical Neuropsychologist*, *31*(1), 193-206. https://doi.org/10.1080/13854046.2016.1217046

Andersen, R., & Newman, J. F. (1973). Societal and individual determinants of medical care utilization in the United States. *The Milbank Memorial Fund Quarterly. Health and Society*, 95-124. https://doi.org/10.2307/3349613

Andreas, S., Schulz, H., Volkert, J., Dehoust, M., Sehner, S., Suling, A., ... & Härter, M. (2017). Prevalence of mental disorders in elderly people: the European MentDis_ICF65+ study. *The British Journal of Psychiatry*, *210*(2), 125-131. https://doi.org/10.1192/bjp.bp.115.180463

Andreescu, C., Lenze, E. J., Dew, M. A., Begley, A. E., Mulsant, B. H., Dombrovski, A. Y., ... & Reynolds, C. F. (2007). Effect of comorbid anxiety on treatment response and relapse risk in late-life depression: controlled study. *The British Journal of Psychiatry*, *190*(4), 344-349. https://doi.org/10.1192/bjp.bp.106.027169

Antal, A., Alekseichuk, I., Bikson, M., Brockmöller, J., Brunoni, A. R., Chen, R., ... & Paulus, W. (2017). Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. *Clinical Neurophysiology*, *128*(9), 1774-1809. https://doi.org/10.1016/j.clinph.2017.06.001

Antal, A., Kincses, T. Z., Nitsche, M. A., Bartfai, O., & Paulus, W. (2004). Excitability changes induced in the human primary visual cortex by transcranial direct current stimulation: direct electrophysiological evidence. *Investigative Ophthalmology & Visual Science*, *45*(2), 702-707. https://doi.org/10.1167/iovs.03-0688

Antonenko, D., Schubert, F., Bohm, F., Ittermann, B., Aydin, S., Hayek, D., ... & Flöel, A. (2017). tDCS-induced modulation of GABA levels and resting-state functional connectivity in older adults. *Journal of Neuroscience*, *37*(15), 4065-4073. https://doi.org/10.1523/JNEUROSCI.0079-17.2017

Anyan, F. (2013). The influence of power shifts in data collection and analysis stages: a focus on qualitative research interview. *Qualitative Report*, *18*, 36.

Aparício, L. V., Guarienti, F., Razza, L. B., Carvalho, A. F., Fregni, F., & Brunoni, A. R. (2016). A systematic review on the acceptability and tolerability of transcranial direct current stimulation treatment in neuropsychiatry trials. *Brain Stimulation*, *9*(5), 671-681. https://doi.org/10.1016/j.brs.2016.05.004

Aspers, P., & Corte, U. (2019). What is qualitative in qualitative research. *Qualitative Sociology*, *42*(2), 139-160. https://doi.org/10.1007/s11133-019-9413-7

Arain, M., Campbell, M. J., Cooper, C. L., & Lancaster, G. A. (2010). What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology*, *10*(1), 1-7. https://doi.org/10.1186/1471-2288-10-67

Attride-Stirling, J. (2001). Thematic networks: an analytic tool for qualitative research. *Qualitative Research*, *1*(3), 385-405. https://doi.org/10.1177/146879410100100307

Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression: possible implications for functional neuropathology. *The British journal of psychiatry*, *178*(3), 200-206. https://doi.org/10.1192/bjp.178.3.200

Austin, M. P., Ross, M., Murray, C., O'Caŕroll, R. E., Ebmeier, K. P., & Goodwin, G. M. (1992). Cognitive function in major depression. *Journal of Affective Disorders*, *25*(1), 21-29. https://doi.org/10.1016/0165-0327(92)90089-O

Aziz, R., & Steffens, D. C. (2013). What are the causes of late-life depression?. *Psychiatric Clinics*, *36*(4), 497-516. https://doi.org/10.1016/j.psc.2013.08.001

Baddeley, A. (1992). Working memory: The interface between memory and cognition. *Journal of cognitive neuroscience*, *4*(3), 281-288. https://doi.org/10.1162/jocn.1992.4.3.281

Baddeley, A. D. (1996). The concept of working memory. *Models of short-term memory*, 1-27. https://doi.org/10.1016/B978-012554465-8/50003-X

Bailey, K. R. (1987). Inter-study differences: How should they influence the interpretation and analysis of results?. *Statistics in Medicine*, *6*(3), 351-358. https://doi.org/10.1002/sim.4780060327

Balduzzi, S., Rücker, G., & Schwarzer, G. (2019). How to perform a meta-analysis with R: a practical tutorial. *Evidence-based Mental Health*, *22*(4), 153-160. https://doi.org/10.1136/ebmental-2019-300117

Ban, T. A. (2014). From melancholia to depression: a history of diagnosis and treatment. *International Network for the History of Neuropsychopharmacology*, *19*, 2015.

Banich, M. T. (2009). Executive function: The search for an integrated account. *Current Directions in Psychological Science*, *18*(2), 89-94. https://doi.org/10.1111/j.1467-8721.2009.01615.x

Baptista, A. F., ABdR, M., Okano, A. H., Moreira, A., Campos, A. C. P., Fernandes, A. M., ... & Zana, Y. (2020). Neuromodulation and inflammatory reflex: Perspectives on the use of non-invasive neuromodulation in the management of disorders related to COVID-19. Preprint. 2020. May: 31.

Bares, M., Brunovsky, M., Stopkova, P., Hejzlar, M., & Novak, T. (2019). Transcranial direct-current stimulation (tDCS) versus venlafaxine ER in the treatment of depression: a randomized, double-blind, single-center study with open-label, follow-up. *Neuropsychiatric Disease and Treatment*, *15*, 3003. https://doi.org/10.2147/NDT.S226577

Barlow, D. H., Ellard, K. K., Sauer-Zavala, S., Bullis, J. R., & Carl, J. R. (2014). The origins of neuroticism. *Perspectives on Psychological Science*, *9*(5), 481-496. https://doi.org/10.1177/1745691614544528

Barlow, D. H., Sauer-Zavala, S., Carl, J. R., Bullis, J. R., & Ellard, K. K. (2014). The nature, diagnosis, and treatment of neuroticism: Back to the future. *Clinical Psychological Science*, *2*(3), 344-365. https://doi.org/10.1177/2167702613505532

Bartfai, A., Åsberg, M., Mårtensson, B., & Gustavsson, P. (1991). Memory effects of clomipramine treatment: relationship to CSF monoamine metabolites and drug concentrations in plasma. *Biological Psychiatry*, *30*(11), 1075-1092. https://doi.org/10.1016/0006-3223(91)90179-P

Bartl, G. J., Blackshaw, E., Crossman, M., Allen, P., & Sandrini, M. (2020). Systematic review and network meta-analysis of anodal tDCS effects on verbal episodic memory: Modeling heterogeneity of stimulation locations. *Zeitschrift für Psychologie*, *228*(1), 3. https://doi.org/10.1027/2151-2604/a000396

Basso, L., Bönke, L., Aust, S., Gärtner, M., Heuser-Collier, I., Otte, C., ... & Grimm, S. (2020). Antidepressant and neurocognitive effects of serial ketamine administration versus ECT in depressed patients. *Journal of Psychiatric Research*, *123*, 1-8. https://doi.org/10.1016/j.jpsychires.2020.01.002

Bates, S. R., & Jenkins, L. (2007). Teaching and learning ontology and epistemology in political science. *Politics*, *27*(1), 55-63. https://doi.org/10.1111/j.1467-9256.2007.00279.x

Bayne, T., Brainard, D., Byrne, R. W., Chittka, L., Clayton, N., Heyes, C., ... & Webb, B. (2019). What is cognition?. *Current Biology*, *29*(13), R608-R615. https://doi.org/10.1016/j.cub.2019.05.044

Bazeley, P. (2004). Issues in mixing qualitative and quantitative approaches to research. *Applying Qualitative Methods to Marketing Management Research*, *141*, 156. Published in: R. Buber, J. Gadner, & L. Richards (eds) (2004) *Applying qualitative methods to marketing management research*. UK: Palgrave Macmillan, pp141-156.

Beath, K. J. (2016). metaplus: An R Package for the Analysis of Robust Meta-Analysis and Meta-Regression. *R Journal*, *8*(1). https://doi.org/10.32614/RJ-2016-001

Beck, A. T. (Ed.). (1979). *Cognitive therapy of depression*. Guilford press.

Beck, A. T. (1963). Thinking and depression: I. Idiosyncratic content and cognitive distortions. *Archives of General Psychiatry*, *9*(4), 324-333. https://doi.org/10.1001/archpsyc.1963.01720160014002

Beck, A. T. (1967). Depression; Clinical. *Experimental, and Theoretical aspects*.

Beck, A. T., & Bredemeier, K. (2016). A unified model of depression: Integrating clinical, cognitive, biological, and evolutionary perspectives. *Clinical Psychological Science*, *4*(4), 596-619. https://doi.org/10.1177/2167702616628523

Beck, A. T., & Clark, D. A. (1988). Anxiety and depression: An information processing perspective. *Anxiety Research*, *1*(1), 23-36. https://doi.org/10.1080/10615808808248218

Beck, J. S. (1995). *Cognitive therapy: Basics and beyond*. New York: Guilford.

Becker, C., Kirchmaier, I., & Trautmann, S. T. (2019). Marriage, parenthood, and social network: Subjective well-being and mental health in old age. *PLoS ONE*, *14*(7), e0218704. https://doi.org/10.1371/journal.pone.0218704

Beekman, A. T., Geerlings, S. W., Deeg, D. J., Smit, J. H., Schoevers, R. S., De Beurs, E., ... & Van Tilburg, W. (2002). The natural history of late-life depression: a 6-year prospective study in the community. *Archives of General Psychiatry*, *59*(7), 605-611. https://doi.org/10.1001/archpsyc.59.7.605

Begemann, M. J., Brand, B. A., Ćurčić-Blake, B., Aleman, A., & Sommer, I. E. (2020). Efficacy of non-invasive brain stimulation on cognitive functioning in brain disorders: a meta-analysis. *Psychological medicine*, *50*(15), 2465-2486. https://doi.org/10.1017/S0033291720003670

Bell, L. V., Cornish, P., Flusk, D., Garland, S. N., & Rash, J. A. (2020). The INternet ThERapy for deprESsion Trial (INTEREST): protocol for a patient-preference, randomised controlled feasibility trial comparing iACT, iCBT and attention control among individuals with comorbid chronic pain and depression. *BMJ Open*, *10*(2), e033350. https://doi.org/10.1136/bmjopen-2019-033350

Belmaker, R. H., & Agam, G. (2008). Major depressive disorder. *New England Journal of Medicine*, *358*(1), 55-68. https://doi.org/10.1056/NEJMra073096

Ben-Ari, A., & Enosh, G. (2013). Power relations and reciprocity: Dialectics of knowledge construction. *Qualitative Health Research*, *23*(3), 422-429.

Bennett, C. B., Ruggero, C. J., Sever, A. C., & Yanouri, L. (2020). eHealth to redress psychotherapy access barriers both new and old: A review of reviews and meta-analyses. *Journal of Psychotherapy Integration*, *30*(2), 188. https://doi.org/10.1037/int0000217

Berlim, M. T., Van den Eynde, F., & Daskalakis, Z. J. (2013). Clinical utility of transcranial direct current stimulation (tDCS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Journal of Psychiatric Research*, *47*(1), 1-7. https://doi.org/10.1016/j.jpsychires.2012.09.025

Berlow, Y. A., Zandvakili, A., Carpenter, L. L., & Philip, N. S. (2019). Transcranial direct current stimulation for unipolar depression and risk of treatment emergent mania: an updated meta-analysis. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *12*(4), 1066-1068. https://doi.org/10.1016/j.brs.2019.03.025

Bernhardt, M., Klauke, S., & Schroeder, A. (2019). Longitudinal course of cognitive function across treatment in patients with MDD: a meta-analysis. *Journal of Affective Disorders*, *249*, 52-62. https://doi.org/10.1016/j.jad.2019.02.021

Bernhardt, M., Schwert, C., Aschenbrenner, S., Weisbrod, M., & Schröder, A. (2021). Longitudinal Changes of Cognitive Deficits and Treatment Outcome of Cognitive Behavioral Therapy for Major Depression. *The Journal of Nervous and Mental Disease*, *209*(5), 336-342. https://doi.org/10.1097/NMD.0000000000001301

Berryhill, M. E., Peterson, D. J., Jones, K. T., & Stephens, J. A. (2014). Hits and misses: leveraging tDCS to advance cognitive research. *Frontiers in psychology*, *5*, 800. https://doi.org/10.3389/fpsyg.2014.00800

Berstock, J. R., & Whitehouse, M. R. (2019). How to prepare and manage a systematic review and meta-analysis of clinical studies. *EFORT Open Reviews*, *4*(5), 213-220. https://doi.org/10.1302/2058-5241.4.180049

Bhandari, A., Lissemore, J. I., Rajji, T. K., Mulsant, B. H., Cash, R. F., Noda, Y., ... & Blumberger, D. M. (2018). Assessment of neuroplasticity in late-life depression with transcranial magnetic stimulation. *Journal of Psychiatric Research*, *105*, 63-70. https://doi.org/10.1016/j.jpsychires.2018.08.022

Bikson, M., Datta, A., & Elwassif, M. (2009). Establishing safety limits for transcranial direct current stimulation. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*, *120*(6), 1033. https://doi.org/10.1016/j.clinph.2009.03.018

Bikson, M., Datta, A., Rahman, A., & Scaturro, J. (2010). Electrode montages for tDCS and weak transcranial electrical stimulation: role of “return” electrode’s position and size. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, *121*(12), 1976. https://doi.org/10.1016/j.clinph.2010.05.020

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., ... & Woods, A. J. (2016). Safety of transcranial direct current stimulation: evidence-based update 2016. *Brain stimulation*, *9*(5), 641-661. https://doi.org/10.1016/j.brs.2016.06.004

Billingham, S. A., Whitehead, A. L., & Julious, S. A. (2013). An audit of sample sizes for pilot and feasibility trials being undertaken in the United Kingdom registered in the United Kingdom Clinical Research Network database. *BMC Medical Research Methodology*, *13*(1), 1-6. https://doi.org/10.1186/1471-2288-13-104

Bird, C. M. (2005). How I stopped dreading and learned to love transcription. *Qualitative inquiry*, *11*(2), 226-248. https://doi.org/10.1177/1077800404273413

Birrer, R. B., & Vemuri, S. P. (2004). Depression in later life: a diagnostic and therapeutic challenge. *American Family Physician*, *69*(10), 2375-2382.

Blatt, S. J., & Zuroff, D. C. (1992). Interpersonal relatedness and self-definition: Two prototypes for depression. *Clinical Psychology Review*, *12*(5), 527-562. https://doi.org/10.1016/0272-7358(92)90070-O

Blazer, D. G. (2009). Depression in late life: review and commentary. *Focus*, *7*(1), 118-136. https://doi.org/10.1176/foc.7.1.foc118

Blenkiron, P. (1999). Who is suitable for cognitive behavioural therapy?. *Journal of the Royal Society of Medicine*, *92*(5), 222-229. https://doi.org/10.1177/014107689909200503

Blom, M. B., Spinhoven, P., Hoffman, T., Jonker, K., Hoencamp, E., Haffmans, P. J., & van Dyck, R. (2007). Severity and duration of depression, not personality factors, predict short term outcome in the treatment of major depression. *Journal of Affective Disorders*, *104*(1-3), 119-126. https://doi.org/10.1016/j.jad.2007.03.010

Bloom, B. S. (2001). Daily regimen and compliance with treatment: fewer daily doses and drugs with fewer side effects improve compliance. *BMJ*, *323*(7314), 647. https://doi.org/10.1136/bmj.323.7314.647

Blumberger, D., Tran, L., Fitzgerald, P., Hoy, K. B., & Daskalakis, Z. J. (2012). A randomized double-blind sham-controlled study of transcranial direct current stimulation for treatment-resistant major depression. *Frontiers in Psychiatry*, *3*, 74. https://doi.org/10.3389/fpsyt.2012.00074

Bock, J. O., Luppa, M., Brettschneider, C., Riedel-Heller, S., Bickel, H., Fuchs, A., ... & König, H. H. (2014). Impact of depression on health care utilization and costs among multimorbid patients–results from the MultiCare cohort study. *PLoS ONE*, *9*(3), e91973. https://doi.org/10.1371/journal.pone.0091973

Bodner, E., Palgi, Y., & Wyman, M. F. (2018). Ageism in mental health assessment and treatment of older adults. *Contemporary perspectives on ageism*, 241-262. https://doi.org/10.1007/978-3-319-73820-8_15

Boehm, K., Berger, B., Weger, U., & Heusser, P. (2017). Does the model of additive effect in placebo research still hold true? A narrative review. *JRSM open*, *8*(3), 2054270416681434. https://doi.org/10.1177/2054270416681434

Boggio, P. S., Bermpohl, F., Vergara, A. O., Muniz, A. L., Nahas, F. H., Leme, P. B., ... & Fregni, F. (2007). Go-no-go task performance improvement after anodal transcranial DC stimulation of the left

dorsolateral prefrontal cortex in major depression. *Journal of affective disorders*, *101*(1-3), 91-98. https://doi.org/10.1016/j.jad.2006.10.026

Boggio, P. S., Rigonatti, S. P., Ribeiro, R. B., Myczkowski, M. L., Nitsche, M. A., Pascual-Leone, A., & Booth, A., Clarke, M., Dooley, G., Ghersi, D., Moher, D., Petticrew, M., & Stewart, L. (2012). The nuts and bolts of PROSPERO: an international prospective register of systematic reviews. *Systematic Reviews*, *1*(1), 1-9. https://doi.org/10.1186/2046-4053-1-2

Boku, S., Nakagawa, S., Toda, H., & Hishimoto, A. (2018). Neural basis of major depressive disorder: beyond monoamine hypothesis. *Psychiatry and Clinical Neurosciences*, *72*(1), 3-12. https://doi.org/10.1111/pcn.12604

Bolla-Wilson, K., & Bleecker, M. L. (1986). Influence of verbal intelligence, sex, age, and education on the Rey Auditory Verbal Learning Test. *Developmental Neuropsychology*, *2*(3), 203-211. https://doi.org/10.1080/87565648609540342

Boone, K. B. (2009). The need for continuous and comprehensive sampling of effort/response bias during neuropsychological examinations. *The Clinical Neuropsychologist*, *23*(4), 729-741. https://doi.org/10.1080/13854040802427803

Bora, E., Fornito, A., Pantelis, C., & Yücel, M. (2012). Gray matter abnormalities in major depressive disorder: a meta-analysis of voxel based morphometry studies. *Journal of affective disorders*, *138*(1-2), 9-18. https://doi.org/10.1016/j.jad.2011.03.049

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*, *1*(2), 97-111. https://doi.org/10.1002/jrsm.12

Borrelli, B., Sepinwall, D., Ernst, D., Bellg, A. J., Czajkowski, S., Breger, R., ... & Orwig, D. (2005). A new tool to assess treatment fidelity and evaluation of treatment fidelity across 10 years of health behavior research. *Journal of Consulting and Clinical Psychology*, *73*(5), 852. https://doi.org/10.1037/0022-006X.73.5.852

Borrelli, B. (2011). The assessment, monitoring, and enhancement of treatment fidelity in public health clinical trials. *Journal of Public Health Dentistry*, *71*, S52-S63. https://doi.org/10.1111/j.1752-7325.2011.00233.x

Borza, T., Engedal, K., Bergh, S., Benth, J. Š., & Selbæk, G. (2015). The course of depression in late life as measured by the Montgomery and Åsberg Depression Rating Scale in an observational study of hospitalized patients. *BMC Psychiatry*, *15*(1), 1-10. https://doi.org/10.1186/s12888-015-0577-8

Bosaipo, N. B., Foss, M. P., Young, A. H., & Juruena, M. F. (2017). Neuropsychological changes in melancholic and atypical depression: A systematic review. *Neuroscience & Biobehavioral Reviews*, *73*, 309-325. https://doi.org/10.1016/j.neubiorev.2016.12.014

Bosc, M. (2000). Assessment of social functioning in depression. *Comprehensive Psychiatry*, *41*(1), 63-69. https://doi.org/10.1016/S0010-440X(00)90133-0

Bosker, F. J., Hartman, C. A., Nolte, I. M., Prins, B. P., Terpstra, P., Posthuma, D., ... & Nolen, W. A. (2011). Poor replication of candidate genes for major depressive disorder using genome-wide association data. *Molecular Psychiatry*, *16*(5), 516-532. https://doi.org/10.1038/mp.2010.38

Bosman, R. C., Huijbregts, K. M., Verhaak, P. F., Ruhé, H. G., van Marwijk, H. W., van Balkom, A. J., & Batelaan, N. M. (2016). Long-term antidepressant use: a qualitative study on perspectives of patients and GPs in primary care. *British Journal of General Practice*, *66*(651), e708-e719. https://doi.org/10.3399/bjgp16X686641

Bottomley, J. M., LeReun, C., Diamantopoulos, A., Mitchell, S., & Gaynes, B. N. (2020). Vagus nerve stimulation (VNS) therapy in patients with treatment resistant depression: A systematic review and meta-analysis. *Comprehensive Psychiatry*, *98*, 152156. https://doi.org/10.1016/j.comppsych.2019.152156

Boucas, A. P., Rheinheimer, J., & Lagopoulos, J. (2022). Why severe COVID-19 patients are at greater risk of developing depression: a molecular perspective. *The Neuroscientist*, *28*(1), 11-19. https://doi.org/10.1177/1073858420967892

Bourke, C., Douglas, K., & Porter, R. (2010). Processing of facial emotion expression in major depression: a review. *Australian & New Zealand Journal of Psychiatry*, *44*(8), 681-696. https://doi.org/10.3109/00048674.2010.496359

Bourmistrova, N. W., Solomon, T., Braude, P., Strawbridge, R., & Carter, B. (2022). Long-term effects of COVID-19 on mental health: A systematic review. *Journal of Affective Disorders*, *299*, 118-125. ttps://doi.org/10.1016/j.jad.2021.11.031

Boutron I, Page MJ, Higgins JPT, Altman DG, Lundh A, Hróbjartsson A. Chapter 7: Considering bias and conflicts of interest among the included studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Bowden, J., Tierney, J. F., Simmonds, M., Copas, A. J., & Higgins, J. P. (2011). Individual patient data meta-analysis of time-to-event outcomes: one-stage versus two-stage approaches for estimating the hazard ratio under a random effects model. *Research Synthesis Methods*, *2*(3), 150-162. https://doi.org/10.1002/jrsm.45

Bowen, D. J., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., ... & Fernandez, M. (2009). How we design feasibility studies. *American Journal of Preventive Medicine*, *36*(5), 452-457. https://doi.org/10.1016/j.amepre.2009.02.002

Bower, G. H. (1981). Mood and memory. *American Psychologist*, *36*(2), 129. https://doi.org/10.1037/0003-066X.36.2.129

Boyatzis, R. E. (1998). *Transforming qualitative information: Thematic Analysis and Code Development*. Sage.

Boyce, M. B., Browne, J. P., & Greenhalgh, J. (2014). The experiences of professionals with using information from patient-reported outcome measures to improve the quality of healthcare: a systematic review of qualitative research. *BMJ Quality & Safety*, *23*(6), 508-518. https://doi.org/10.1136/bmjqs-2013-002524

Bradshaw, C., Atkinson, S., & Doody, O. (2017). Employing a qualitative description approach in health care research. *Global Qualitative Nursing Research*, *4*, 2333393617742282. https://doi.org/10.1177/2333393617742282

Bramham, C. R., & Messaoudi, E. (2005). BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. *Progress in Neurobiology*, *76*(2), 99-125. https://doi.org/10.1016/j.pneurobio.2005.06.003

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative Research in Psychology*, *3*(2), 77-101. https://doi.org/10.1191/1478088706qp063oa

Brearly, T. W., Shura, R. D., Martindale, S. L., Lazowski, R. A., Luxton, D. D., Shenal, B. V., & Rowland, J. A. (2017). Neuropsychological test administration by videoconference: A systematic review and meta-analysis. *Neuropsychology Review*, *27*(2), 174-186. https://doi.org/10.1007/s11065-017-9349-1

Bride, B. E., Abraham, A. J., Kintzle, S., & Roman, P. M. (2013). Social workers' knowledge and perceptions of effectiveness and acceptability of medication assisted treatment of substance use disorders. *Social Work in Health Care*, *52*(1), 43-58. https://doi.org/10.1080/00981389.2012.725457

Briguglio, M., Vitale, J. A., Galentino, R., Banfi, G., Dina, C. Z., Bona, A., ... & Glick, I. D. (2020). Healthy eating, physical activity, and sleep hygiene (HEPAS) as the winning triad for sustaining physical and mental health in patients at risk for or with neuropsychiatric disorders: Considerations for clinical practice. *Neuropsychiatric disease and treatment*, *16*, 55. https://doi.org/10.2147/NDT.S229206

Brinkmann, S., & Kvale, S. (2005). Confronting the ethics of qualitative research. *Journal of Constructivist Psychology*, *18*(2), 157-181. https://doi.org/10.1080/10720530590914789

Brodaty, H., Luscombe, G., Parker, G., Wilhelm, K., Hickie, I., Austin, M. P., & Mitchell, P. (2001). Early and late onset depression in old age: different aetiologies, same phenomenology. *Journal of Affective Disorders*, *66*(2-3), 225-236. https://doi.org/10.1016/S0165-0327(00)00317-7

Brooks, J. S., & Normore, A. H. (2015). Qualitative Research and Educational Leadership: Essential Dynamics to Consider When Designing and Conducting Studies. *International Journal of Educational Management*, *29*(7), 798-806. https://doi.org/10.1108/IJEM-06-2015-0083

Brown, D. W., Anda, R. F., Tiemeier, H., Felitti, V. J., Edwards, V. J., Croft, J. B., & Giles, W. H. (2009). Adverse childhood experiences and the risk of premature mortality. *American Journal of Preventive Medicine*, *37*(5), 389-396. https://doi.org/10.1016/j.amepre.2009.06.021

Brown, P. J., Roose, S. P., O'Boyle, K. R., Ciarleglio, A., Maas, B., Igwe, K. C., ... & Rutherford, B. R. (2020). Frailty and its correlates in adults with late life depression. *The American Journal of Geriatric Psychiatry*, *28*(2), 145-154. https://doi.org/10.1016/j.jagp.2019.10.005

Bruce, M. L. (2002). Depression and disability. In *Physical Illness and Depression in Older Adults* (pp. 11-29). Springer, Boston, MA. https://doi.org/10.1007/0-306-47178-7_2

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology*, *14*(8), 1133-1145. https://doi.org/10.1017/S1461145710001690

Brunoni, A. R., Boggio, P. S., De Raedt, R., Benseñor, I. M., Lotufo, P. A., Namur, V., ... & Vanderhasselt, M. A. (2014). Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. *Journal of Affective Disorders*, *162*, 43-49. https://doi.org/10.1016/j.jad.2014.03.026

Brunoni, A. R., Kemp, A. H., Shiozawa, P., Cordeiro, Q., Valiengo, L. C. L., Goulart, A. C., ... & Benseñor, I. M. (2013a). Impact of 5-HTTLPR and BDNF polymorphisms on response to sertraline versus transcranial direct current stimulation: implications for the serotonergic system. *European Neuropsychopharmacology*, *23*(11), 1530-1540. https://doi.org/10.1016/j.euroneuro.2013.03.009

Brunoni, A., Loo, C., & Nitsche, M. (2016). Safety and tolerability. In *Transcranial Direct Current Stimulation in Neuropsychiatric Disorders* (pp. 343-350). Springer, Cham.

Brunoni, A. R., Moffa, A. H., Fregni, F., Palm, U., Padberg, F., Blumberger, D. M., ... & Loo, C. K. (2016a). Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *The British Journal of Psychiatry*, *208*(6), 522-531. https://doi.org/10.1192/bjp.bp.115.164715

Brunoni, A. R., Moffa, A. H., Sampaio-Junior, B., Borrione, L., Moreno, M. L., Fernandes, R. A., … Benseñor, I. M. (2017). Trial of electrical direct-current therapy versus escitalopram for depression. *New England Journal of Medicine*, *376*(26), 2523–2533. https://doi.org/10.1056/NEJMoa1612999

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., ... & Fregni, F. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain stimulation*, *5*(3), 175-195. https://doi.org/10.1016/j.brs.2011.03.002

Brunoni, A. R., Tortella, G., Benseñor, I. M., Lotufo, P. A., Carvalho, A. F., & Fregni, F. (2016). Cognitive effects of transcranial direct current stimulation in depression: results from the SELECT-TDCS trial and insights for further clinical trials. *Journal of affective disorders*, *202*, 46-52. https://doi.org/10.1016/j.jad.2016.03.066

Brunoni, A. R., Valiengo, L., Baccaro, A., Zanao, T. A., de Oliveira, J. F., Goulart, A., ... & Fregni, F. (2013). The sertraline vs electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry*, *70*(4), 383-391. https://doi.org/10.1001/2013.jamapsychiatry.32

Bryk, A. S., & Raudenbush, S. W. (1992). *Hierarchical linear models: Applications and data analysis methods*. Sage Publications, Inc.

Bucciarelli, V., Nasi, M., Bianco, F., Seferovic, J., Ivkovic, V., Gallina, S., & Mattioli, A. V. (2022). Depression pandemic and cardiovascular risk in the COVID-19 era and long COVID syndrome: Gender makes a difference. *Trends in Cardiovascular Medicine*, *32*(1), 12. https://doi.org/10.1016/j.tcm.2021.09.009

Büchtemann, D., Luppa, M., Bramesfeld, A., & Riedel-Heller, S. (2012). Incidence of late-life depression: a systematic review. *Journal of Affective Disorders*, *142*(1-3), 172-179. https://doi.org/10.1016/j.jad.2012.05.010

Burgio, L. D., Hardin, J. M., Sinnott, J., Janosky, J., & Hohman, M. J. (1995). Nurses' acceptance of behavioral treatments and pharmacotherapy for behavioral disturbances in older adults. *Applied Nursing Research*, *8*(4), 174-181. https://doi.org/10.1016/S0897-1897(95)80393-9

Burke, S. (1998). Missing values, outliers, robust statistics & non-parametric methods. *Scientific Data Management*, *1*, 32-38.

Burman, E. (1991). What discourse is not. *Philosophical Psychology*, *4*(3), 325-342. https://doi.org/10.1080/09515089108573034

Burroughs, H., Lovell, K., Morley, M., Baldwin, R., Burns, A., & Chew-Graham, C. (2006). 'Justifiable depression': how primary care professionals and patients view late-life depression? A qualitative study. *Family Practice*, *23*(3), 369-377. https://doi.org/10.1093/fampra/cmi115

Button, K. S., Ioannidis, J. P., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S., & Munafò, M. R. (2013). Power failure: why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, *14*(5), 365-376. https://doi.org/10.1038/nrn3475

Byers, A. L., & Yaffe, K. (2011). Depression and risk of developing dementia. *Nature Reviews Neurology*, *7*(6), 323-331. https://doi.org/10.1038/nrneurol.2011.60

Byers, A. L., Yaffe, K., Covinsky, K. E., Friedman, M. B., & Bruce, M. L. (2010). High occurrence of mood and anxiety disorders among older adults: The National Comorbidity Survey Replication. *Archives of General Psychiatry*, *67*(5), 489-496. https://doi.org/10.1001/archgenpsychiatry.2010.35

Bystad, M., Bystad, C., & Wynn, R. (2015). How can placebo effects best be applied in clinical practice? A narrative review. *Psychology Research and Behavior Management*, *8*, 41. https://doi.org/10.2147/PRBM.S75670

Cabrera, L. Y., Nowak, G. R., McCright, A. M., Achtyes, E., & Bluhm, R. (2021). A qualitative study of key stakeholders' perceived risks and benefits of psychiatric electroceutical interventions. *Health, risk & society*, *23*(5-6), 217-235.

Calabritto, M. (2012). Curing melancholia in sixteenth-century medical consilia between theory and practice. *Medicina nei secoli*, *24*(3), 627-664.

Callahan, C. M., Wolinsky, F. D., Stump, T. E., Nienaber, N. A., Hui, S. L., & Tierney, W. M. (1998). Mortality, symptoms, and functional impairment in late-life depression. *Journal of General Internal Medicine*, *13*(11), 746-752. https://doi.org/10.1046/j.1525-1497.1998.00226.x

Calvert, S. C., & McMahon, R. J. (1987). The treatment acceptability of a behavioral parent training program and its components. *Behavior Therapy*, *18*(2), 165-179. https://doi.org/10.1016/S0005-7894(87)80040-0

Cambridge, O. R., Knight, M. J., Mills, N., & Baune, B. T. (2018). The clinical relationship between cognitive impairment and psychosocial functioning in major depressive disorder: A systematic review. *Psychiatry Research*, *269*, 157-171. https://doi.org/10.1016/j.psychres.2018.08.033

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G. M. (2004). Lower hippocampal volume in patients suffering from depression: a meta-analysis. *American Journal of Psychiatry*, *161*(4), 598-607. https://doi.org/10.1176/appi.ajp.161.4.598

Cao, B., Zhu, J., Zuckerman, H., Rosenblat, J. D., Brietzke, E., Pan, Z., ... & McIntyre, R. S. (2019). Pharmacological interventions targeting anhedonia in patients with major depressive disorder: a systematic review. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *92*, 109-117. https://doi.org/10.1016/j.pnpbp.2019.01.002

Cape, J., Whittington, C., Buszewicz, M., Wallace, P., & Underwood, L. (2010). Brief psychological therapies for anxiety and depression in primary care: meta-analysis and meta-regression. *BMC Medicine*, *8*(1), 1-13. https://doi.org/10.1186/1741-7015-8-38

Carlin, J. B. (1992). Meta-analysis for 2× 2 tables: a Bayesian approach. *Statistics in Medicine*, *11*(2), 141-158. https://doi.org/10.1002/sim.4780110202

Carman, K. L., Dardess, P., Maurer, M., Sofaer, S., Adams, K., Bechtel, C., & Sweeney, J. (2013). Patient and family engagement: a framework for understanding the elements and developing interventions and policies. *Health Affairs*, *32*(2), 223-231. https://doi.org/10.1377/hlthaff.2012.1133

Carr, C. P., Martins, C. M. S., Stingel, A. M., Lemgruber, V. B., & Juruena, M. F. (2013). The role of early life stress in adult psychiatric disorders: a systematic review according to childhood trauma subtypes. *The Journal of Nervous and Mental Disease*, *201*(12), 1007-1020. https://doi.org/10.1097/NMD.0000000000000049

Carter, S. L. (2007). Review of recent treatment acceptability research. *Education and Training in Developmental Disabilities*, 301-316.

Carvalho, J. P., & Hopko, D. R. (2011). Behavioral theory of depression: Reinforcement as a mediating variable between avoidance and depression. *Journal of Behavior Therapy and Experimental Psychiatry*, *42*(2), 154-162. https://doi.org/10.1016/j.jbtep.2010.10.001

Casaletto, K. B., & Heaton, R. K. (2017). Neuropsychological assessment: Past and future. *Journal of the International Neuropsychological Society*, *23*(9-10), 778-790. https://doi.org/10.1017/S1355617717001060

Caspi, A., Hariri, A. R., Holmes, A., Uher, R., & Moffitt, T. E. (2010). Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *American Journal of Psychiatry*, *167*(5), 509-527. https://doi.org/10.1176/appi.ajp.2010.09101452

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., ... & Poulton, R. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science*, *301*(5631), 386-389. https://doi.org/10.1126/science.1083968

Castleberry, A., & Nolen, A. (2018). Thematic analysis of qualitative research data: is it as easy as it sounds? *Currents in Pharmacy Teaching and Learning*, *10*(6), 807-815. https://doi.org/10.1016/j.cptl.2018.03.019

Caulfield, K. A., & George, M. S. (2020). Treating the mental health effects of COVID-19: The need for at-home neurotherapeutics is now. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *13*(4), 939-940. https://doi.org/10.1016/j.brs.2020.04.005

Chachamovich, E., Fleck, M., Laidlaw, K., & Power, M. (2008). Impact of major depression and subsyndromal symptoms on quality of life and attitudes toward aging in an international sample of older adults. *The Gerontologist*, *48*(5), 593-602. https://doi.org/10.1093/geront/48.5.593

Chakrabarty, T., Hadjipavlou, G., & Lam, R. W. (2016). Cognitive dysfunction in major depressive disorder: assessment, impact, and management. *Focus*, *14*(2), 194-206. https://doi.org/10.1176/appi.focus.20150043

Chalmers, I., Bracken, M. B., Djulbegovic, B., Garattini, S., Grant, J., Gülmezoglu, A. M., ... & Oliver, S. (2014). How to increase value and reduce waste when research priorities are set. *The Lancet*, *383*(9912), 156-165. https://doi.org/10.1016/S0140-6736(13)62229-1

Chang-Quan, H., Xue-Mei, Z., Bi-Rong, D., Zhen-Chan, L., Ji-Rong, Y., & Qing-Xiu, L. (2010). Health status and risk for depression among the elderly: a meta-analysis of published literature. *Age and Ageing*, *39*(1), 23-30. https://doi.org/10.1093/ageing/afp187

Chapman, D. P., & Perry, G. S. (2008). Peer reviewed: depression as a major component of public health for older adults. *Preventing Chronic Disease*, *5*(1).

Charlton, R. A., Lamar, M., Zhang, A., Ren, X., Ajilore, O., Pandey, G. N., & Kumar, A. (2018). Associations between pro-inflammatory cytokines, learning, and memory in late-life depression and healthy aging. *International Journal of Geriatric Psychiatry*, *33*(1), 104-112. https://doi.org/10.1002/gps.4686

Charmaz, K., & Smith, J. (2003). Grounded theory. *Qualitative psychology: A Practical Guide to Research Methods*, *2*, 81-110.

Chase, H. W., Boudewyn, M. A., Carter, C. S., & Phillips, M. L. (2020). Transcranial direct current stimulation: a roadmap for research, from mechanism of action to clinical implementation. *Molecular psychiatry*, *25*(2), 397-407.

Chen, P., Furukawa, T. A., Shinohara, K., Honyashiki, M., Imai, H., Ichikawa, K., ... & Churchill, R. (2014). Quantity and quality of psychotherapy trials for depression in the past five decades. *Journal of Affective Disorders*, *165*, 190-195. https://doi.org/10.1016/j.jad.2014.04.071

Chenail, R. J. (2011). Interviewing the investigator: Strategies for addressing instrumentation and researcher bias concerns in qualitative research. *Qualitative Report*, *16*(1), 255-262.

Cheung, M. W. L., & Vijayakumar, R. (2016). A guide to conducting a meta-analysis. *Neuropsychology Review*, *26*(2), 121-128. https://doi.org/10.1007/s11065-016-9319-z

Chevance, A., Ravaud, P., Tomlinson, A., Le Berre, C., Teufer, B., Touboul, S., ... & Tran, V. T. (2020). Identifying outcomes for depression that matter to patients, informal caregivers, and health-care professionals: qualitative content analysis of a large international online survey. *The Lancet Psychiatry*, *7*(8), 692-702. https://doi.org/10.1016/S2215-0366(20)30191-7

Chiseri-Strater, E. (1996). and Reflexivity in Case Study and Ethnographic. *Ethics and Representation in Qualitative Studies*, *1*, 115-133. Available from: https://files.eric.ed.gov/fulltext/ED400543.pdf#page=147

Cipolotti, L., & Warrington, E. K. (1995). Neuropsychological assessment. *Journal of Neurology, Neurosurgery, and Psychiatry*, *58*(6), 655. https://doi.org/10.1136/jnnp.58.6.655

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., ... & Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. *Focus*, *16*(4), 420-429. https://doi.org/10.1176/appi.focus.16407

Clark, L., & Elliott, S. N. (1988). The influence of treatment strength information on knowledgeable teachers' pretreatment evaluations of social skills training methods. *Professional School Psychology*, *3*(4), 241-251. https://doi.org/10.1037/h0090567

Clarke, V., & Braun, V. (2017). Thematic analysis. *The Journal of Positive Psychology*, *12*(3), 297-298. https://doi.org/10.1080/17439760.2016.1262613

Cohen, L., Manion, L., & Morrison, K. (2002). *Research Methods in Education*. Routledge.

Çökmüş, F. P., Özkan, H. M., Sücüllüoğlu-Dikici, D., Aşçibaşi, K., Alçi, D., Altunsoy, N., ... & Aydemir, Ö. (2021) The Assessment of Cognitive Dysfunction in Major Depressive Disorder: A 16-Week Prospective Case-Control Study. *Psychiatry and Clinical Psychopharmacology, 31*(1), 25-33. https://doi.org/10.5152/pcp.2021.20148

Cole, M. G., & Dendukuri, N. (2003). Risk factors for depression among elderly community subjects: a systematic review and meta-analysis. *American Journal of Psychiatry*, *160*(6), 1147-1156. https://doi.org/10.1176/appi.ajp.160.6.1147

Correia, A. F., & Osorio, I. C. (2014). The Rey Auditory Verbal Learning Test: Normative Data Developed for the Venezuelan Population. *Archives of Clinical Neuropsychology*, *29*(2), 206-215. https://doi.org/10.1093/arclin/act070

Crabb, R., & Hunsley, J. (2006). Utilization of mental health care services among older adults with depression. *Journal of Clinical Psychology*, *62*(3), 299-312. https://doi.org/10.1002/jclp.20231

Crabtree, B., & Miller, W. (1999). A template approach to text analysis: Developing and using codebooks. In B. Crabtree & W. Miller (Eds.), Doing qualitative research (pp. 163-177.) Newbury Park, CA: Sage.

Craig, P., Dieppe, P., Macintyre, S., Michie, S., Nazareth, I., & Petticrew, M. (2008). Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*, *337*. https://doi.org/10.1136/bmj.a1655

Crawford, J. R., Stewart, L. E., & Moore, J. W. (1989). Demonstration of savings on the AVLT and development of a parallel form. *Journal of Clinical and Experimental Neuropsychology*, *11*(6), 975-981. https://doi.org/10.1080/01688638908400950

Creutzfeldt, O. D., Fromm, G. H., & Kapp, H. (1962). Influence of transcortical dc currents on cortical neuronal activity. *Experimental Neurology*, *5*(6), 436-452. https://doi.org/10.1016/0014-4886(62)90056-0

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S. D., & van Straten, A. (2014). The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. *Journal of affective disorders*, *159*, 118-126. https://doi.org/10.1016/j.jad.2014.02.026

Cuijpers, P., Noma, H., Karyotaki, E., Vinkers, C. H., Cipriani, A., & Furukawa, T. A. (2020). A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry*, *19*(1), 92-107. https://doi.org/10.1002/wps.20701

Cuijpers, P., Sijbrandij, M., Koole, S. L., Andersson, G., Beekman, A. T., & Reynolds III, C. F. (2013). The efficacy of psychotherapy and pharmacotherapy in treating depressive and anxiety disorders: A meta-analysis of direct comparisons. *World Psychiatry*, *12*(2), 137-148. https://doi.org/10.1002/wps.20038

Cuijpers, P., Smit, F., Bohlmeijer, E., Hollon, S. D., & Andersson, G. (2010a). Efficacy of cognitive–behavioural therapy and other psychological treatments for adult depression: meta-analytic study of publication bias. *The British Journal of Psychiatry*, *196*(3), 173-178. https://doi.org/10.1192/bjp.bp.109.066001

Cuijpers, P., Van Straten, A., Andersson, G., & Van Oppen, P. (2008). Psychotherapy for depression in adults: a meta-analysis of comparative outcome studies. *Journal of consulting and clinical psychology*, *76*(6), 909. https://doi.org/10.1037/a0013075

Cuijpers, P., van Straten, A., Bohlmeijer, E., Hollon, S. D., & Andersson, G. (2010b). The effects of psychotherapy for adult depression are overestimated: a meta-analysis of study quality and effect size. *Psychological medicine*, *40*(2), 211-223. https://doi.org/10.1017/S0033291709006114

Cuijpers, P., van Straten, A., & Smit, F. (2006). Psychological treatment of late-life depression: a meta-analysis of randomized controlled trials. *International Journal of Geriatric Psychiatry: Journal of the Psychiatry of Late Life and Allied Sciences*, *21*(12), 1139-1149. https://doi.org/10.1002/gps.1620

Curry, L. A., Nembhard I. M. and Bradley E. H. (2009). Qualitative and mixed methods provide unique contributions to outcomes research. *Circulation* 119, 1442-1452. https://doi.org/10.1161/CIRCULATIONAHA.107.742775

Dalili, M. N., Penton-Voak, I. S., Harmer, C. J., & Munafò, M. R. (2015). Meta-analysis of emotion recognition deficits in major depressive disorder. *Psychological Medicine*, *45*(6), 1135-1144. https://doi.org/10.1017/S0033291714002591

Daly, R. W. (2007). Before depression: The medieval vice of acedia. *Psychiatry: Interpersonal and Biological Processes*, *70*(1), 30-51. https://doi.org/10.1521/psyc.2007.70.1.30

Darwin Adams, C (1868) *The Genuine Works of Hippocrates By Hippocrates (trans.)* New York, Dover Retrieved from: The Genuine Works of Hippocrates (umkc.edu)

Davidoff, G., Roth, E., Thomas, P., Doljanac, R., Dijkers, M., Berent, S., ... & Yarkony, G. (1990). Depression and neuropsychological test peformance in acute spinal cord injury patients: lack of correlation. *Archives of Clinical Neuropsychology*, *5*(1), 77-88. https://doi.org/10.1093/arclin/5.1.77

Davidson, R. J., & McEwen, B. S. (2012). Social influences on neuroplasticity: stress and interventions to promote well-being. *Nature Neuroscience*, *15*(5), 689-695. https://doi.org/10.1038/nn.3093

Davies, S. (2012). The importance of PROSPERO to the National Institute for Health Research. *Systematic Reviews*, *1*(1), 1-2. https://doi.org/10.1186/2046-4053-1-5

De Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nature Reviews Neuroscience*, *6*(6), 463-475. https://doi.org/10.1038/nrn1683

De Moor, M. H., Van Den Berg, S. M., Verweij, K. J., Krueger, R. F., Luciano, M., Vasquez, A. A., ... & Genetics of Personality Consortium. (2015). Meta-analysis of genome-wide association studies for neuroticism, and the polygenic association with major depressive disorder. *JAMA Psychiatry*, *72*(7), 642-650. https://doi.org/10.1001/jamapsychiatry.2015.0554

Debray, T. P., Moons, K. G., van Valkenhoef, G., Efthimiou, O., Hummel, N., Groenwold, R. H., ... & GetReal Methods Review Group. (2015). Get real in individual participant data (IPD) meta-analysis: a review of the methodology. *Research Synthesis Methods*, *6*(4), 293-309. https://doi.org/10.1002/jrsm.1160

Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M. A. (2016). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. *Brain Stimulation*, *9*(4), 501-517. https://doi.org/10.1016/j.brs.2016.04.006

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1987). California Verbal Learning Test. *Assessment*. https://doi.org/10.1037/t15072-000

Demenescu, L. R., Kortekaas, R., den Boer, J. A., & Aleman, A. (2010). Impaired attribution of emotion to facial expressions in anxiety and major depression. *PloS One*, *5*(12), e15058. https://doi.org/10.1371/journal.pone.0015058

Dickson-Swift, V., James, E. L., Kippen, S., & Liamputtong, P. (2007). Doing sensitive research: what challenges do qualitative researchers face?. *Qualitative Research*, *7*(3), 327-353. https://doi.org/10.1177/1468794107078515

Diener, E. (2000). Subjective well-being: The science of happiness and a proposal for a national index. *American Psychologist*, *55*(1), 34. https://doi.org/10.1037/0003-066X.55.1.34

Diniz, B. S., Butters, M. A., Albert, S. M., Dew, M. A., & Reynolds, C. F. (2013). Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *The British Journal of Psychiatry*, *202*(5), 329-335. https://doi.org/10.1192/bjp.bp.112.118307

Direk, N., Williams, S., Smith, J. A., Ripke, S., Air, T., Amare, A. T., ... & Sullivan, P. F. (2017). An analysis of two genome-wide association meta-analyses identifies a new locus for broad depression phenotype. *Biological Psychiatry*, *82*(5), 322-329. https://doi.org/10.1016/j.biopsych.2016.11.013

Disabato, B. M., Morris, C., Hranilovich, J., D'Angelo, G. M., Zhou, G., Wu, N., ... & Sheline, Y. I. (2014). Comparison of brain structural variables, neuropsychological factors, and treatment outcome in early-onset versus late-onset late-life depression. *The American Journal of Geriatric Psychiatry*, *22*(10), 1039-1046. https://doi.org/10.1016/j.jagp.2013.02.005

Dols, M. W. (1987). Insanity and its treatment in Islamic society. *Medical History*, *31*(1), 1-14. https://doi.org/10.1017/S0025727300046287

Dominick, K. L., Ahern, F. M., Gold, C. H., & Heller, D. A. (2002). Relationship of health-related quality of life to health care utilization and mortality among older adults. *Aging Clinical and Experimental Research*, *14*(6), 499-508. https://doi.org/10.1007/BF03327351

Donaghy, E., Atherton, H., Hammersley, V., McNeilly, H., Bikker, A., Robbins, L., ... & McKinstry, B. (2019). Acceptability, benefits, and challenges of video consulting: a qualitative study in primary care. *British Journal of General Practice*, *69*(686), e586-e594. https://doi.org/10.3399/bjgp19X704141

Doody, O., & Noonan, M. (2013). Preparing and conducting interviews to collect data. *Nurse Researcher*, *20*(5). https://doi.org/10.7748/nr2013.05.20.5.28.e327

Douglas, K. M., Groves, S., Crowe, M. T., Inder, M. L., Jordan, J., Carlyle, D., ... & Porter, R. J. (2022). A randomised controlled trial of psychotherapy and cognitive remediation to target cognition in mood disorders. *Acta Psychiatrica Scandinavica*, *145*(3), 278-292. https://doi.org/10.1111/acps.13387

Doraiswamy, P. M. (2010). Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Archives of General Psychiatry*, *67*(3), 277-285. https://doi.org/10.1001/archgenpsychiatry.2009.204

Driscoll, D. L., Appiah-Yeboah, A., Salib, P., & Rupert, D. J. (2007). Merging qualitative and quantitative data in mixed methods research: How to and why not. *Ecological and Environmental Anthropology, (University of Georgia) 18.*

Duman, R. S., Aghajanian, G. K., Sanacora, G., & Krystal, J. H. (2016). Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. *Nature Medicine*, *22*(3), 238-249. https://doi.org/10.1038/nm.4050

Duman, R. S., & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biological Psychiatry*, *59*(12), 1116-1127. https://doi.org/10.1016/j.biopsych.2006.02.013

Duman, R. S., & Li, N. (2012). A neurotrophic hypothesis of depression: role of synaptogenesis in the actions of NMDA receptor antagonists. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *367*(1601), 2475-2484. https://doi.org/10.1098/rstb.2011.0357

Dwyer, S. C., & Buckle, J. L. (2009). The space between: On being an insider-outsider in qualitative research. *International Journal of Qualitative Methods*, *8*(1), 54-63. https://doi.org/10.1177/160940690900800105

e Silva, N. M. L., Barros-Aragão, F. G., De Felice, F. G., & Ferreira, S. T. (2022). Inflammation at the crossroads of COVID-19, cognitive deficits and depression. *Neuropharmacology*, *209*, 109023. https://doi.org/10.1016/j.neuropharm.2022.109023

Easterbrook, P. J., Gopalan, R., Berlin, J. A., & Matthews, D. R. (1991). Publication bias in clinical research. *The Lancet*, *337*(8746), 867-872. https://doi.org/10.1016/0140-6736(91)90201-Y

Ebert, A., & Bar, K. J. (2010). Emil Kraepelin: A pioneer of scientific understanding of psychiatry and psychopharmacology. *Indian Journal of Psychiatry*, *52*(2), 191. https://doi.org/10.4103/0019-5545.64591

Ebert, D. D., Zarski, A. C., Christensen, H., Stikkelbroek, Y., Cuijpers, P., Berking, M., & Riper, H. (2015). Internet and computer-based cognitive behavioral therapy for anxiety and depression in youth: a meta-analysis of randomized controlled outcome trials. *PloS One*, *10*(3), e0119895. https://doi.org/10.1371/journal.pone.0119895

Edgcumbe, D. R., Thoma, V., Rivolta, D., Nitsche, M. A., & Fu, C. H. (2019). Anodal transcranial direct current stimulation over the right dorsolateral prefrontal cortex enhances reflective judgment and decision-making. *Brain Stimulation*, *12*(3), 652-658. https://doi.org/10.1016/j.brs.2018.12.003

Egger, M., & Smith, G. D. (1997). Meta-analysis: potentials and promise. *BMJ*, *315*(7119), 1371-1374. https://doi.org/10.1136/bmj.315.7119.1371

Egger, M., Smith, G. D., & Phillips, A. N. (1997). Meta-analysis: principles and procedures. *BMJ*, *315*(7121), 1533-1537. https://doi.org/10.1136/bmj.315.7121.1533

Elderkin-Thompson, V., Kumar, A., Bilker, W. B., Dunkin, J. J., Mintz, J., Moberg, P. J., ... & Gur, R. E. (2003). Neuropsychological deficits among patients with late-onset minor and major depression. *Archives of Clinical Neuropsychology*, *18*(5), 529-549. https://doi.org/10.1016/S0887-6177(03)00022-2

Eldridge, S. M., Ashby, D., Feder, G. S., Rudnicka, A. R., & Ukoumunne, O. C. (2004). Lessons for cluster randomized trials in the twenty-first century: a systematic review of trials in primary care. *Clinical trials*, *1*(1), 80-90. https://doi.org/10.1191/1740774504cn006rr

Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L., & Lancaster, G. A. (2016b). CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*, *355*:i5239. https://doi.org/10.1136/bmj.i5239

Eldridge, S. M., Lancaster, G. A., Campbell, M. J., Thabane, L., Hopewell, S., Coleman, C. L., & Bond, C. M. (2016a). Defining feasibility and pilot studies in preparation for randomised controlled trials: development of a conceptual framework. *PloS one*, *11*(3), e0150205. https://doi.org/10.1371/journal.pone.0150205

Eling, P. (2019). History of neuropsychological assessment. *A History of Neuropsychology*, *44*, 164-178. https://doi.org/10.1159/000494963

Elliott, A. J., & Fuqua, R. W. (2002). Acceptability of treatments for trichotillomania: Effects of age and severity. *Behavior Modification*, *26*(3), 378-399. https://doi.org/10.1177/0145445502026003005

Elliott, S. N. (1988). Acceptability of behavioral treatments: Review of variables that influence treatment selection. *Professional Psychology: Research and Practice*, *19*(1), 68. https://doi.org/10.1037/0735-7028.19.1.68

Elmer, T., Mepham, K., & Stadtfeld, C. (2020). Students under lockdown: Comparisons of students' social networks and mental health before and during the COVID-19 crisis in Switzerland. *Plos One*, *15*(7), e0236337. https://doi.org/10.1371/journal.pone.0236337

Evans, V. C., Iverson, G. L., Yatham, L. N., & Lam, R. W. (2014). The relationship between neurocognitive and psychosocial functioning in major depressive disorder: a systematic review. *The Journal of Clinical Psychiatry*, *75*(12), 17306. https://doi.org/10.4088/JCP.13r08939

Fadok, J. P., Markovic, M., Tovote, P., & Lüthi, A. (2018). New perspectives on central amygdala function. *Current opinion in neurobiology*, *49*, 141-147. https://doi.org/10.1016/j.conb.2018.02.009

Farhat, L. C., Carvalho, A. F., Solmi, M., & Brunoni, A. R. (2022). Evidence-based umbrella review of cognitive effects of prefrontal tDCS. *Social Cognitive and Affective Neuroscience*, *17*(1), 43-60. https://doi.org/10.1093/scan/nsaa084

Farrin, L., Hull, L., Unwin, C., Wykes, T., & David, A. (2003). Effects of depressed mood on objective and subjective measures of attention. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *15*(1), 98-104. https://doi.org/10.1176/jnp.15.1.98

Fava, M., & Kendler, K. S. (2000). Major depressive disorder. *Neuron*, *28*(2), 335-341. https://doi.org/10.1016/S0896-6273(00)00112-4

Felger, J. C., Haroon, E., Patel, T. A., Goldsmith, D. R., Wommack, E. C., Woolwine, B. J., ... & Miller, A. H. (2020). What does plasma CRP tell us about peripheral and central inflammation in depression?. *Molecular Psychiatry*, *25*(6), 1301-1311. https://doi.org/10.1038/s41380-018-0096-3

Fereday, J., & Muir-Cochrane, E. (2006). Demonstrating rigor using thematic analysis: A hybrid approach of inductive and deductive coding and theme development. *International Journal of Qualitative Methods*, *5*(1), 80-92. https://doi.org/10.1177/160940690600500107

Ferrari, A. J., Somerville, A. J., Baxter, A. J., Norman, R., Patten, S. B., Vos, T., & Whiteford, H. A. (2013). Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychological Medicine*, *43*(3), 471-481. https://doi.org/10.1017/S0033291712001511

Ferster, C. B. (1973). A functional analysis of depression. *The American Psychologist*, *28*(10), 857-870. https://doi.org/10.1037/h0035605

Fineman, M. A. (2008). The vulnerable subject: Anchoring equality in the human condition. *Yale JL & Feminism*, *20*, 1.

Finlay, L. (2002). "Outing" the researcher: The provenance, process, and practice of reflexivity. *Qualitative Health Research*, *12*(4), 531-545. https://doi.org/10.1177/104973202129120052

Finlay, L. (2002b). Negotiating the swamp: the opportunity and challenge of reflexivity in research practice. *Qualitative research*, *2*(2), 209-230.

Finn, C. A., & Sladeczek, I. E. (2001). Assessing the social validity of behavioral interventions: A review of treatment acceptability measures. *School Psychology Quarterly*, *16*(2), 176. https://doi.org/10.1521/scpq.16.2.176.18703

Fischer, S., Macare, C., & Cleare, A. J. (2017). Hypothalamic-pituitary-adrenal (HPA) axis functioning as predictor of antidepressant response–Meta-analysis. *Neuroscience & Biobehavioral Reviews*, *83*, 200-211. https://doi.org/10.1016/j.neubiorev.2017.10.012

Fisher, D. J., Copas, A. J., Tierney, J. F., & Parmar, M. K. B. (2011). A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners. *Journal of Clinical Epidemiology*, *64*(9), 949-967. https://doi.org/10.1016/j.jclinepi.2010.11.016

Flick, U. (2004). Design and process in qualitative research. *A Companion to Qualitative Research*, 146-152.

Flick, U. (2007). Qualitative research designs. *Designing Qualitative Research*, 109-114. https://doi.org/10.4135/9781849208826.n11

Fornaro, M., Anastasia, A., Novello, S., Fusco, A., Pariano, R., De Berardis, D., ... & Carvalho, A. F. (2019). The emergence of loss of efficacy during antidepressant drug treatment for major depressive disorder: an integrative review of evidence, mechanisms, and clinical implications. *Pharmacological Research*, *139*, 494-502. https://doi.org/10.1016/j.phrs.2018.10.025

Fournier, J. C., DeRubeis, R. J., Hollon, S. D., Dimidjian, S., Amsterdam, J. D., Shelton, R. C., & Fawcett, J. (2010). Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA*, *303*(1), 47-53. https://doi.org/10.1001/jama.2009.1943

Francis-Taylor, R., Ophel, G., Martin, D., & Loo, C. (2020). The ictal EEG in ECT: a systematic review of the relationships between ictal features, ECT technique, seizure threshold and outcomes. *Brain Stimulation*. *13*(6) 1644-1654. https://doi.org/10.1016/j.brs.2020.09.009

Frank, E., Prien, R. F., Jarrett, R. B., Keller, M. B., Kupfer, D. J., Lavori, P. W., ... & Weissman, M. M. (1991). Conceptualization and rationale for consensus definitions of terms in major depressive

disorder: remission, recovery, relapse, and recurrence. *Archives of General Psychiatry*, *48*(9), 851-855. https://doi.org/10.1001/archpsyc.1991.01810330075011

Fregni, F. (2008). A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *International Journal of Neuropsychopharmacology*, *11*(2), 249-254. https://doi.org/10.1017/S1461145707007833

Fregni, F., Boggio, P. S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., ... & Pascual-Leone, A. (2005). Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Experimental brain research*, *166*(1), 23-30. https://doi.org/10.1007/s00221-005-2334-6

Frels, R. K., & Onwuegbuzie, A. J. (2012). Interviewing the Interpretive Researcher: An Impressionist Tale. *Qualitative Report*, *17*, 60.

Freud, S. (1917). Mourning and melancholia. *The standard edition of the complete psychological works of Sigmund Freud*, *14*(1914–1916), 237-258.

Freud, S. (1986). Overview of transfer neuroses. *Complete Works*, *13*, 281-302.

Friedrich, M. J. (2017). Depression is the leading cause of disability around the world. *JAMA*, *317*(15), 1517-1517. https://doi.org/10.1001/jama.2017.3826

Frodl, T., Schaub, A., Banac, S., Charypar, M., Jäger, M., Kümmler, P., ... & Meisenzahl, E. M. (2006). Reduced hippocampal volume correlates with executive dysfunctioning in major depression. *Journal of Psychiatry and Neuroscience*, *31*(5), 316-323.

Frost, R., Bauernfreund, Y., & Walters, K. (2019). Non-pharmacological interventions for depression/anxiety in older adults with physical comorbidities affecting functioning: systematic review and meta-analysis. *International Psychogeriatrics*, *31*(8), 1121-1136. https://doi.org/10.1017/S1041610218001564

Fu, Z., Brouwer, M., Kennis, M., Williams, A., Cuijpers, P., & Bockting, C. (2021). Psychological factors for the onset of depression: a meta-analysis of prospective studies. *BMJ open*, *11*(7), e050129. https://doi.org/10.1136/bmjopen-2021-050129

Fumagalli, M., Vergari, M., Pasqualetti, P., Marceglia, S., Mameli, F., Ferrucci, R., ... & Priori, A. (2010). Brain switches utilitarian behavior: does gender make the difference?. *PLoS One*, *5*(1), e8865. https://doi.org/10.1371/journal.pone.0008865

Furukawa, T. A., Cipriani, A., Cowen, P. J., Leucht, S., Egger, M., & Salanti, G. (2019). Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: a systematic review and dose-response meta-analysis. *The Lancet Psychiatry*, *6*(7), 601-609. https://doi.org/10.1016/S2215-0366(19)30217-2

Furukawa, T. A., Salanti, G., Atkinson, L. Z., Leucht, S., Ruhe, H. G., Turner, E. H., ... & Cipriani, A. (2016). Comparative efficacy and acceptability of first-generation and second-generation antidepressants in the acute treatment of major depression: protocol for a network meta-analysis. *BMJ open*, *6*(7), e010919. https://doi.org/10.1136/bmjopen-2015-010919

Gagnon, J. C., & Barber, B. R. (2018). The SAGE Encyclopedia of Educational Research, Measurement, and Evaluation. In *The SAGE Encyclopedia of Educational Research, Measurement and Evaluation* (p. 668). Sage.

Gallagher, D., Kiss, A., Lanctot, K., & Herrmann, N. (2018). Depression and risk of Alzheimer dementia: a longitudinal analysis to determine predictors of increased risk among older adults with depression. *The American Journal of Geriatric Psychiatry*, *26*(8), 819-827. https://doi.org/10.1016/j.jagp.2018.05.002

Gallagher, D., Mhaolain, A. N., Greene, E., Walsh, C., Denihan, A., Bruce, I., ... & Lawlor, B. A. (2010). Late life depression: a comparison of risk factors and symptoms according to age of onset in community dwelling older adults. *International Journal of Geriatric Psychiatry*, *25*(10), 981-987. https://doi.org/10.1002/gps.2438

Gálvez, V., Alonzo, A., Martin, D., Mitchell, P. B., Sachdev, P., & Loo, C. K. (2011). Hypomania induction in a patient with bipolar II disorder by transcranial direct current stimulation (tDCS). *The Journal of ECT*, *27*(3), 256-258. https://doi.org/10.1097/YCT.0b013e3182012b89

Gautam, S. (1999). Mental health in ancient India & its relevance to modern psychiatry. *Indian Journal of Psychiatry*, *41*(1), 5. Available from: MENTAL HEALTH IN ANCIENT INDIA & ITS RELEVANCE TO MODERN PSYCHIATRY - PMC (nih.gov)

Geerlings, M. I., & Gerritsen, L. (2017). Late-life depression, hippocampal volumes, and hypothalamic-pituitary-adrenal axis regulation: a systematic review and meta-analysis. *Biological Psychiatry*, *82*(5), 339-350. https://doi.org/10.1016/j.biopsych.2016.12.032

Geffen, G., Moar, K. J., O'hanlon, A. P., Clark, C. R., & Geffen, L. B. (1990). Performance measures of 16–to 86-year-old males and females on the auditory verbal learning test. *Clinical Neuropsychologist*, *4*(1), 45-63. https://doi.org/10.1080/13854049008401496

Geffen, G. M., Butterworth, P., & Geffen, L. B. (1994). Test-retest reliability of a new form of the auditory verbal learning test (AVLT). *Archives of Clinical Neuropsychology*, *9*(4), 303-316. https://doi.org/10.1093/arclin/9.4.303

Gertner, A. K., Domino, M. E., & Dow, W. H. (2017). Risk factors for late-life depression and correlates of antidepressant use in Costa Rica: Results from a nationally-representative longitudinal survey of older adults. *Journal of Affective Disorders*, *208*, 338-344. https://doi.org/10.1016/j.jad.2016.08.063

Gilbody, S., Lewis, H., Adamson, J., Atherton, K., Bailey, D., Birtwistle, J., ... & McMillan, D. (2017). Effect of collaborative care vs usual care on depressive symptoms in older adults with subthreshold depression: the CASPER randomized clinical trial. *JAMA*, *317*(7), 728-737. https://doi.org/10.1001/jama.2017.0130

Giglia, G., Brighina, F., Rizzo, S., Puma, A., Indovino, S., Maccora, S., ... & Fierro, B. (2014). Anodal transcranial direct current stimulation of the right dorsolateral prefrontal cortex enhances memory-guided responses in a visuospatial working memory task. *Functional Neurology*, *29*(3), 189. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4264786/

Glass, G. V. (1976). Primary, secondary, and meta-analysis of research. *Educational Researcher*, *5*(10), 3-8. https://doi.org/10.3102/0013189X005010003

Glen, T., Hostetter, G., Roebuck-Spencer, T. M., Garmoe, W. S., Scott, J. G., Hilsabeck, R. C., ... & Espe-Pfeifer, P. (2020). Return on investment and value research in neuropsychology: A call to arms. *Archives of Clinical Neuropsychology*, *35*(5), 459-468. https://doi.org/10.1093/arclin/acaa010

Godfrey, K. E., Gardner, A. C., Kwon, S., Chea, W., & Muthukumaraswamy, S. D. (2018). Differences in excitatory and inhibitory neurotransmitter levels between depressed patients and healthy controls: a systematic review and meta-analysis. *Journal of Psychiatric Research*, *105*, 33-44. https://doi.org/10.1016/j.jpsychires.2018.08.015

Goldfried, M. R., & Davison, G. C. (1994). *Clinical Behavior Therapy, Exp*. John Wiley & Sons.

Godlewska, B. R. (2019). Cognitive neuropsychological theory: Reconciliation of psychological and biological approaches for depression. *Pharmacology & Therapeutics*, *197*, 38-51. https://doi.org/10.1016/j.pharmthera.2018.12.010

Godlewska, B. R., & Harmer, C. J. (2021). Cognitive neuropsychological theory of antidepressant action: a modern-day approach to depression and its treatment. *Psychopharmacology*, *238*(5), 1265-1278. https://doi.org/10.1007/s00213-019-05448-0

Goertz, G., & Mahoney, J. (2012). Concepts and measurement: Ontology and epistemology. *Social Science Information*, *51*(2), 205-216. https://doi.org/10.1177/0539018412437108

Gómez, L., Vidal, B., Cabrera, Y., Hernández, L., & Rondón, Y. (2021). Successful treatment of post-covid symptoms with transcranial direct current stimulation. *The Primary Care Companion for CNS Disorders*, *23*(6), 38522. https://doi.org/10.4088/PCC.21cr03059

Gopinath, S., Katon, W. J., Russo, J. E., & Ludman, E. J. (2007). Clinical factors associated with relapse in primary care patients with chronic or recurrent depression. *Journal of Affective Disorders*, *101*(1-3), 57-63. https://doi.org/10.1016/j.jad.2006.10.023

Goyal, M., Singh, S., Sibinga, E. M., Gould, N. F., Rowland-Seymour, A., Sharma, R., ... & Haythornthwaite, J. A. (2014). Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. *JAMA internal medicine*, *174*(3), 357-368.

Grace, J., & O'Brien, J. T. (2003). Association of life events and psychosocial factors with early but not late onset depression in the elderly: implications for possible differences in aetiology. *International Journal of Geriatric Psychiatry*, *18*(6), 473-478. https://doi.org/10.1002/gps.856

Gray, D. E. (2016). *Doing research in the real world.* Sage Publications, London. Available from: Gray__Doing_Research_in_the_Real_World20190530-2982-1eo5xiw-with-cover-page-v2.pdf (d1wqtxts1xzle7.cloudfront.net)

Gray, J. P., Müller, V. I., Eickhoff, S. B., & Fox, P. T. (2020). Multimodal abnormalities of brain structure and function in major depressive disorder: a meta-analysis of neuroimaging studies. *American Journal of Psychiatry*, *177*(5), 422-434. https://doi.org/10.1176/appi.ajp.2019.19050560

Grayson, L., & Thomas, A. (2013). A systematic review comparing clinical features in early age at onset and late age at onset late-life depression. *Journal of Affective Disorders*, *150*(2), 161-170. https://doi.org/10.1016/j.jad.2013.03.021

Greenfield, S., Kaplan, S., & Ware Jr, J. E. (1985). Expanding patient involvement in care: effects on patient outcomes. *Annals of Internal Medicine*, *102*(4), 520-528. https://doi.org/10.7326/0003-4819-102-4-520

Greiver, M., Dahrouge, S., O'Brien, P., Manca, D., Lussier, M. T., Wang, J., ... & Farrell, B. (2019). Improving care for elderly patients living with polypharmacy: protocol for a pragmatic cluster

randomized trial in community-based primary care practices in Canada. *Implementation Science*, *14*(1), 1-15. https://doi.org/10.1186/s13012-019-0904-4

Groves, J. O. (2007). Is it time to reassess the BDNF hypothesis of depression?. *Molecular psychiatry*, *12*(12), 1079-1088. https://doi.org/10.1038/sj.mp.4002075

Groves, S. J., Douglas, K. M., & Porter, R. J. (2018). A systematic review of cognitive predictors of treatment outcome in major depression. *Frontiers in Psychiatry*, *9*, 382. https://doi.org/10.3389/fpsyt.2018.00382

Gruber, S., Rathgeber, K., Bräunig, P., & Gauggel, S. (2007). Stability and course of neuropsychological deficits in manic and depressed bipolar patients compared to patients with major depression. *Journal of Affective Disorders*, *104*(1-3), 61-71. https://doi.org/10.1016/j.jad.2007.02.011

Grützner, T. M., Sharma, A., Listunova, L., Bartolovic, M., Weisbrod, M., & Roesch-Ely, D. (2019). Neurocognitive performance in patients with depression compared to healthy controls: association of clinical variables and remission state. *Psychiatry Research*, *271*, 343-350. https://doi.org/10.1016/j.psychres.2018.11.047

Gu, C. Z., He, H. L., Duan, H. F., Su, Z. H., Chen, H., & Gan, J. L. (2016). Predictors of neurocognitive impairment at 2 years after a first-episode major depressive disorder. *Comprehensive Psychiatry*, *68*, 24-33. https://doi.org/10.1016/j.comppsych.2016.03.009

Gualtieri, C. T., & Johnson, L. G. (2008). Age-related cognitive decline in patients with mood disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(4), 962-967. https://doi.org/10.1016/j.pnpbp.2007.12.030

Gudka, S., Marshall, L., Creagh, A., & Clifford, R. M. (2013). To develop and measure the effectiveness and acceptability of a pharmacy-based chlamydia screening intervention in Australia. *BMJ open*, *3*(8), e003338. https://doi.org/10.1136/bmjopen-2013-003338

Guest, G., MacQueen, K. M., & Namey, E. E. (2012). *Applied Thematic Analysis*. SAGE Publications, Inc. https://www.doi.org/10.4135/9781483384436

Guest, G., Namey, E., & Chen, M. (2020). A simple method to assess and report thematic saturation in qualitative research. *PLoS One*, *15*(5), e0232076. https://doi.org/10.1371/journal.pone.0232076

Guillaumie, L., Moisan, J., Grégoire, J. P., Villeneuve, D., Beaucage, C., Bujold, M., & Lauzier, S. (2015). Perspective of community pharmacists on their practice with patients who have an antidepressant drug treatment: Findings from a focus group study. *Research in Social and Administrative Pharmacy*, *11*(2), e43-e56. https://doi.org/10.1016/j.sapharm.2014.07.180

Gum, A. M., Areán, P. A., Hunkeler, E., Tang, L., Katon, W., Hitchcock, P., ... & Unützer, J. (2006). Depression treatment preferences in older primary care patients. *The Gerontologist*, *46*(1), 14-22. https://doi.org/10.1093/geront/46.1.14

Haapakoski, R., Mathieu, J., Ebmeier, K. P., Alenius, H., & Kivimäki, M. (2015). Cumulative meta-analysis of interleukins 6 and 1β, tumour necrosis factor α and C-reactive protein in patients with major depressive disorder. *Brain, behavior, and immunity*, *49*, 206-215. https://doi.org/10.1016/j.bbi.2015.06.001

Haberstick, B. C., Boardman, J. D., Wagner, B., Smolen, A., Hewitt, J. K., Killeya-Jones, L. A., ... & Mullan Harris, K. (2016). Depression, stressful life events, and the impact of variation in the

serotonin transporter: Findings from the National Longitudinal Study of Adolescent to Adult Health (Add Health). *PloS one*, *11*(3), e0148373. https://doi.org/10.1371/journal.pone.0148373

Hajek, T., Kopecek, M., Kozeny, J., Gunde, E., Alda, M., & Höschl, C. (2009). Amygdala volumes in mood disorders—meta-analysis of magnetic resonance volumetry studies. *Journal of affective disorders*, *115*(3), 395-410. https://doi.org/10.1016/j.jad.2008.10.007

Hall, C. A., & Reynolds-III, C. F. (2014). Late-life depression in the primary care setting: challenges, collaborative care, and prevention. *Maturitas*, *79*(2), 147-152. https://doi.org/10.1016/j.maturitas.2014.05.026

Hallett, M. (2000). Transcranial magnetic stimulation and the human brain. *Nature*, *406*(6792), 147-150. https://doi.org/10.1038/35018000

Hamilton M. (1959) The assessment of anxiety states by rating. *British Journal of Medical Psychology 32,* 50–55 https://doi.org/10.1111/j.2044-8341.1959.tb00467.x

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, *23*(1), 56. https://jnnp.bmj.com/content/23/1/56

Hamilton, J. P., Siemer, M., & Gotlib, I. H. (2008). Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Molecular psychiatry*, *13*(11), 993-1000. https://doi.org/10.1038/mp.2008.57

Han, C., Kwak, K. P., Marks, D. M., Pae, C. U., Wu, L. T., Bhatia, K. S., ... & Patkar, A. A. (2009). The impact of the CONSORT statement on reporting of randomized clinical trials in psychiatry. *Contemporary Clinical Trials*, *30*(2), 116-122. https://doi.org/10.1016/j.cct.2008.11.004

Harmer, C. J., & Cowen, P. J. (2013). 'It's the way that you look at it'—a cognitive neuropsychological account of SSRI action in depression. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *368*(1615), 20120407. https://doi.org/10.1098/rstb.2012.0407

Harmer, C. J., Duman, R. S., & Cowen, P. J. (2017). How do antidepressants work? New perspectives for refining future treatment approaches. *The Lancet Psychiatry*, *4*(5), 409-418. https://doi.org/10.1016/S2215-0366(17)30015-9

Hawkins, K. A., Dean, D., & Pearlson, G. D. (2004). Alternative forms of the Rey auditory verbal learning test: a review. *Behavioural neurology*, *15*(3, 4), 99-107. https://doi.org/10.1155/2004/940191

Hawkins, K. A., & Sayward, H. K. (1994). Examiner judgment and actual stability of psychiatric inpatient intelligence quotients. *The Clinical Neuropsychologist*, *8*(4), 394-404. https://doi.org/10.1080/13854049408402042

Hayek, D., Antonenko, D., Witte, A. V., Lehnerer, S. M., Meinzer, M., Külzow, N., ... & Flöel, A. (2021). Impact of COMT val158met on tDCS-induced cognitive enhancement in older adults. *Behavioural Brain Research*, *401*, 113081. https://doi.org/10.1016/j.bbr.2020.113081

Hazlett-Stevens, H., & Craske, M.G. (2008). Brief Cognitive-Behavioral Therapy: Definition and Scientific Foundations. https://doi.org/10.1002/9780470713020.ch1

Heale, R., & Twycross, A. (2015). Validity and reliability in quantitative studies. *Evidence-Based Nursing*, *18*(3), 66-67. https://doi.org/10.1136/eb-2015-102129

Hegeman, J. M., De Waal, M. W. M., Comijs, H. C., Kok, R. M., & Van der Mast, R. C. (2015). Depression in later life: a more somatic presentation?. *Journal of Affective Disorders*, *170*, 196-202. https://doi.org/10.1016/j.jad.2014.08.032

Henry, J. D., & Crawford, J. R. (2005). A meta-analytic review of verbal fluency deficits in depression. *Journal of Clinical and Experimental Neuropsychology*, *27*(1), 78-101. https://doi.org/10.1080/138033990513654

Heo, M., Murphy, C. F., & Meyers, B. S. (2007). Relationship between the Hamilton depression rating scale and the Montgomery-Åsberg depression rating scale in depressed elderly: A meta-analysis. *The American Journal of Geriatric Psychiatry*, *15*(10), 899-905. https://doi.org/10.1097/JGP.0b013e318098614e

Herrmann, L. L., Le Masurier, M., & Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: a systematic review. *Journal of Neurology, Neurosurgery & Psychiatry*, *79*(6), 619-624. https://doi.org/10.1136/jnnp.2007.124651

Hertel, P. T. (1998). Relation between rumination and impaired memory in dysphoric moods. *Journal of Abnormal Psychology*, *107*(1), 166. https://doi.org/10.1037/0021-843X.107.1.166

Hewitt, K. C., & Loring, D. W. (2020). Emory university telehealth neuropsychology development and implementation in response to the COVID-19 pandemic. *The Clinical Neuropsychologist*, *34*(7-8), 1352-1366. https://doi.org/10.1080/13854046.2020.1791960

Hibbert, P., Sillince, J., Diefenbach, T., & Cunliffe, A. L. (2014). Relationally reflexive practice: A generative approach to theory development in qualitative research. *Organizational Research Methods*, *17*(3), 278-298. https://doi.org/10.1177/1094428114524829

Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2. (Updated September 2009). The Cochrane Collaboration, 2009.

Higgins, J. P., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., ... & Sterne, J. A. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*, *343*. https://doi.org/10.1136/bmj.d5928

Hill, A. T., Fitzgerald, P. B., & Hoy, K. E. (2016). Effects of anodal transcranial direct current stimulation on working memory: a systematic review and meta-analysis of findings from healthy and neuropsychiatric populations. *Brain stimulation*, *9*(2), 197-208. https://doi.org/10.1016/j.brs.2015.10.006

Ho, M. P., Gonzalez, J. M., Lerner, H. P., Neuland, C. Y., Whang, J. M., McMurry-Heath, M., ... & Irony, T. (2015). Incorporating patient-preference evidence into regulatory decision making. *Surgical Endoscopy*, *29*(10), 2984-2993. https://doi.org/10.1007/s00464-014-4044-2

Holmes, A. G. D. (2020). Researcher Positionality--A Consideration of Its Influence and Place in Qualitative Research--A New Researcher Guide. *Shanlax International Journal of Education*, *8*(4), 1-10. https://doi.org/10.34293/education.v8i4.3232

Holvast, F., Oude Voshaar, R. C., Wouters, H., Hek, K., Schellevis, F., Burger, H., & Verhaak, P. F. (2019). Non-adherence to antidepressants among older patients with depression: a longitudinal cohort study in primary care. *Family Practice*, *36*(1), 12-20. https://doi.org/10.1093/fampra/cmy106

Horackova, K., Kopecek, M., Machů, V., Kagstrom, A., Aarsland, D., Motlova, L. B., & Cermakova, P. (2019). Prevalence of late-life depression and gap in mental health service use across European regions. *European Psychiatry*, *57*, 19-25. https://doi.org/10.1016/j.eurpsy.2018.12.002

Hordacre, B. (2018). The role of telehealth to assist in-home tDCS: opportunities, promising results and acceptability. *Brain Sciences*, *8*(6), 102. https://doi.org/10.3390/brainsci8060102

Howard, D. M., Adams, M. J., Shirali, M., Clarke, T. K., Marioni, R. E., Davies, G., ... & McIntosh, A. M. (2018). Genome-wide association study of depression phenotypes in UK Biobank identifies variants in excitatory synaptic pathways. *Nature Communications*, *9*(1), 1-10. https://doi.org/10.1038/s41467-018-03819-3

Hsieh, H. F., & Shannon, S. E. (2005). Three approaches to qualitative content analysis. *Qualitative Health Research*, *15*(9), 1277-1288. https://doi.org/10.1177/1049732305276687

Huang, A. X., Delucchi, K., Dunn, L. B., & Nelson, J. C. (2015). A systematic review and meta-analysis of psychotherapy for late-life depression. *The American Journal of Geriatric Psychiatry*, *23*(3), 261-273. https://doi.org/10.1016/j.jagp.2014.04.003

Huls, S. P., Whichello, C. L., van Exel, J., Uyl-de Groot, C. A., & de Bekker-Grob, E. W. (2019). What is next for patient preferences in health technology assessment? A systematic review of the challenges. *Value in Health*, *22*(11), 1318-1328. https://doi.org/10.1016/j.jval.2019.04.1930

Hunsley, J., Hanson, R. K., & Parker, K. C. (1988). A summary of the reliability and stability of MMPI scales. *Journal of Clinical Psychology*, *44*(1), 44-46. https://doi.org/10.1002/1097-4679(198801)44:1<44::AID-JCLP2270440109>3.0.CO;2-A

Hunter, J. E., & Schmidt, F. L. (2000). Fixed effects vs. random effects meta-analysis models: Implications for cumulative research knowledge. *International Journal of Selection and Assessment*, *8*(4), 275-292. https://doi.org/10.1111/1468-2389.00156

Hunter, J. E., & Schmidt, F. L. (2004). *Methods of meta-analysis: Correcting error and bias in research findings*. Sage.

Huo, L., Zhu, X., Zheng, Z., Ma, J., Ma, Z., Gui, W., & Li, J. (2021). Effects of transcranial direct current stimulation on episodic memory in older adults: a meta-analysis. *The Journals of Gerontology: Series B*, *76*(4), 692-702. https://doi.org/10.1093/geronb/gbz130

Huy, Q. N. (2012). Improving the odds of publishing inductive qualitative research in premier academic journals. *The Journal of Applied Behavioral Science*, *48*(2), 282-287. https://doi.org/10.1177/0021886312438864

IBM Corp. (2019). *IBM SPSS Statistics for Windows*, Version 26.0. Armonk, NY: IBM Corp

Ioannidis, J. P., Patsopoulos, N. A., & Evangelou, E. (2007). Uncertainty in heterogeneity estimates in meta-analyses. *BMJ*, *335*(7626), 914-916. https://doi.org/10.1136/bmj.39343.408449.80

Indahlastari, A., Albizu, A., Boutzoukas, E. M., O'Shea, A., & Woods, A. J. (2021). White matter hyperintensities affect transcranial electrical stimulation in the aging brain. *Brain stimulation*, *14*(1), 69-73. https://doi.org/10.1016/j.brs.2020.11.009

Indahlastari, A., Albizu, A., Kraft, J. N., O'Shea, A., Nissim, N. R., Dunn, A. L., ... & Woods, A. J. (2021). Individualized tDCS modeling predicts functional connectivity changes within the working memory

network in older adults. *Brain Stimulation*, *14*(5), 1205-1215. https://doi.org/10.1016/j.brs.2021.08.003

Indahlastari, A., Albizu, A., O'Shea, A., Forbes, M. A., Nissim, N. R., Kraft, J. N., ... & Alzheimer's Disease Neuroimaging Initiative. (2020). Modeling transcranial electrical stimulation in the aging brain. *Brain Stimulation*, *13*(3), 664-674. https://doi.org/10.1016/j.brs.2020.02.007

Ingram, R. E. (1984). Toward an information-processing analysis of depression. *Cognitive Therapy and Research*, *8*(5), 443-477. https://doi.org/10.1007/BF01173284

Ironside, M., & Perlo, S. (2018). Transcranial direct current stimulation for the treatment of depression: A review of the candidate mechanisms of action. *Current Behavioral Neuroscience Reports*, *5*(1), 26-35. https://doi.org/10.1007/s40473-018-0138-9

Israel, J. A. (2010). The impact of residual symptoms in major depression. *Pharmaceuticals*, *3*(8), 2426-2440. https://doi.org/10.3390/ph3082426

Ito, T. A., Larsen, J. T., Smith, N. K., & Cacioppo, J. T. (1998). Negative information weighs more heavily on the brain: the negativity bias in evaluative categorizations. *Journal of personality and social psychology*, *75*(4), 887.

Ivnik, R. J., Malec, J. F., Smith, G. E., Tangalos, E. G., Petersen, R. C., Kokmen, E., & Kurland, L. T. (1992). Mayo's older Americans normative studies: updated AVLT norms for ages 56 to 97. *The Clinical Neuropsychologist*, *6*(S1), 83-104. https://doi.org/10.1080/13854049208401880

Jacobson, N. S., Martell, C. R., & Dimidjian, S. (2001). Behavioral activation treatment for depression: returning to contextual roots. *Clinical Psychology: Science and Practice*, *8*(3), 255. https://doi.org/10.1093/clipsy.8.3.255

Jaeger, J., Berns, S., Uzelac, S., & Davis-Conway, S. (2006). Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Research*, *145*(1), 39-48. https://doi.org/10.1016/j.psychres.2005.11.011

James, T. A., Weiss-Cowie, S., Hopton, Z., Verhaeghen, P., Dotson, V. M., & Duarte, A. (2021). Depression and episodic memory across the adult lifespan: A meta-analytic review. *Psychological Bulletin*, *147*(11), 1184. https://doi.org/10.1037/bul0000344

Jansson, Å. (2011). Mood disorders and the brain: Depression, melancholia, and the historiography of psychiatry. *Medical History*, *55*(3), 393-399. https://doi.org/10.1017/S0025727300005469

Jeon, S. W., & Kim, Y. K. (2016). Neuroinflammation and cytokine abnormality in major depression: Cause or consequence in that illness?. *World Journal of Psychiatry*, *6*(3), 283. https://doi.org/10.5498/wjp.v6.i3.283

Jeong, H. G., Han, C., Park, M. H., Ryu, S. H., Pae, C. U., Lee, J. Y., ... & Steffens, D. C. (2014). Influence of the number and severity of somatic symptoms on the severity of depression and suicidality in community-dwelling elders. *Asia-Pacific Psychiatry*, *6*(3), 274-283. https://doi.org/10.1111/appy.12138

Jivraj, S., Nazroo, J., Vanhoutte, B., & Chandola, T. (2014). Aging and subjective well-being in later life. *Journals of Gerontology Series B: Psychological Sciences and Social Sciences*, *69*(6), 930-941. https://doi.org/10.1093/geronb/gbu006

Joëls, M., & Baram, T. Z. (2009). The neuro-symphony of stress. *Nature reviews neuroscience*, *10*(6), 459-466. https://doi.org/10.1038/nrn2632

Joseph-Williams, N., Edwards, A., & Elwyn, G. (2014). Power imbalance prevents shared decision making. *Bmj*, *348*.

Jüni, P., Altman, D. G., & Egger, M. (2001). Assessing the quality of controlled clinical trials. *BMJ*, *323*(7303), 42-46. https://doi.org/10.1136/bmj.323.7303.42

Kaiser, R. H., Andrews-Hanna, J. R., Wager, T. D., & Pizzagalli, D. A. (2015). Large-scale network dysfunction in major depressive disorder: a meta-analysis of resting-state functional connectivity. *JAMA psychiatry*, *72*(6), 603-611. https://doi.org/10.1001/jamapsychiatry.2015.0071

Kajungu, D., Muhoozi, M., Stark, J., Weibel, D., & Sturkenboom, M. C. (2020). Vaccines safety and maternal knowledge for enhanced maternal immunization acceptability in rural Uganda: A qualitative study approach. *PLoS One*, *15*(12), e0243834. https://doi.org/10.1371/journal.pone.0243834

Kalfus, G. R., & Burk, B. K. (1989). The influence of case history and treatment mediator on ratings of acceptability of child treatment. *Child & Family Behavior Therapy*, *11*(2), 45-56. https://doi.org/10.1300/J019v11n02_04

Kalu, F. A., & Bwalya, J. C. (2017). What makes qualitative research good research? An exploratory analysis of critical elements. *International Journal of Social Science Research*, *5*(2), 43-56. https://doi.org/10.5296/ijssr.v5i2.10711

Kalu, U. G., Sexton, C. E., Loo, C. K., & Ebmeier, K. P. (2012). Transcranial direct current stimulation in the treatment of major depression: a meta-analysis. *Psychological Medicine*, *42*(9), 1791-1800. https://doi.org/10.1017/S0033291711003059

Kandasamy, S., & Campbell, K. (2019). Psychotherapy and Pharmacotherapy for Major Depressive Disorder and Generalized Anxiety Disorder: A Rapid Qualitative Review. [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Jun 4. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562927/

Kant, S. L. (2014). The distinction and relationship between ontology and epistemology: does it matter?. *Politikon: The IAPSS Journal of Political Science*, *24*, 68-85. https://doi.org/10.22151/politikon.24.4

Kaplan, E. (1988). *A process approach to neuropsychological assessment*. American Psychological Association. https://doi.org/10.1037/10063-004

Karyotaki, E., Smit, Y., de Beurs, D. P., Henningsen, K. H., Robays, J., Huibers, M. J., ... & Cuijpers, P. (2016). The long-term efficacy of acute-phase psychotherapy for depression: A meta-analysis of randomized trials. *Depression and anxiety*, *33*(5), 370-383. https://doi.org/10.1002/da.22491

Kaster, T. S., Daskalakis, Z. J., Noda, Y., Knyahnytska, Y., Downar, J., Rajji, T. K., ... & Blumberger, D. M. (2018). Efficacy, tolerability, and cognitive effects of deep transcranial magnetic stimulation for late-life depression: a prospective randomized controlled trial. *Neuropsychopharmacology*, *43*(11), 2231-2238. https://doi.org/10.1038/s41386-018-0121-x

Katon, W. J. (2003). Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biological Psychiatry*, *54*(3), 216-226. https://doi.org/10.1016/S0006-3223(03)00273-7

Kazdin, A. E. (1977). Assessing the clinical or applied importance of behavior change through social validation. *Behavior Modification*, *1*(4), 427-452. https://doi.org/10.1177/014544557714001

Kazdin, A. E. (1980). Acceptability of alternative treatments for deviant child behavior. *Journal of Applied Behavior Analysis*, *13*(2), 259-273. https://doi.org/10.1901/jaba.1980.13-259

Keefe, R. S., McClintock, S. M., Roth, R. M., Doraiswamy, P. M., Tiger, S., & Madhoo, M. (2014). Cognitive effects of pharmacotherapy for major depressive disorder: a systematic review. *The Journal of Clinical Psychiatry*, *75*(8), 3169. https://doi.org/10.4088/JCP.13r08609

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., ... & Padberg, F. (2011). Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. *Journal of Neuroscience*, *31*(43), 15284-15293. https://doi.org/10.1523/JNEUROSCI.0542-11.2011

Keller, M. B. (2003). Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. *JAMA*, *289*(23), 3152-3160. https://doi.org/10.1001/jama.289.23.3152

Keller, A. S., Leikauf, J. E., Holt-Gosselin, B., Staveland, B. R., & Williams, L. M. (2019). Paying attention to attention in depression. *Translational Psychiatry*, *9*(1), 1-12. https://doi.org/10.1038/s41398-019-0616-1

Kelley, M. L., Heffer, R. W., Gresham, F. M., & Elliott, S. N. (1989). Development of a modified treatment evaluation inventory. *Journal of psychopathology and behavioral assessment*, *11*(3), 235-247. https://doi.org/10.1007/BF00960495

Kennedy, N., Foy, K., Sherazi, R., McDonough, M., & McKeon, P. (2007). Long-term social functioning after depression treated by psychiatrists: a review. *Bipolar Disorders*, *9*(1-2), 25-37. https://doi.org/10.1111/j.1399-5618.2007.00326.x

Kessing, L. V., Forman, J. L., & Andersen, P. K. (2011). Do continued antidepressants protect against dementia in patients with severe depressive disorder?. *International clinical psychopharmacology*, *26*(6), 316-322. https://doi.org/10.1097/YIC.0b013e32834ace0f

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual review of psychology*, *48*(1), 191-214. https://doi.org/10.1146/annurev.psych.48.1.191

Kessler, R. C., & Bromet, E. J. (2013). The epidemiology of depression across cultures. *Annual review of public health*, *34*, 119-138. https://doi.org/10.1146/annurev-publhealth-031912-114409

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., ... & Wang, P. S. (2003). The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*, *289*(23), 3095-3105. https://doi.org/10.1001/jama.289.23.3095

Kessler, S. K., Turkeltaub, P. E., Benson, J. G., & Hamilton, R. H. (2012). Differences in the experience of active and sham transcranial direct current stimulation. *Brain Stimulation*, *5*(2), 155-162. https://doi.org/10.1016/j.brs.2011.02.007

Khalaf, A., Edelman, K., Tudorascu, D., Andreescu, C., Reynolds, C. F., & Aizenstein, H. (2015). White matter hyperintensity accumulation during treatment of late-life depression. *Neuropsychopharmacology*, *40*(13), 3027-3035. https://doi.org/10.1038/npp.2015.158

Kiebs, M., Hurlemann, R., & Mutz, J. (2019). Repetitive transcranial magnetic stimulation in non-treatment-resistant depression. *The British Journal of Psychiatry*, *215*(2), 445-446.

Kim, B. S., Lee, D. H., Lee, D. W., Bae, J. N., Chang, S. M., Kim, S., & Cho, M. J. (2011). The role of vascular risk factors in the development of DED syndrome among an elderly community sample. *The American Journal of Geriatric Psychiatry*, *19*(2), 104-114. https://doi.org/10.1097/JGP.0b013e31820119b6

Kim, H., Thyer, B. A., & Munn, J. C. (2019). The relationship between perceived ageism and depressive symptoms in later life: Understanding the mediating effects of self-perception of aging and purpose in life, using structural equation modeling. *Educational Gerontology*, *45*(2), 105-119. https://doi.org/10.1080/03601277.2019.1583403

Kim, Y. K., & Han, K. M. (2021). Neural substrates for late-life depression: A selective review of structural neuroimaging studies. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *104*, 110010. https://doi.org/10.1016/j.pnpbp.2020.110010

Kirsch, I. (2000). Are drug and placebo effects in depression additive?. *Biological psychiatry*, *47*(8), 733-735. https://doi.org/10.1016/S0006-3223(00)00832-5

Kishimoto, T., Chawla, J. M., Hagi, K., Zarate, C. A., Kane, J. M., Bauer, M., & Correll, C. (2016). Single-dose infusion ketamine and non-ketamine N-methyl-d-aspartate receptor antagonists for unipolar and bipolar depression: a meta-analysis of efficacy, safety and time trajectories. *Psychological Medicine*, *46*(7), 1459-1472. https://doi.org/10.1017/S0033291716000064

Kishita, N., Takei, Y., & Stewart, I. (2017). A meta-analysis of third wave mindfulness-based cognitive behavioral therapies for older people. *International Journal of Geriatric Psychiatry*, *32*(12), 1352-1361. https://doi.org/10.1002/gps.4621

Kizilbash, A. H., Vanderploeg, R. D., & Curtiss, G. (2002). The effects of depression and anxiety on memory performance. *Archives of clinical neuropsychology*, *17*(1), 57-67. https://doi.org/10.1093/arclin/17.1.57

Knight, M. J., Air, T., & Baune, B. T. (2018). The role of cognitive impairment in psychosocial functioning in remitted depression. *Journal of Affective Disorders*, *235*, 129-134. https://doi.org/10.1016/j.jad.2018.04.051

Knight, R. G., McMahon, J., Skeaff, C. M., & Green, T. J. (2007). Reliable Change Index scores for persons over the age of 65 tested on alternate forms of the Rey AVLT. *Archives of Clinical Neuropsychology*, *22*(4), 513-518. https://doi.org/10.1016/j.acn.2007.03.005

Kober, H., Barrett, L. F., Joseph, J., Bliss-Moreau, E., Lindquist, K., & Wager, T. D. (2008). Functional grouping and cortical–subcortical interactions in emotion: a meta-analysis of neuroimaging studies. *Neuroimage*, *42*(2), 998-1031. https://doi.org/10.1016/j.neuroimage.2008.03.059

Koenig, A. M., Bhalla, R. K., & Butters, M. A. (2014). Cognitive functioning and late-life depression. *Journal of the International Neuropsychological Society*, *20*(5), 461-467. https://doi.org/10.1017/S1355617714000198

Koenigs, M., & Grafman, J. (2009). The functional neuroanatomy of depression: distinct roles for ventromedial and dorsolateral prefrontal cortex. *Behavioural brain research*, *201*(2), 239-243.

Köhler, C. A., Freitas, T. H., Maes, M. D., De Andrade, N. Q., Liu, C. S., Fernandes, B. S., ... & Carvalho, A. (2017). Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. *Acta Psychiatrica Scandinavica*, *135*(5), 373-387. https://doi.org/10.1111/acps.12698

Köhler, S., Thomas, A. J., Barnett, N. A., & O'Brien, J. T. (2010). The pattern and course of cognitive impairment in late-life depression. *Psychological Medicine*, *40*(4), 591-602. https://doi.org/10.1017/S0033291709990833

Kohn, R., Saxena, S., Levav, I., & Saraceno, B. (2004). The treatment gap in mental health care. *Bulletin of the World Health Organization*, *82*, 858-866.

Kok, R. M., & Reynolds, C. F. (2017). Management of depression in older adults: a review. *JAMA*, *317*(20), 2114-2122. https://doi.org/10.1001/jama.2017.5706

Kok, R. M., Nolen, W. A., & Heeren, T. J. (2012). Efficacy of treatment in older depressed patients: a systematic review and meta-analysis of double-blind randomized controlled trials with antidepressants. *Journal of Affective Disorders*, *141*(2-3), 103-115. https://doi.org/10.1016/j.jad.2012.02.036

Kolovos, S., Kleiboer, A., & Cuijpers, P. (2016). Effect of psychotherapy for depression on quality of life: meta-analysis. *The British Journal of Psychiatry*, *209*(6), 460-468. https://doi.org/10.1192/bjp.bp.115.175059

Kontis, V., Bennett, J. E., Mathers, C. D., Li, G., Foreman, K., & Ezzati, M. (2017). Future life expectancy in 35 industrialised countries: projections with a Bayesian model ensemble. *The Lancet*, *389*(10076), 1323-1335. https://doi.org/10.1016/S0140-6736(16)32381-9

Korte, J., Bohlmeijer, E. T., Cappeliez, P., Smit, F., & Westerhof, G. J. (2012). Life review therapy for older adults with moderate depressive symptomatology: A pragmatic randomized controlled trial. *Psychological Medicine*, *42*(6), 1163-1173. https://doi.org/10.1017/S0033291711002042

Kraus, C., Wasserman, D., Henter, I. D., Acevedo-Diaz, E., Kadriu, B., & Zarate Jr, C. A. (2019). The influence of ketamine on drug discovery in depression. *Drug Discovery Today*, *24*(10), 2033-2043. https://doi.org/10.1016/j.drudis.2019.07.007

Krause, M., Gutsmiedl, K., Bighelli, I., Schneider-Thoma, J., Chaimani, A., & Leucht, S. (2019). Efficacy and tolerability of pharmacological and non-pharmacological interventions in older patients with major depressive disorder: A systematic review, pairwise and network meta-analysis. *European Neuropsychopharmacology*, *29*(9), 1003-1022. https://doi.org/10.1016/j.euroneuro.2019.07.130

Krishnan, V., & Nestler, E. J. (2010). Linking molecules to mood: new insight into the biology of depression. *American Journal of Psychiatry*, *167*(11), 1305-1320. https://doi.org/10.1176/appi.ajp.2009.10030434

Kroenke, K., Spitzer, R. L., & Williams, J. B. (2001). The PHQ-9: validity of a brief depression severity measure. *Journal of general internal medicine*, *16*(9), 606-613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Krogh, J., Benros, M. E., Jørgensen, M. B., Vesterager, L., Elfving, B., & Nordentoft, M. (2014). The association between depressive symptoms, cognitive function, and inflammation in major depression. *Brain, Behavior, and Immunity*, *35*, 70-76. https://doi.org/10.1016/j.bbi.2013.08.014

Kühberger, A., Fritz, A., & Scherndl, T. (2014). Publication bias in psychology: A diagnosis based on the correlation between effect size and sample size. *PloS One*, *9*(9), e105825. https://doi.org/10.1371/journal.pone.0105825

Kulas, J. F., & Naugle, R. I. (2003). Indications for neuropsychological assessment. *Cleveland Clinic Journal of Medicine*, *70*(9), 785-792. https://doi.org/10.3949/ccjm.70.9.785

Kumar, S., Batist, J., Ghazala, Z., Zomorrodi, R. M., Brooks, H., Goodman, M., ... & Rajji, T. K. (2020). Effects of bilateral transcranial direct current stimulation on working memory and global cognition in older patients with remitted major depression: A pilot randomized clinical trial. *International Journal of Geriatric Psychiatry*, *35*(10), 1233-1242. https://doi.org/10.1002/gps.5361

Kundermann, B., Hemmeter-Spernal, J., Strate, P., Gebhardt, S., Huber, M. T., Krieg, J. C., & Lautenbacher, S. (2015). Neuropsychological predictors of the clinical response to cognitive-behavioral therapy in patients with major depression. *Zeitschrift für Neuropsychologie*, *26*(2), 87-97. https://doi.org/10.1024/1016-264X/a000130

Kupferberg, A., Bicks, L., & Hasler, G. (2016). Social functioning in major depressive disorder. *Neuroscience & Biobehavioral Reviews*, *69*, 313-332. https://doi.org/10.1016/j.neubiorev.2016.07.002

Kurzeck, A. K., Dechantsreiter, E., Wilkening, A., Kumpf, U., Nenov-Matt, T., Padberg, F., & Palm, U. (2021). Transcranial Direct Current Stimulation (tDCS) for Depression during Pregnancy: Results from an Open-Label Pilot Study. *Brain Sciences*, *11*(7), 947. https://doi.org/10.3390/brainsci11070947

Kurzeck, A. K., Kirsch, B., Weidinger, E., Padberg, F., & Palm, U. (2018). Transcranial Direct Current Stimulation (tDCS) for Depression during Pregnancy: Scientific Evidence and What Is Being Said in the Media--A Systematic Review. *Brain Sciences (2076-3425)*, *8*(8). https://doi.org/10.3390/brainsci8080155

Kvale, S. (2006). Dominance through interviews and dialogues. *Qualitative inquiry*, *12*(3), 480-500.

Lamers, F., Vogelzangs, N., Merikangas, K. R., De Jonge, P., Beekman, A. T. F., & Penninx, B. W. J. H. (2013). Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Molecular Psychiatry*, *18*(6), 692-699. https://doi.org/10.1038/mp.2012.144

Lancaster, G. A., Dodd, S., & Williamson, P. R. (2004). Design and analysis of pilot studies: recommendations for good practice. *Journal of Evaluation in Clinical Practice*, *10*(2), 307-312. https://doi.org/10.1111/j..2002.384.doc.x

Lattie, E. G., Adkins, E. C., Winquist, N., Stiles-Shields, C., Wafford, Q. E., & Graham, A. K. (2019). Digital mental health interventions for depression, anxiety, and enhancement of psychological well-being among college students: systematic review. *Journal of Medical Internet Research*, *21*(7), e12869. https://doi.org/10.2196/12869

Lazard, L., & McAvoy, J. (2020). Doing reflexivity in psychological research: What's the point? What's the practice?. *Qualitative research in psychology*, *17*(2), 159-177.

Lebowitz, B. D., Pearson, J. L., Schneider, L. S., Reynolds, C. F., Alexopoulos, G. S., Bruce, M. L., ... & Parmelee, P. (1997). Diagnosis and treatment of depression in late life: consensus statement update. *JAMA*, *278*(14), 1186-1190. https://doi.org/10.1001/jama.1997.03550140078045

Lee, E. E., Della Selva, M. P., Liu, A., & Himelhoch, S. (2015). Ketamine as a novel treatment for major depressive disorder and bipolar depression: a systematic review and quantitative meta-analysis. *General Hospital Psychiatry*, *37*(2), 178-184. https://doi.org/10.1016/j.genhosppsych.2015.01.003

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, Noel-Storr A, Rader T, Shokraneh F, Thomas J, Wieland LS. Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

Legon, W., Adams, S., Bansal, P., Patel, P. D., Hobbs, L., Ai, L., ... & Gillick, B. T. (2020). A retrospective qualitative report of symptoms and safety from transcranial focused ultrasound for neuromodulation in humans. *Scientific reports*, *10*(1), 1-10.

LeMoult, J., & Gotlib, I. H. (2019). Depression: A cognitive perspective. *Clinical Psychology Review*, *69*, 51-66. https://doi.org/10.1016/j.cpr.2018.06.008

Lenze, E. J., Mulsant, B. H., Shear, M. K., Alexopoulos, G. S., Frank, E., & Reynolds, C. F. (2001). Comorbidity of depression and anxiety disorders in later life. *Depression and Anxiety*, *14*(2), 86-93. https://doi.org/10.1002/da.1050

Leshikar, E. D., Leach, R. C., McCurdy, M. P., Trumbo, M. C., Sklenar, A. M., Frankenstein, A. N., & Matzen, L. E. (2017). Transcranial direct current stimulation of dorsolateral prefrontal cortex during encoding improves recall but not recognition memory. *Neuropsychologia*, *106*, 390-397. https://doi.org/10.1016/j.neuropsychologia.2017.10.022

Levinson, D. F., Mostafavi, S., Milaneschi, Y., Rivera, M., Ripke, S., Wray, N. R., & Sullivan, P. F. (2014). Genetic studies of major depressive disorder: why are there no genome-wide association study findings and what can we do about it?. *Biological Psychiatry*, *76*(7), 510-512. https://doi.org/10.1016/j.biopsych.2014.07.029

Lewin, S., Glenton, C., & Oxman, A. D. (2009). Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: methodological study. *Bmj*, *339*.

Lewis, S., & Clarke, M. (2001). Forest plots: trying to see the wood and the trees. *Bmj*, *322*(7300), 1479-1480. https://doi.org/10.1136/bmj.322.7300.1479

Lewinsohn, P. M. (1974). A behavioral approach to depression. *Essential Papers on Depression*, 150-172.

Lezak, M. D., Howieson, D. B., Loring, D. W., & Fischer, J. S. (2004). *Neuropsychological assessment*. Oxford University Press, USA.

Li, L. M., Uehara, K., & Hanakawa, T. (2015). The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in cellular neuroscience*, *9*, 181. https://doi.org/10.1002/da.1050

Liao, W., Zhang, X., Shu, H., Wang, Z., Liu, D., & Zhang, Z. (2017). The characteristic of cognitive dysfunction in remitted late life depression and amnestic mild cognitive impairment. *Psychiatry Research*, *251*, 168-175. https://doi.org/10.1016/j.psychres.2017.01.024

Lichtenthal, W. G., Cruess, D. G., & Prigerson, H. G. (2004). A case for establishing complicated grief as a distinct mental disorder in DSM-V. *Clinical Psychology Review*, *24*(6), 637-662. https://doi.org/10.1016/j.cpr.2004.07.002

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*, *125*(10), 2238-2247. https://doi.org/10.1093/brain/awf238

Lin, E. H., Von Korff, M., Ludman, E. J., Rutter, C., Bush, T. M., Simon, G. E., ... & Katon, W. J. (2003). Enhancing adherence to prevent depression relapse in primary care. *General Hospital Psychiatry*, *25*(5), 303-310. https://doi.org/10.1016/S0163-8343(03)00074-4

Lin, L. (2018). Bias caused by sampling error in meta-analysis with small sample sizes. *PLoS ONE*, *13*(9), e0204056. https://doi.org/10.1371/journal.pone.0204056

Lincoln, Y. S., & Guba, E. G. (1985). *Naturalistic inquiry*. Sage.

Linnemayr, S., MacCarthy, S., Kim, A., Giguere, R., Carballo-Dieguez, A., & Barreras, J. L. (2018). Behavioral economics-based incentives supported by mobile technology on HIV knowledge and testing frequency among Latino/a men who have sex with men and transgender women: protocol for a randomized pilot study to test intervention feasibility and acceptability. *Trials*, *19*(1), 1-9. https://doi.org/10.1186/s13063-018-2867-1

Locher, C., Kossowsky, J., Gaab, J., Kirsch, I., Bain, P., & Krummenacher, P. (2015). Moderation of antidepressant and placebo outcomes by baseline severity in late-life depression: a systematic review and meta-analysis. *Journal of Affective Disorders*, *181*, 50-60. https://doi.org/10.1016/j.jad.2015.03.062

Lockwood, K. A., Alexopoulos, G. S., & van Gorp, W. G. (2002). Executive dysfunction in geriatric depression. *American Journal of Psychiatry*, *159*(7), 1119-1126. https://doi.org/10.1176/appi.ajp.159.7.1119

Loo, C. K., Alonzo, A., Martin, D., Mitchell, P. B., Galvez, V., & Sachdev, P. (2012). Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *The British Journal of Psychiatry*, *200*(1), 52-59. doi: 10.1192/bjp.bp.111.097634 https://doi.org/10.1192/bjp.bp.111.097634

Loo, C. K., Sachdev, P., Martin, D., Pigot, M., Alonzo, A., Malhi, G. S., ... & Mitchell, P. (2010). A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *The International Journal of Neuropsychopharmacology*, *13*(1), 61-69. https://doi.org/10.1017/S1461145709990411

Loo, C. K., Husain, M. M., McDonald, W. M., Aaronson, S., O'Reardon, J. P., Alonzo, A., ... & Lisanby, S. H. (2017). International randomized-controlled trial of transcranial Direct Current Stimulation in depression. *Brain Stimulation*, *11*(1), 125-133. https://doi.org/10.1016/j.brs.2017.10.011

Lorem, G. F., Hem, M. H., & Molewijk, B. (2015). Good coercion: Patients' moral evaluation of coercion in mental health care. *International journal of mental health nursing*, *24*(3), 231-240.

Luber, B., Fisher, C., Appelbaum, P. S., Ploesser, M., & Lisanby, S. H. (2009). Non-invasive brain stimulation in the detection of deception: Scientific challenges and ethical consequences. *Behavioral Sciences & the Law*, *27*(2), 191-208. https://doi.org/10.1002/bsl.860

Luijendijk, H. J., van den Berg, J. F., Dekker, M. J., van Tuijl, H. R., Otte, W., Smit, F., ... & Tiemeier, H. (2008). Incidence and recurrence of late-life depression. *Archives of General Psychiatry*, *65*(12), 1394-1401. https://doi.org/10.1001/archpsyc.65.12.1394

Luppa, M., Sikorski, C., Luck, T., Weyerer, S., Villringer, A., König, H. H., & Riedel-Heller, S. G. (2012). Prevalence and risk factors of depressive symptoms in latest life—results of the Leipzig Longitudinal Study of the Aged (LEILA 75+). *International Journal of Geriatric Psychiatry*, *27*(3), 286-295. https://doi.org/10.1002/gps.2718

Luppa, M., Luck, T., König, H. H., Angermeyer, M. C., & Riedel-Heller, S. G. (2012). Natural course of depressive symptoms in late life. An 8-year population-based prospective study. *Journal of Affective Disorders*, *142*(1-3), 166-171. https://doi.org/10.1016/j.jad.2012.05.009

Luria, A.R. (1966). *Higher cortical functions in man.* Basic Books.

MacCallum, R. C., Widaman, K. F., Zhang, S., & Hong, S. (1999). Sample size in factor analysis. *Psychological Methods*, *4*(1), 84. https://doi.org/10.1037/1082-989X.4.1.84

Machado-Vieira, R., Salvadore, G., Luckenbaugh, D. A., Manji, H. K., & Zarate Jr, C. A. (2008). Rapid onset of antidepressant action: a new paradigm in the research and treatment of major depression. *The Journal of clinical psychiatry*, *69*(6), 946. https://doi.org/10.4088/JCP.v69n0610

MacPhillamy, D. J., & Lewinsohn, P. M. (1974). Depression as a function of levels of desired and obtained pleasure. *Journal of Abnormal Psychology*, *83*(6), 651. https://doi.org/10.1037/h0037467

MacPhillamy, D. J., & Lewinsohn, P. M. (1982). The pleasant events schedule: Studies on reliability, validity, and scale intercorrelation. *Journal of Consulting and Clinical Psychology*, *50*(3), 363. https://doi.org/10.1037/0022-006X.50.3.363

Maeoka, H., Matsuo, A., Hiyamizu, M., Morioka, S., & Ando, H. (2012). Influence of transcranial direct current stimulation of the dorsolateral prefrontal cortex on pain related emotions: a study using electroencephalographic power spectrum analysis. *Neuroscience letters*, *512*(1), 12-16. https://doi.org/10.1016/j.neulet.2012.01.037

Majdan, A., Sziklas, V., & Jones-Gotman, M. (1996). Performance of healthy subjects and patients with resection from the anterior temporal lobe on matched tests of verbal and visuoperceptual learning. *Journal of Clinical and Experimental Neuropsychology*, *18*(3), 416-430. https://doi.org/10.1080/01688639608408998

Majid, U., & Gagliardi, A. (2019). Conceptual frameworks and degrees of patient engagement in the planning and designing of health services: a scoping review of qualitative studies. *Patient Experience Journal*, *6*(3), 82-90. https://doi.org/10.35680/2372-0247.1356

Mannell, J., & Davis, K. (2019). Evaluating complex health interventions with randomized controlled trials: how do we improve the use of qualitative methods?. *Qualitative Health Research*, *29*(5), 623-631. https://doi.org/10.1177/1049732319831032

Manos, R. C., Kanter, J. W., & Busch, A. M. (2010). A critical review of assessment strategies to measure the behavioral activation model of depression. *Clinical Psychology Review*, *30*(5), 547-561. https://doi.org/10.1016/j.cpr.2010.03.008

Manthorpe, J., & Iliffe, S. (2010). Suicide in later life: public health and practitioner perspectives. *International Journal of Geriatric Psychiatry*, *25*(12), 1230-1238. https://doi.org/10.1002/gps.2473

Maroun, R. A., Thackeray, L. A., & Midgley, N. (2018). Meaning and medication: a thematic analysis of depressed adolescents' views and experiences of SSRI antidepressants alongside psychological therapies. *BMC Psychiatry*, *18*(1), 1-11. https://doi.org/10.1186/s12888-018-1961-y

Martin, D. M., Alonzo, A., Mitchell, P. B., Sachdev, P., Gálvez, V., & Loo, C. K. (2011). Fronto-extracephalic transcranial direct current stimulation as a treatment for major depression: an open-label pilot study. *Journal of Affective Disorders*, *134*(1-3), 459-463. https://doi.org/10.1016/j.jad.2011.05.018

Martin, D. M., Alonzo, A., Ho, K. A., Player, M., Mitchell, P. B., Sachdev, P., & Loo, C. K. (2013). Continuation transcranial direct current stimulation for the prevention of relapse in major depression. *Journal of Affective Disorders*, *144*(3), 274-278. https://doi.org/10.1016/j.jad.2012.10.012

Martin, D. M., Moffa, A., Nikolin, S., Bennabi, D., Brunoni, A. R., Flannery, W., ... & Palm, U. (2018). Cognitive effects of transcranial direct current stimulation treatment in patients with major depressive disorder: an individual patient data meta-analysis of randomised, sham-controlled trials. *Neuroscience & Biobehavioral Reviews*, *90*, 137-145. https://doi.org/10.1016/j.neubiorev.2018.04.008

Matsumoto, H., & Ugawa, Y. (2017). Adverse events of tDCS and tACS: a review. *Clinical Neurophysiology Practice*, *2*, 19-25. https://doi.org/10.1016/j.cnp.2016.12.003

Maxwell, J. A. (2015). A critical realist perspective for qualitative research. *Qualitative inquiry—past, present, and future: a critical reader*, *88*.

Maxwell, J. A. (2008). Designing a qualitative study. *The SAGE Handbook of Applied Social Research Methods*, *2*, 214-253. https://doi.org/10.4135/9781483348858.n7

Mazza, M. G., De Lorenzo, R., Conte, C., Poletti, S., Vai, B., Bollettini, I., ... & COVID-19 BioB Outpatient Clinic Study Group. (2020). Anxiety and depression in COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain, Behavior, and Immunity*, *89*, 594-600. https://doi.org/10.1016/j.bbi.2020.07.037

McClintock, S. M., Husain, M. M., Greer, T. L., & Cullum, C. M. (2010). Association between depression severity and neurocognitive function in major depressive disorder: a review and synthesis. *Neuropsychology*, *24*(1), 9. https://doi.org/10.1037/a0017336

McClintock, S. M., Martin, D. M., Lisanby, S. H., Alonzo, A., McDonald, W. M., Aaronson, S. T., ... & Loo, C. K. (2020). Neurocognitive effects of transcranial direct current stimulation (tDCS) in unipolar and bipolar depression: findings from an international randomized controlled trial. *Depression and Anxiety*, *37*(3), 261-272. https://doi.org/10.1002/da.22988

McClintock, S. M., Reti, I. M., Carpenter, L. L., McDonald, W. M., Dubin, M., Taylor, S. F., ... & Lisanby, S. H. (2017). Consensus recommendations for the clinical application of repetitive transcranial

magnetic stimulation (rTMS) in the treatment of depression. *The Journal of clinical psychiatry*, *79*(1), 3651.

McDermott, L. M., & Ebmeier, K. P. (2009). A meta-analysis of depression severity and cognitive function. *Journal of Affective Disorders*, *119*(1-3), 1-8. https://doi.org/10.1016/j.jad.2009.04.022

McHugh, R. K., Whitton, S. W., Peckham, A. D., Welge, J. A., & Otto, M. W. (2013). Patient preference for psychological vs pharmacologic treatment of psychiatric disorders: a meta-analytic review. *The Journal of Clinical Psychiatry*, *74*(6), 0-0. https://doi.org/10.4088/JCP.12r07757

McKinney, B. C., & Sibille, E. (2013). The age-by-disease interaction hypothesis of late-life depression. *The American Journal of Geriatric Psychiatry*, *21*(5), 418-432. https://doi.org/10.1016/j.jagp.2013.01.053

McMinn, M. R., Wiens, A. N., & Crossen, J. R. (1988). Rey Auditory-Verbal Learning Test: Development of norms for healthy young adults. *The Clinical Neuropsychologist*, *2*(1), 67-87. https://doi.org/10.1080/13854048808520087

McNeish, D. (2016). On using Bayesian methods to address small sample problems. *Structural Equation Modeling: A Multidisciplinary Journal*, *23*(5), 750-773. https://doi.org/10.1080/10705511.2016.1186549

Mead, N., & Bower, P. (2000). Patient-centredness: a conceptual framework and review of the empirical literature. *Social Science & Medicine*, *51*(7), 1087-1110. https://doi.org/10.1016/S0277-9536(00)00098-8

Mendes, T., Cardoso, S., Guerreiro, M., Maroco, J., Silva, D., Alves, L., ... & de Mendonça, A. (2021). Memory awareness in patients with Major Depressive Disorder. *Journal of Psychiatric Research*, *137*, 411-418. https://doi.org/10.1016/j.jpsychires.2021.03.016

Mennin, D. S., Holaway, R. M., Fresco, D. M., Moore, M. T., & Heimberg, R. G. (2007). Delineating components of emotion and its dysregulation in anxiety and mood psychopathology. *Behavior Therapy*, *38*(3), 284-302. https://doi.org/10.1016/j.beth.2006.09.001

Mergl, R., Henkel, V., Allgaier, A. K., Kramer, D., Hautzinger, M., Kohnen, R., ... & Hegerl, U. (2011). Are treatment preferences relevant in response to serotonergic antidepressants and cognitive-behavioral therapy in depressed primary care patients? Results from a randomized controlled trial including a patients' choice arm. *Psychotherapy and Psychosomatics*, *80*(1), 39-47. https://doi.org/10.1159/000318772

Meron, D., Hedger, N., Garner, M., & Baldwin, D. S. (2015). Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability. *Neuroscience & Biobehavioral Reviews, 57*, 46-62. https://doi.org/10.1016/j.neubiorev.2015.07.012

Merriam, S. B., Johnson-Bailey, J., Lee, M. Y., Kee, Y., Ntseane, G., & Muhamad, M. (2001). Power and positionality: Negotiating insider/outsider status within and across cultures. *International Journal of Lifelong Education*, *20*(5), 405-416. https://doi.org/10.1080/02601370120490

Metts, A. V., Keilp, J. G., Kishon, R., Oquendo, M. A., Mann, J. J., & Miller, J. M. (2018). Neurocognitive performance predicts treatment outcome with cognitive behavioral therapy for

major depressive disorder. *Psychiatry Research*, *269*, 376-385. https://doi.org/10.1016/j.psychres.2018.08.011

Meyrick, J. (2006). What is good qualitative research? A first step towards a comprehensive approach to judging rigour/quality. *Journal of Health Psychology*, *11*(5), 799-808. https://doi.org/10.1177/1359105306066643

Milev, R., Abraham, G., Hasey, G., & Cabaj, J. L. (2009). Repetitive transcranial magnetic stimulation for treatment of medication-resistant depression in older adults: a case series. *The Journal of ECT*, *25*(1), 44-49. https://doi.org/10.1097/YCT.0b013e3181770237

Millan, M. J., Agid, Y., Brüne, M., Bullmore, E. T., Carter, C. S., Clayton, N. S., ... & Young, L. J. (2012). Cognitive dysfunction in psychiatric disorders: characteristics, causes and the quest for improved therapy. *Nature Reviews Drug Discovery*, *11*(2), 141-168. https://doi.org/10.1038/nrd3628

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biological Psychiatry*, *65*(9), 732-741. https://doi.org/10.1016/j.biopsych.2008.11.029

Miller, D. B., & O'callaghan, J. P. (2005). Aging, stress, and the hippocampus. *Ageing Research Reviews*, *4*(2), 123-140. https://doi.org/10.1016/j.arr.2005.03.002

Miller, T. I. (1979). Comparative Effects of Drug Therapy, Psychotherapy and Drug Plus Psychotherapy: A Meta-Analysis. (Abstract only)

Miller, D. L., & Kelley, M. L. (1992). Treatment acceptability: The effects of parent gender, marital adjustment, and child behavior. *Child & Family Behavior Therapy*, *14*(1), 11-23. https://doi.org/10.1300/J019v14n01_02

Miller, D. L., Manne, S., & Palevsky, S. (1998). Brief report: Acceptance of behavioral interventions for children with cancer: Perceptions of parents, nurses, and community controls. *Journal of Pediatric Psychology*, *23*(4), 267-271. https://doi.org/10.1093/jpepsy/23.4.267

Miltenberger, R. G. (1990). Assessment of treatment acceptability: A review of the literature. *Topics in Early Childhood Special Education*, *10*(3), 24-38. https://doi.org/10.1177/027112149001000304

Miskowiak, K. W., & Carvalho, A. F. (2014). 'Hot'Cognition in Major Depressive Disorder: A Systematic Review. *CNS & Neurological Disorders-Drug Targets*, *13*, 1787-1803. https://doi.org/10.2174/1871527313666141130205713

Mitchell, A. J., Rao, S., & Vaze, A. (2010). Do primary care physicians have particular difficulty identifying late-life depression? A meta-analysis stratified by age. *Psychotherapy and Psychosomatics*, *79*(5), 285-294. https://doi.org/10.1159/000318295

Mitchell, A. J., Vaze, A., & Rao, S. (2009). Clinical diagnosis of depression in primary care: a meta-analysis. *The Lancet*, *374*(9690), 609-619. https://doi.org/10.1016/S0140-6736(09)60879-5

Mitrushina, M., Boone, K. B., Razani, J., & D'Elia, L. F. (2005). *Handbook of normative data for neuropsychological assessment*. Oxford University Press.

Miyake, A., & Friedman, N. P. (2012). The nature and organization of individual differences in executive functions: Four general conclusions. *Current Directions in Psychological Science*, *21*(1), 8-14. https://doi.org/10.1177/0963721411429458

Moffa, A. H., Brunoni, A. R., Fregni, F., Palm, U., Padberg, F., Blumberger, D. M., ... & Loo, C. K. (2017). Safety and acceptability of transcranial direct current stimulation for the acute treatment of major depressive episodes: analysis of individual patient data. *Journal of Affective Disorders*, *221*, 1-5. https://doi.org/10.1016/j.jad.2017.06.021

Moffa, A. H., Martin, D., Alonzo, A., Bennabi, D., Blumberger, D. M., Benseñor, I. M., ... & Brunoni, A. R. (2020). Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: an individual patient data meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *99*, 109836. https://doi.org/10.1016/j.pnpbp.2019.109836

Mohammadkhanizadeh, A., & Nikbakht, F. (2021). Investigating the potential mechanisms of depression induced-by COVID-19 infection in patients. *Journal of Clinical Neuroscience*, *91*, 283-287. https://doi.org/10.1016/j.jocn.2021.07.023

Moher, D., Fortin, P., Jadad, A. R., Jüni, P., Klassen, T., Le Lorier, J., ... & Linde, K. (1996). Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. *The Lancet*, *347*(8998), 363-366. https://doi.org/10.1016/S0140-6736(96)90538-3

Møller, A. M., & Myles, P. S. (2016). What makes a good systematic review and meta-analysis?. *British Journal of Anaesthesia*, *117*(4), 428-430. https://doi.org/10.1093/bja/aew264

Molodynski, A., Rugkåsa, J., & Burns, T. (2010). Coercion and compulsion in community mental health care. *British medical bulletin*, *95*(1), 105-119.

Moncrieff, J., Cooper, R. E., Stockmann, T., Amendola, S., Hengartner, M. P., & Horowitz, M. A. (2022). The serotonin theory of depression: a systematic umbrella review of the evidence. *Molecular psychiatry*, 1-14.

Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain Stimulation*, *6*(3), 424-432. https://doi.org/10.1016/j.brs.2012.04.011

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: implications for the depressive disorders. *Psychological bulletin*, *110*(3), 406. https://doi.org/10.1037/0033-2909.110.3.406

Montgomery, S. A., & Åsberg, M. A. (1979). A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry*, *134*(4), 382-389. https://doi.org/10.1192/bjp.134.4.382

Moosa, M. Y. H., Jeenah, F. Y., & Kazadi, N. (2007). Treatment adherence. *South African Journal of Psychiatry*, *13*(2), 40-45. https://doi.org/10.4102/sajpsychiatry.v13i2.26

Moreno, M. L., Goerigk, S. A., Bertola, L., Suemoto, C. K., Razza, L. B., Moffa, A. H., ... & Brunoni, A. R. (2020). Cognitive changes after tDCS and escitalopram treatment in major depressive disorder: results from the placebo-controlled ELECT-TDCS trial. *Journal of Affective Disorders*, *263*, 344-352. https://doi.org/10.1016/j.jad.2019.12.009

Morgan, B., Hejdenberg, J., Hinrichs-Krapels, S., & Armstrong, D. (2018). Do feasibility studies contribute to, or avoid, waste in research?. *PloS One*, *13*(4), e0195951. https://doi.org/10.1371/journal.pone.0195951

Morgello, S. (2020). Coronaviruses and the central nervous system. *Journal of Neurovirology*, *26*(4), 459-473. https://doi.org/10.1007/s13365-020-00868-7

Morse, J. M. (1995). *The significance of saturation*. 147-149 Available from: The Significance of Saturation (sagepub.com) https://doi.org/10.1177/104973239500500201

Moss, H., Donnellan, C., & O'Neill, D. (2012). A review of qualitative methodologies used to explore patient perceptions of arts and healthcare. *Medical Humanities*, *38*(2), 106-109. https://doi.org/10.1136/medhum-2012-010196

Midgley, N., Ansaldo, F., & Target, M. (2014). The meaningful assessment of therapy outcomes: Incorporating a qualitative study into a randomized controlled trial evaluating the treatment of adolescent depression. *Psychotherapy*, *51*(1), 128. https://doi.org/10.1037/a0034179

Mulinari, S. (2012). Monoamine theories of depression: historical impact on biomedical research. *Journal of the History of the Neurosciences*, *21*(4), 366-392. https://doi.org/10.1080/0964704X.2011.623917

Muka, T., Glisic, M., Milic, J., Verhoog, S., Bohlius, J., Bramer, W., ... & Franco, O. H. (2020). A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research. *European Journal of Epidemiology*, *35*(1), 49-60. https://doi.org/10.1007/s10654-019-00576-5

Mulder, Roger T., Peter R. Joyce, and Chris Frampton. "Relationships among measures of treatment outcome in depressed patients." *Journal of Affective Disorders* 76.1-3 (2003): 127-135. https://doi.org/10.1016/S0165-0327(02)00080-0

Munkholm, K., Paludan-Müller, A. S., & Boesen, K. (2019). Considering the methodological limitations in the evidence base of antidepressants for depression: a reanalysis of a network meta-analysis. *BMJ Open*, *9*(6), e024886. https://doi.org/10.1136/bmjopen-2018-024886

Murad, M. H., Wang, Z., Chu, H., & Lin, L. (2019). When continuous outcomes are measured using different scales: guide for meta-analysis and interpretation. *BMJ*, *364*. https://doi.org/10.1136/bmj.k4817

Murray, G., Gottlieb, J., & Swartz, H. A. (2021). Maintaining daily routines to stabilize mood: theory, data, and potential intervention for circadian consequences of COVID-19. *The Canadian Journal of Psychiatry*, *66*(1), 9-13.

Musselman, D. L., & Nemeroff, C. B. (1996). Depression and endocrine disorders: focus on the thyroid and adrenal system. *The British Journal of Psychiatry*, *168*(S30), 123-128.

Mutz, J., Edgcumbe, D. R., Brunoni, A. R., & Fu, C. H. (2018). Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic review and meta-analysis of randomised sham-controlled trials. *Neuroscience & Biobehavioral Reviews*, *92*, 291-303. https://doi.org/10.1016/j.neubiorev.2018.05.015

Mutz, J., Vipulananthan, V., Carter, B., Hurlemann, R., Fu, C. H., & Young, A. H. (2019). Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *BMJ*, *364*. https://doi.org/10.1136/bmj.l1079

Naarding, P., Schoevers, R. A., Janzing, J. G., Jonker, C., Koudstaal, P. J., & Beekman, A. T. (2005). A study on symptom profiles of late-life depression: the influence of vascular, degenerative, and inflammatory risk-indicators. *Journal of Affective Disorders*, *88*(2), 155-162. https://doi.org/10.1016/j.jad.2005.07.002

Naismith, S. L., Norrie, L. M., Mowszowski, L., & Hickie, I. B. (2012). The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. *Progress in Neurobiology*, *98*(1), 99-143. https://doi.org/10.1016/j.pneurobio.2012.05.009

National Institute for Health and Care Excellence (2022) *Depression in Adults: recognition and management* [NICE guidance No:90] Overview | Depression in adults: recognition and management | Guidance | NICE

National Health Service England (2015) *Guidance to support the introduction of access and waiting time standards for mental health services in 2015/16 [02932] https://www.england.nhs.uk/wp-content/uploads/2015/02/mh-access-wait-time-guid.pdf*

NICE (2015) Repetitive transcranial magnetic stimulation for depression, London, available from: Overview | Repetitive transcranial magnetic stimulation for depression | Guidance | NICE

Nelson, J. C., Clary, C. M., Leon, A. C., & Schneider, L. S. (2005). Symptoms of late-life depression: frequency and change during treatment. *The American Journal of Geriatric Psychiatry*, *13*(6), 520-526. https://doi.org/10.1097/00019442-200506000-00011

Nelson, J. C., Delucchi, K. L., & Schneider, L. S. (2013). Moderators of outcome in late-life depression: a patient-level meta-analysis. *American Journal of Psychiatry*, *170*(6), 651-659. https://doi.org/10.1176/appi.ajp.2012.12070927

Nelson, J. C., Delucchi, K., & Schneider, L. S. (2008). Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. *The American Journal of Geriatric Psychiatry*, *16*(7), 558-567. https://doi.org/10.1097/01.JGP.0000308883.64832.ed

Nemeroff, C. B. (2007). Prevalence and management of treatment-resistant depression. *Journal of Clinical Psychiatry*, *68*(8), 17.

Neu, P., Bajbouj, M., Schilling, A., Godemann, F., Berman, R. M., & Schlattmann, P. (2005). Cognitive function over the treatment course of depression in middle-aged patients: correlation with brain MRI signal hyperintensities. *Journal of Psychiatric Research*, *39*(2), 129-135. https://doi.org/10.1016/j.jpsychires.2004.06.004

Neubauer, B. E., Witkop, C. T., & Varpio, L. (2019). How phenomenology can help us learn from the experiences of others. *Perspectives on Medical Education*, *8*(2), 90-97. https://doi.org/10.1007/s40037-019-0509-2

Neuendorf, K. A. (2018). Content analysis and thematic analysis. In *Advanced Research Methods for Applied Psychology* (pp. 211-223). Routledge. https://doi.org/10.4324/9781315517971-21

Nicolaides, N. C., Kyratzi, E., Lamprokostopoulou, A., Chrousos, G. P., & Charmandari, E. (2015). Stress, the stress system and the role of glucocorticoids. *Neuroimmunomodulation*, *22*(1-2), 6-19. https://doi.org/10.1159/000362736

Nierenberg, A. A., Petersen, T. J., & Alpert, J. E. (2003). Prevention of relapse and recurrence in depression: the role of long-term pharmacotherapy and psychotherapy. *Journal of Clinical Psychiatry*, *64*(15), 13-17. https://doi.org/10.4088/JCP.v64n0108

Nieuwsma, J. A., Trivedi, R. B., McDuffie, J., Kronish, I., Benjamin, D., & Williams Jr, J. W. (2012). Brief psychotherapy for depression: a systematic review and meta-analysis. *The International Journal of Psychiatry in Medicine*, *43*(2), 129-151. https://doi.org/10.2190/PM.43.2.c

Nikolin, S., Tan, Y. Y., Schwaab, A., Moffa, A., Loo, C. K., & Martin, D. (2021). An investigation of working memory deficits in depression using the n-back task: A systematic review and meta-analysis. *Journal of Affective Disorders*, *284*, 1-8. https://doi.org/10.1016/j.jad.2021.01.084

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., ... & Paulus, W. (2003). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of physiology*, *553*(1), 293-301. https://doi.org/10.1113/jphysiol.2003.049916

Nitsche, M. A., Jaussi, W., Liebetanz, D., Lang, N., Tergau, F., & Paulus, W. (2004). Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology*, *29*(8), 1573-1578. https://doi.org/10.1038/sj.npp.1300517

Nitsche, M. A., Koschack, J., Pohlers, H., Hullemann, S., Paulus, W., & Happe, S. (2012). Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. *Frontiers in Psychiatry*, *3*, 58. https://doi.org/10.3389/fpsyt.2012.00058

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527*(3), 633-639.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*(10), 1899-1901. https://doi.org/10.1212/WNL.57.10.1899

Nitschke, J. B., Heller, W., Etienne, M. A., & Miller, G. A. (2004). Prefrontal cortex activity differentiates processes affecting memory in depression. *Biological Psychology*, *67*(1-2), 125-143. https://doi.org/10.1016/j.biopsycho.2004.03.004

Norcross, J. C., & Wampold, B. E. (2018). A new therapy for each patient: Evidence-based relationships and responsiveness. *Journal of clinical psychology*, *74*(11), 1889-1906.

Nowell, L. S., Norris, J. M., White, D. E., & Moules, N. J. (2017). Thematic analysis: Striving to meet the trustworthiness criteria. *International Journal of Qualitative Methods*, *16*(1), 1609406917733847. https://doi.org/10.1177/1609406917733847

Nuño, L., Gómez-Benito, J., Carmona, V. R., & Pino, O. (2021). A systematic review of executive function and information processing speed in major depression disorder. *Brain Sciences*, *11*(2), 147. https://doi.org/10.3390/brainsci11020147

O'BRIEN, A. J., & Golding, C. G. (2003). Coercion in mental healthcare: the principle of least coercive care. *Journal of psychiatric and mental health nursing*, *10*(2), 167-173.

O'Cathain, A., Thomas, K. J., Drabble, S. J., Rudolph, A., Goode, J., & Hewison, J. (2014). Maximising the value of combining qualitative research and randomised controlled trials in health research: the

QUAlitative Research in Trials (QUART) study--a mixed methods study. *Health Technology Assessment (Winchester, England)*, *18*(38), 1-197. https://doi.org/10.3310/hta18380

Oliveira, J. F., Zanão, T. A., Valiengo, L., Lotufo, P. A., Benseñor, I. M., Fregni, F., & Brunoni, A. R. (2013). Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder. *Neuroscience letters*, *537*, 60-64. https://doi.org/10.1016/j.neulet.2013.01.023

Orsmond, G. I., & Cohn, E. S. (2015). The distinctive features of a feasibility study: objectives and guiding questions. *OTJR: Occupation, Participation and Health*, *35*(3), 169-177. https://doi.org/10.1177/1539449215578649

Overvliet, G. M., Jansen, R. A., van Balkom, A. J., van Campen, D. C., Oudega, M. L., Van Der Werf, Y. D., ... & Dols, A. (2021). Adverse events of repetitive transcranial magnetic stimulation in older adults with depression, a systematic review of the literature. *International journal of geriatric psychiatry*, *36*(3), 383-392. https://doi.org/10.1002/gps.5440

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). Updating guidance for reporting systematic reviews: development of the PRISMA 2020 statement. *Journal of Clinical Epidemiology*, *134*, 103-112. https://doi.org/10.1016/j.jclinepi.2021.02.003

Palm, U., Feichtner, K. B., Hasan, A., Gauglitz, G., Langguth, B., Nitsche, M. A., ... & Padberg, F. (2014). The role of contact media at the skin-electrode interface during transcranial direct current stimulation (tDCS). *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *7*(5), 762-764. https://doi.org/10.1016/j.brs.2014.06.006

Palm, U., Hasan, A., Strube, W., & Padberg, F. (2016). tDCS for the treatment of depression: a comprehensive review. *European archives of psychiatry and clinical neuroscience*, *266*(8), 681-694 https://doi.org/10.1007/s00406-016-0674-9

Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Baghai, T. C., ... & Padberg, F. (2009). Transcranial direct current stimulation in a patient with therapy-resistant major depression. *The World Journal of Biological Psychiatry*, *10*(4-2), 632-635. https://doi.org/10.1080/15622970802480905

Palm, U., Kumpf, U., Behler, N., Wulf, L., Kirsch, B., Wörsching, J., ... & Padberg, F. (2018). Home use, remotely supervised, and remotely controlled transcranial direct current stimulation: a systematic review of the available evidence. *Neuromodulation: Technology at the Neural Interface*, *21*(4), 323-333. https://doi.org/10.1111/ner.12686

Palm, U., Schiller, C., Fintescu, Z., Obermeier, M., Keeser, D., Reisinger, E., ... & Padberg, F. (2012). Transcranial direct current stimulation in treatment resistant depression: a randomized double-blind, placebo-controlled study. *Brain Stimulation*, *5*(3), 242-251. https://doi.org/10.1016/j.brs.2011.08.005

Panic, N., Leoncini, E., De Belvis, G., Ricciardi, W., & Boccia, S. (2013). Evaluation of the endorsement of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement on the quality of published systematic review and meta-analyses. *PLoS ONE*, *8*(12), e83138. https://doi.org/10.1371/journal.pone.0083138

Panza, F., Frisardi, V., Capurso, C., D'Introno, A., Colacicco, A. M., Imbimbo, B. P., ... & Solfrizzi, V. (2010). Late-life depression, mild cognitive impairment, and dementia: possible continuum?. *The*

American Journal of Geriatric Psychiatry, *18*(2), 98-116. https://doi.org/10.1097/JGP.0b013e3181b0fa13

Pariante, C. M., & Lightman, S. L. (2008). The HPA axis in major depression: classical theories and new developments. *Trends in Neurosciences*, *31*(9), 464-468. https://doi.org/10.1016/j.tins.2008.06.006

Park, C., Pan, Z., Brietzke, E., Subramaniapillai, M., Rosenblat, J. D., Zuckerman, H., ... & McIntyre, R. S. (2018). Predicting antidepressant response using early changes in cognition: a systematic review. *Behavioural brain research*, *353*, 154-160. https://doi.org/10.1016/j.bbr.2018.07.011

Park, C., Rosenblat, J. D., Lee, Y., Pan, Z., Cao, B., Iacobucci, M., & McIntyre, R. S. (2019). The neural systems of emotion regulation and abnormalities in major depressive disorder. *Behavioural Brain Research*, *367*, 181-188. https://doi.org/10.1016/j.bbr.2019.04.002

Parsey, C. M., & Schmitter-Edgecombe, M. (2013). Applications of technology in neuropsychological assessment. *The Clinical Neuropsychologist*, *27*(8), 1328-1361. https://doi.org/10.1080/13854046.2013.834971

Parsons, T., & Duffield, T. (2020). Paradigm shift toward digital neuropsychology and high-dimensional neuropsychological assessments. *Journal of Medical Internet Research*, *22*(12), e23777. https://doi.org/10.2196/23777

Patel, K., Abdool, P. S., Rajji, T. K., & Mulsant, B. H. (2017). Pharmacotherapy of major depression in late life: what is the role of new agents?. *Expert Opinion on Pharmacotherapy*, *18*(6), 599-609. https://doi.org/10.1080/14656566.2017.1308484

Patel, S., Akhtar, A., Malins, S., Wright, N., Rowley, E., Young, E., ... & Morriss, R. (2020). The acceptability and usability of digital health interventions for adults with depression, anxiety, and somatoform disorders: qualitative systematic review and meta-synthesis. *Journal of Medical Internet Research*, *22*(7), e16228. https://doi.org/10.2196/16228

Patel, N., & Bajaj, N. S. (2018). Meta-analyses: How to critically appraise them?. *Journal of Nuclear Cardiology*, *25*(5), 1598-1600. https://doi.org/10.1007/s12350-017-0898-8

Pazdur, R. (2008). Endpoints for assessing drug activity in clinical trials. *The Oncologist*, *13*(S2), 19-21. https://doi.org/10.1634/theoncologist.13-S2-19

Pechtel, P., & Pizzagalli, D. A. (2011). Effects of early life stress on cognitive and affective function: an integrated review of human literature. *Psychopharmacology*, *214*(1), 55-70. https://doi.org/10.1007/s00213-010-2009-2

Pence, B. W., O'Donnell, J. K., & Gaynes, B. N. (2012). The depression treatment cascade in primary care: a public health perspective. *Current psychiatry reports*, *14*(4), 328-335. https://doi.org/10.1007/s11920-012-0274-y

Peña-Gómez, C., Vidal-Pineiro, D., Clemente, I. C., Pascual-Leone, Á., & Bartres-Faz, D. (2011). Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. *PloS one*, *6*(7), e22812. https://doi.org/10.1371/journal.pone.0022812

Perera, T., George, M. S., Grammer, G., Janicak, P. G., Pascual-Leone, A., & Wirecki, T. S. (2016). The clinical TMS society consensus review and treatment recommendations for TMS therapy for major

depressive disorder. *Brain stimulation*, *9*(3), 336-346. http://dx.doi.org/doi:10.1016/j.brs.2016.03.010

Perceval, G., Martin, A. K., Copland, D. A., Laine, M., & Meinzer, M. (2020). Multisession transcranial direct current stimulation facilitates verbal learning and memory consolidation in young and older adults. *Brain and Language*, *205*, 104788. https://doi.org/10.1016/j.bandl.2020.104788

Philip, N. S., Nelson, B. G., Frohlich, F., Lim, K. O., Widge, A. S., & Carpenter, L. L. (2017). Low-intensity transcranial current stimulation in psychiatry. *American Journal of Psychiatry*, *174*(7), 628-639. https://doi.org/10.1176/appi.ajp.2017.16090996

Pimontel, M. A., Rindskopf, D., Rutherford, B. R., Brown, P. J., Roose, S. P., & Sneed, J. R. (2016). A meta-analysis of executive dysfunction and antidepressant treatment response in late-life depression. *The American Journal of Geriatric Psychiatry*, *24*(1), 31-41. https://doi.org/10.1016/j.jagp.2015.05.010

Pittenger, C., & Duman, R. S. (2008). Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology*, *33*(1), 88-109. https://doi.org/10.1038/sj.npp.1301574

Player, M. J., Taylor, J. L., Weickert, C. S., Alonzo, A., Sachdev, P., Martin, D., ... & Loo, C. K. (2013). Neuroplasticity in depressed individuals compared with healthy controls. *Neuropsychopharmacology*, *38*(11), 2101-2108. https://doi.org/10.1038/npp.2013.126

Plewnia, C., Schroeder, P. A., Kunze, R., Faehling, F., & Wolkenstein, L. (2015). Keep calm and carry on: improved frustration tolerance and processing speed by transcranial direct current stimulation (tDCS). *PLoS One*, *10*(4), e0122578. https://doi.org/10.1371/journal.pone.0122578

Polanía, R., Nitsche, M. A., & Paulus, W. (2011). Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. *Human Brain Mapping*, *32*(8), 1236-1249. https://doi.org/10.1002/hbm.21104

Polanía, R., Paulus, W., Antal, A., & Nitsche, M. A. (2011). Introducing graph theory to track for neuroplastic alterations in the resting human brain: a transcranial direct current stimulation study. *Neuroimage*, *54*(3), 2287-2296. https://doi.org/10.1016/j.neuroimage.2010.09.085

Polanía, R., Paulus, W., & Nitsche, M. A. (2012). Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. *Human Brain Mapping*, *33*(10), 2499-2508. https://doi.org/10.1002/hbm.21380

Pope, C., & Mays, N. (1995). Qualitative research: reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. *BMJ*, *311*(6996), 42-45. https://doi.org/10.1136/bmj.311.6996.42

Pope, C., & Mays, N. (2009). Critical reflections on the rise of qualitative research. *BMJ*, *339*. https://doi.org/10.1136/bmj.b3425

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin*, *72*(4-6), 208-214. https://doi.org/10.1016/j.brainresbull.2007.01.004

Porter, R. J., Bourke, C., & Gallagher, P. (2007). Neuropsychological impairment in major depression: its nature, origin and clinical significance. *Australian & New Zealand Journal of Psychiatry*, *41*(2), 115-128. https://doi.org/10.1080/00048670601109881

Post, R. M., Leverich, G. S., Nolen, W. A., Kupka, R. W., Altshuler, L. L., Frye, M. A., ... & Walden, J. (2003). A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network. *Bipolar Disorders*, *5*(6), 396-406.

Price, R. B., & Duman, R. (2020). Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model. *Molecular Psychiatry*, *25*(3), 530-543. https://doi.org/10.1038/s41380-019-0615-x

Prien, R. F., Carpenter, L. L., & Kupfer, D. J. (1991). The definition and operational criteria for treatment outcome of major depressive disorder: a review of the current research literature. *Archives of General Psychiatry*, *48*(9), 796-800.

Priori, A. (2003). Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clinical Neurophysiology*, *114*(4), 589-595. https://doi.org/10.1016/S1388-2457(02)00437-6

Priori, A., Hallett, M., & Rothwell, J. C. (2009). Repetitive transcranial magnetic stimulation or transcranial direct current stimulation?. *Brain Stimulation*, *2*(4), 241-245. https://doi.org/10.1016/j.brs.2009.02.004

Proctor, E., Silmere, H., Raghavan, R., Hovmand, P., Aarons, G., Bunger, A., ... & Hensley, M. (2011). Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Administration and Policy in Mental Health and Mental Health Services Research*, *38*(2), 65-76. https://doi.org/10.1007/s10488-010-0319-7

Pu, J., Liu, Y., Zhang, H., Tian, L., Gui, S., Yu, Y., ... & Xie, P. (2020). An integrated meta-analysis of peripheral blood metabolites and biological functions in major depressive disorder. *Molecular Psychiatry*, 1-12.

Pyszczynski, T., & Greenberg, J. (1987). Self-regulatory perseveration and the depressive self-focusing style: a self-awareness theory of reactive depression. *Psychological Bulletin*, *102*(1), 122. https://doi.org/10.1037/0033-2909.102.1.122

R Core Team (2018) R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna. Available from: (https://www.R-project.org)

Raber, J. (1998). Detrimental effects of chronic hypothalamic—pituitary—adrenal axis activation. *Molecular Neurobiology*, *18*(1), 1-22. https://doi.org/10.1007/BF02741457

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*(1), 24-31. https://doi.org/10.1016/j.it.2005.11.006

Råheim, M., Magnussen, L. H., Sekse, R. J. T., Lunde, Å., Jacobsen, T., & Blystad, A. (2016). Researcher–researched relationship in qualitative research: Shifts in positions and researcher vulnerability. *International Journal of Qualitative Studies on Health and Well-being*, *11*(1), 30996. https://doi.org/10.3402/qhw.v11.30996

Ramirez-Mahaluf, J. P., Roxin, A., Mayberg, H. S., & Compte, A. (2017). A computational model of major depression: the role of glutamate dysfunction on cingulo-frontal network dynamics. *Cerebral Cortex*, *27*(1), 660-679. https://doi.org/10.1093/cercor/bhv249

Rapp, M. A., Dahlman, K., Sano, M., Grossman, H. T., Haroutunian, V., & Gorman, J. M. (2005). Neuropsychological differences between late-onset and recurrent geriatric major depression. *American Journal of Psychiatry*, *162*(4), 691-698. https://doi.org/10.1176/appi.ajp.162.4.691

Rapp, M. A., Schnaider-Beeri, M., Wysocki, M., Guerrero-Berroa, E., Grossman, H. T., Heinz, A., & Haroutunian, V. (2011). Cognitive decline in patients with dementia as a function of depression. *The American Journal of Geriatric Psychiatry*, *19*(4), 357-363. https://doi.org/10.1097/JGP.0b013e3181e898d0

Rasing, S. P., Stikkelbroek, Y. A., & Bodden, D. H. (2020). Is digital treatment the Holy Grail? Literature review on computerized and blended treatment for depressive disorders in youth. *International Journal of Environmental Research and Public Health*, *17*(1), 153. https://doi.org/10.3390/ijerph17010153

Rasnake, L. K., Martin, J., Tarnowski, K. J., & Mulick, J. A. (1993). Acceptability of behavioral treatments: Influence of knowledge of behavioral principles. *Mental Retardation*, *31*(4), 247.

Razza, L. B., De Smet, S., Moffa, A., Sudbrack-Oliveira, P., Vanderhasselt, M. A., & Brunoni, A. R. (2021). Follow-up effects of transcranial direct current stimulation (tDCS) for the major depressive episode: A systematic review and meta-analysis. *Psychiatry research*, *302*, 114024. https://doi.org/10.1016/j.psychres.2021.114024

Razza, L. B., Palumbo, P., Moffa, A. H., Carvalho, A. F., Solmi, M., Loo, C. K., & Brunoni, A. R. (2020). A systematic review and meta-analysis on the effects of transcranial direct current stimulation in depressive episodes. *Depression and Anxiety*, *37*(7), 594-608. https://doi.org/10.1002/da.23004

Reed, G. M., First, M. B., Kogan, C. S., Hyman, S. E., Gureje, O., Gaebel, W., ... & Saxena, S. (2019). Innovations and changes in the ICD-11 classification of mental, behavioural, and neurodevelopmental disorders. *World Psychiatry*, *18*(1), 3-19. https://doi.org/10.1002/wps.20611

Reimers, T. M., & Wacker, D. P. (1988). Parents' ratings of the acceptability of behavioral treatment recommendations made in an outpatient clinic: A preliminary analysis of the influence of treatment effectiveness. *Behavioral Disorders*, *14*(1), 7-15. https://doi.org/10.1177/019874298801400104

Reimers, T. M., Wacker, D. P., Cooper, L. J., & DeRaad, A. O. (1992). Clinical evaluation of the variables associated with treatment acceptability and their relation to compliance. *Behavioral Disorders*, *18*(1), 67-76. https://doi.org/10.1177/019874299201800108

Reitan, R. M., & Davidson, L. A. (1974). Neuropsychology: Current status and application. *Winston and Sons*.

Rennie, D. (1996). How to report randomized controlled trials: the CONSORT statement. *JAMA*, *276*(8), 649-649. https://doi.org/10.1001/jama.1996.03540080071033

Rensma, S. P., van Sloten, T. T., Launer, L. J., & Stehouwer, C. D. (2018). Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: a systematic review

and meta-analysis. *Neuroscience & Biobehavioral Reviews*, *90*, 164-173. https://doi.org/10.1016/j.neubiorev.2018.04.003

Reppermund, S., Zihl, J., Lucae, S., Horstmann, S., Kloiber, S., Holsboer, F., & Ising, M. (2007). Persistent cognitive impairment in depression: the role of psychopathology and altered hypothalamic-pituitary-adrenocortical (HPA) system regulation. *Biological Psychiatry*, *62*(5), 400-406. https://doi.org/10.1016/j.biopsych.2006.09.027

Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014

Rey, A. (1964). L'examen clinique en psychologie, Paris: Presses Universitaires de France, 1964. *Chemotherapy and Objective Cognitive Functioning*, *95*.

Reynolds III, C. F., Alexopoulos, G. S., & Katz, I. R. (2002). Geriatric depression: Diagnosis and treatment. *Generations: Journal of the American Society on Aging*, *26*(1), 28-31.

Reynolds III, C. F., Dew, M. A., Pollock, B. G., Mulsant, B. H., Frank, E., Miller, M. D., ... & Kupfer, D. J. (2006). Maintenance treatment of major depression in old age. *New England Journal of Medicine*, *354*(11), 1130-1138. https://doi.org/10.1056/NEJMoa052619

Reynolds, E. H., & Wilson, J. V. K. (2013). Depression and anxiety in Babylon. *Journal of the Royal Society of Medicine*, *106*(12), 478-481. https://doi.org/10.1177/0141076813486262

Richards, H. M., & Schwartz, L. J. (2002). Ethics of qualitative research: are there special issues for health services research?. *Family Practice*, *19*(2), 135-139. https://doi.org/10.1093/fampra/19.2.135

Richardson, K., & Barkham, M. (2020). Recovery from depression: A systematic review of perceptions and associated factors. *Journal of Mental Health*, *29*(1), 103-115.

Riggall, K., Forlini, C., Carter, A., Hall, W., Weier, M., Partridge, B., & Meinzer, M. (2015). Researchers' perspectives on scientific and ethical issues with transcranial direct current stimulation: An international survey. *Scientific Reports*, *5*(1), 1-10. https://doi.org/10.1038/srep10618

Rihmer, Z., Dome, P., & Katona, C. (2022). Serotonin and depression–a riposte to Moncrieff et al.(2022). *Neuropsychopharmacologia Hungarica: a Magyar Pszichofarmakologiai Egyesulet Lapja= Official Journal of the Hungarian Association of Psychopharmacology*, *24*(3), 120-125.

Riley, R. D., Lambert, P. C., & Abo-Zaid, G. (2010). Meta-analysis of individual participant data: rationale, conduct, and reporting. *BMJ*, *340*. https://doi.org/10.1136/bmj.c221

Ritchie, K., Chan, D., & Watermeyer, T. (2020). The cognitive consequences of the COVID-19 epidemic: collateral damage?. *Brain Communications*, *2*(2), fcaa069. https://doi.org/10.1093/braincomms/fcaa069

Ritchie J, Lewis J (2003) Qualitative Research Practice. Sage Publications, London

Ritter, E. K., & Wilson, J. K. (1980). Prescription for an anxiety state: a study of BAM 234. *Anatolian Studies*, *30*, 23-30. https://doi.org/10.2307/3642773

Roberts, T., Miguel Esponda, G., Krupchanka, D., Shidhaye, R., Patel, V., & Rathod, S. (2018). Factors associated with health service utilisation for common mental disorders: a systematic review. *BMC psychiatry*, *18*, 1-19. https://doi.org/10.1186/s12888-018-1837-1

Rock, P. L., Roiser, J. P., Riedel, W. J., & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine*, *44*(10), 2029-2040. https://doi.org/10.1017/S0033291713002535

Rodríguez, N., Opisso, E., Pascual-Leone, Á., & Soler, M. D. (2014). Skin lesions induced by transcranial direct current stimulation (tDCS). *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *7*(5), 765-767. https://doi.org/10.1016/j.brs.2014.06.005

Röhr, S., Reininghaus, U., & Riedel-Heller, S. G. (2020). Mental wellbeing in the German old age population largely unaltered during COVID-19 lockdown: results of a representative survey. *BMC Geriatrics*, *20*(1), 1-12. https://doi.org/10.1186/s12877-020-01889-x

Roiser, J. P., & Sahakian, B. J. (2013). Hot and cold cognition in depression. *CNS spectrums*, *18*(3), 139-149. https://doi.org/10.1017/S1092852913000072

Rosenblat, J. D., Cha, D. S., Mansur, R. B., & McIntyre, R. S. (2014). Inflamed moods: a review of the interactions between inflammation and mood disorders. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *53*, 23-34. https://doi.org/10.1016/j.pnpbp.2014.01.013

Ross, J., Stevenson, F., Lau, R., & Murray, E. (2016). Factors that influence the implementation of e-health: a systematic review of systematic reviews (an update). *Implementation Science*, *11*(1), 1-12. https://doi.org/10.1186/s13012-016-0510-7

Rush, S., & Driscoll, D. A. (1968). Current distribution in the brain from surface electrodes. *Anesthesia & Analgesia*, *47*(6), 717-723. https://doi.org/10.1213/00000539-196811000-00016

Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., ... & Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biological Psychiatry*, *54*(5), 573-583. https://doi.org/10.1016/S0006-3223(02)01866-8

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Ward en, D., ... & Fava, M. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *American Journal of Psychiatry*, *163*(11), 1905-1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Ryan, F., Coughlan, M., & Cronin, P. (2009). Interviewing in qualitative research: The one-to-one interview. *International Journal of Therapy and Rehabilitation*, *16*(6), 309-314. https://doi.org/10.12968/ijtr.2009.16.6.42433

Salehinejad, M. A., Ghanavai, E., Rostami, R., & Nejati, V. (2017). Cognitive control dysfunction in emotion dysregulation and psychopathology of major depression (MD): Evidence from transcranial brain stimulation of the dorsolateral prefrontal cortex (DLPFC). *Journal of affective disorders*, *210*, 241-248. https://doi.org/10.1016/j.jad.2016.12.036

Salehinejad, M. A., Rostami, R., & Ghanavati, E. (2015). Transcranial direct current stimulation of dorsolateral prefrontal cortex of major depression: improving visual working memory, reducing depressive symptoms. *NeuroRegulation*, *2*(1), 37-37. https://doi.org/10.15540/nr.2.1.37

Sandi, C., & Richter-Levin, G. (2009). From high anxiety trait to depression: a neurocognitive hypothesis. *Trends in Neurosciences*, *32*(6), 312-320. https://doi.org/10.1016/j.tins.2009.02.004

Sanjari, M., Bahramnezhad, F., Fomani, F. K., Shoghi, M., & Cheraghi, M. A. (2014). Ethical challenges of researchers in qualitative studies: The necessity to develop a specific guideline. *Journal of Medical Ethics and History of Medicine*, *7*.

Saracutu, M., Edwards, D. J., Davies, H., & Rance, J. (2018). Protocol for a feasibility and acceptability study using a brief ACT-based intervention for people from Southwest Wales who live with persistent pain. *BMJ Open*, *8*(11), e021866. https://doi.org/10.1136/bmjopen-2018-021866

Sarmiento, C. I., San-Juan, D., & Prasath, V. B. S. (2016). Brief history of transcranial direct current stimulation (tDCS): from electric fishes to microcontrollers. *Psychological Medicine*, *46*(15), 3259-3261. https://doi.org/10.1017/S0033291716001926

Sattler, S., & Pietralla, D. (2022). Public attitudes towards neurotechnology: Findings from two experiments concerning Brain Stimulation Devices (BSDs) and Brain-Computer Interfaces (BCIs). *Plos one*, *17*(11), e0275454.

Sauvaget, A., Tostivint, A., Etcheverrigaray, F., Pichot, A., Dert, C., Schirr-Bonnais, S., ... & Riche, V. P. (2019). Hospital production cost of transcranial direct current stimulation (tDCS) in the treatment of depression. *Neurophysiologie Clinique*, *49*(1), 11-18. https://doi.org/10.1016/j.neucli.2018.11.001

Say, R. E., & Thomson, R. (2003). The importance of patient preferences in treatment decisions—challenges for doctors. *BMJ*, *327*(7414), 542-545. https://doi.org/10.1136/bmj.327.7414.542

Schiepers, O. J., Wichers, M. C., & Maes, M. (2005). Cytokines and major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *29*(2), 201-217. https://doi.org/10.1016/j.pnpbp.2004.11.003

Schmidt, M. (1996). *Rey auditory verbal learning test: A handbook* (Vol. 17). Los Angeles, CA: Western Psychological Services.

Schmidt, F. L., & Oh, I. S. (2016). The crisis of confidence in research findings in psychology: Is lack of replication the real problem? Or is it something else? *Archives of Scientific Psychology*, *4*(1), 32. https://doi.org/10.1037/arc0000029

Schmidt, F. L., Oh, I. S., & Hayes, T. L. (2009). Fixed-versus random-effects models in meta-analysis: Model properties and an empirical comparison of differences in results. *British Journal of Mathematical and Statistical Psychology*, *62*(1), 97-128. https://doi.org/10.1348/000711007X255327

Schulz, K. F., Altman, D. G., & Moher, D. (2010). CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Trials*, *11*(1), 1-8. https://doi.org/10.1186/1745-6215-11-32

Schulz, R., Beach, S. R., Ives, D. G., Martire, L. M., Ariyo, A. A., & Kop, W. J. (2000). Association between depression and mortality in older adults: the Cardiovascular Health Study. *Archives of Internal Medicine*, *160*(12), 1761-1768. https://doi.org/10.1001/archinte.160.12.1761

Scotland, J. (2012). Exploring the philosophical underpinnings of research: Relating ontology and epistemology to the methodology and methods of the scientific, interpretive, and critical research paradigms. *English Language Teaching*, *5*(9), 9-16. https://doi.org/10.5539/elt.v5n9p9

Scott, D. (1997). The researcher's personal responses as a source of insight in the research process. *Nursing Inquiry*, *4*(2), 130-134. https://doi.org/10.1111/j.1440-1800.1997.tb00086.x

Segrave, R. A., Arnold, S., Hoy, K., & Fitzgerald, P. B. (2014). Concurrent cognitive control training augments the antidepressant efficacy of tDCS: a pilot study. *Brain Stimulation*, *7*(2), 325-331. https://doi.org/10.1016/j.brs.2013.12.008

Sekhon, M., Cartwright, M., & Francis, J. J. (2017). Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. *BMC Health Services Research*, *17*(1), 1-13. https://doi.org/10.1186/s12913-017-2031-8

Sekhon, M., Cartwright, M., & Francis, J. J. (2018). Acceptability of health care interventions: A theoretical framework and proposed research agenda. *British Journal of Health Psychology*, *23*(3), 519-531. https://doi.org/10.1111/bjhp.12295

Seligman, M. E. (1972). Learned helplessness. *Annual Review of Medicine*, *23*(1), 407-412. https://doi.org/10.1146/annurev.me.23.020172.002203

Seligman, M. E. (1975). *Helplessness: On depression, development, and health*. WH Freeman.

Seligman, M. E., Abramson, L. Y., Semmel, A., & Von Baeyer, C. (1979). Depressive attributional style. *Journal of Abnormal Psychology*, *88*(3), 242.

Semahegn, A., Torpey, K., Manu, A., Assefa, N., Tesfaye, G., & Ankomah, A. (2020). Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis. *Systematic reviews*, *9*(1), 1-18.

Semkovska, M., Quinlivan, L., O'Grady, T., Johnson, R., Collins, A., O'Connor, J., ... & Gload, T. (2019). Cognitive function following a major depressive episode: a systematic review and meta-analysis. *The Lancet Psychiatry*, *6*(10), 851-861. https://doi.org/10.1016/S2215-0366(19)30291-3

Senecal, C., Widmer, R. J., Bailey, K., Lerman, L. O., & Lerman, A. (2018). Usage of a digital health workplace intervention based on socioeconomic environment and race: Retrospective secondary cross-sectional study. *Journal of medical Internet research*, *20*(4), e145.

Shah, A., Bhat, R., Zarate-Escudero, S., DeLeo, D., & Erlangsen, A. (2016). Suicide rates in five-year age-bands after the age of 60 years: the international landscape. *Aging & Mental Health*, *20*(2), 131-138. https://doi.org/10.1080/13607863.2015.1055552

Shahani, R., Streutker, C., Dickson, B., & Stewart, R. J. (2007). Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology*, *69*(5), 810-812. https://doi.org/10.1016/j.urology.2007.01.038

Shaw, R. L., Larkin, M., & Flowers, P. (2014). Expanding the evidence within evidence-based healthcare: thinking about the context, acceptability and feasibility of interventions. *BMJ Evidence-Based Medicine*, *19*(6), 201-203. https://doi.org/10.1136/eb-2014-101791

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., ... & Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of clinical psychiatry*, *59*(20), 22-33. https://doi.org/10.1037/t18597-000

Sheehan, K. H., & Sheehan, D. V. (2008). Assessing treatment effects in clinical trials with the discan metric of the Sheehan Disability Scale. *International Clinical Psychopharmacology*, *23*(2), 70-83. https://doi.org/10.1097/YIC.0b013e3282f2b4d6

Sheikh, S. A. (2007). The importance of ethics in health care system. *Journal of the Dow University of Health Sciences*, *1*(1), 46-48. https://doi.org/10.1186/s13643-020-1274-3

Sheline, Y. I., Pieper, C. F., Barch, D. M., Welsh-Boehmer, K., McKinstry, R. C., MacFall, J. R., ... & Doraiswamy, P. M. (2010). Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Archives of General Psychiatry*, *67*(3), 277-285. https://doi.org/10.1001/archgenpsychiatry.2009.204

Shinjo, S. K., Brunoni, A. R., Okano, A. H., Tanaka, C., & Baptista, A. F. (2020). Transcranial direct current stimulation relieves the severe anxiety of a patient with COVID-19. *Brain Stimulation*, *13*(5), 1352. https://doi.org/10.1016/j.brs.2020.07.004

Shiozawa, P., da Silva, M. E., Dias, D. R., Chaves, A. C., de Oliveira Diniz, B. S., & Cordeiro, Q. (2014). Transcranial direct current stimulation for depression in a 92-year-old patient: a case study. *Psychogeriatrics*, *14*(4), 269-270. https://doi.org/10.1111/psyg.12100

Shiozawa, P., Fregni, F., Benseñor, I. M., Lotufo, P. A., Berlim, M. T., Daskalakis, J. Z., ... & Brunoni, A. R. (2014). Transcranial direct current stimulation for major depression: an updated systematic review and meta-analysis. *International Journal of Neuropsychopharmacology*, *17*(9), 1443-1452. https://doi.org/10.1017/S1461145714000418

Shorten, A., & Shorten, B. (2013). What is meta-analysis?. *Evidence-Based Nursing*, *16*(1), 3-4. https://doi.org/10.1136/eb-2012-101118

Sidani, S., Epstein, D. R., Bootzin, R. R., Moritz, P., & Miranda, J. (2009). Assessment of preferences for treatment: validation of a measure. *Research in Nursing & Health*, *32*(4), 419-431. https://doi.org/10.1002/nur.20329

Simmons-Mackie, N., & Damico, J. S. (2001). Intervention outcomes: A clinical application of qualitative methods. *Topics in Language Disorders*, *22*(1), 21-36. https://doi.org/10.1097/00011363-200111000-00004

Simmonds-Buckley, M., Kellett, S., & Waller, G. (2019). Acceptability and efficacy of group behavioral activation for depression among adults: a meta-analysis. *Behavior Therapy*, *50*(5), 864-885. https://doi.org/10.1016/j.beth.2019.01.003

Singh-Manoux, A., Dugravot, A., Fournier, A., Abell, J., Ebmeier, K., Kivimäki, M., & Sabia, S. (2017). Trajectories of depressive symptoms before diagnosis of dementia: a 28-year follow-up study. *JAMA Psychiatry*, *74*(7), 712-718. https://doi.org/10.1001/jamapsychiatry.2017.0660

Sinyor, M., Cheung, C. P., Abraha, H. Y., Lanctôt, K. L., Saleem, M., Liu, C. S., ... & Schaffer, A. (2020). Antidepressant-placebo differences for specific adverse events in major depressive disorder: a systematic review. *Journal of Affective Disorders*, *267*, 185-190. https://doi.org/10.1016/j.jad.2020.02.013

Sivaramakrishnan, A., Datta, A., Bikson, M., & Madhavan, S. (2019). Remotely supervised transcranial direct current stimulation: a feasibility study for amyotrophic lateral sclerosis. *NeuroRehabilitation*, *45*(3), 369-378. https://doi.org/10.3233/NRE-192851

Smith, A. (1991). Symbol modalities test. *Western Psychological Services, Los Angeles, CA*.

Smith, D. J., Nicholl, B. I., Cullen, B., Martin, D., Ul-Haq, Z., Evans, J., ... & Pell, J. P. (2013). Prevalence and characteristics of probable major depression and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. *PloS ONE*, *8*(11), e75362. https://doi.org/10.1371/journal.pone.0075362

Smits, F. M., Geuze, E., Schutter, D. J., van Honk, J., & Gladwin, T. E. (2021). Effects of tDCS during inhibitory control training on performance and PTSD, aggression and anxiety symptoms: a randomized-controlled trial in a military sample. *Psychological Medicine*, 1-11. https://doi.org/10.1017/S0033291721000817

Snyder, H. R. (2013). Major depressive disorder is associated with broad impairments on neuropsychological measures of executive function: a meta-analysis and review. *Psychological Bulletin*, *139*(1), 81. https://doi.org/10.1037/a0028727

Snyder, K. A., & Harrison, D. W. (1997). The affective auditory verbal learning test. *Archives of Clinical Neuropsychology*, *12*(5), 477-482. https://doi.org/10.1093/arclin/12.5.477

Sommerlad, A., Marston, L., Huntley, J., Livingston, G., Lewis, G., Steptoe, A., & Fancourt, D. (2021). Social relationships and depression during the COVID-19 lockdown: longitudinal analysis of the COVID-19 Social Study. *Psychological Medicine*, 1-10. https://doi.org/10.1017/S0033291721000039

Sonsin-Diaz, N., Gottesman, R. F., Fracica, E., Walston, J., Windham, B. G., Knopman, D. S., & Walker, K. A. (2020). Chronic systemic inflammation is associated with symptoms of late-life depression: the ARIC Study. *The American Journal of Geriatric Psychiatry*, *28*(1), 87-98. https://doi.org/10.1016/j.jagp.2019.05.011

Spezia Adachi, L. N., Quevedo, A. S., de Souza, A., Scarabelot, V. L., Rozisky, J. R., de Oliveira, C., ... & Torres, I. L. (2015). Exogenously induced brain activation regulates neuronal activity by top-down modulation: conceptualized model for electrical brain stimulation. *Experimental brain research*, *233*(5), 1377-1389. https://doi.org/10.1007/s00221-015-4212-1

Spreat, S., & Walsh, D. E. (1994). Impact of treatment efficacy and professional affiliation on ratings of treatment acceptability. *Mental Retardation*, *32*(3), 227-233.

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., ... & Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *Journal of Neuroscience*, *29*(16), 5202-5206. https://doi.org/10.1523/JNEUROSCI.4432-08.2009

Stagg, C. J., Antal, A., & Nitsche, M. A. (2018). Physiology of transcranial direct current stimulation. *The Journal of ECT*, *34*(3), 144-152. https://doi.org/10.1097/YCT.0000000000000510

Stahl, S. M. (2010). Enhancing outcomes from major depression: using antidepressant combination therapies with multifunctional pharmacologic mechanisms from the initiation of treatment. *CNS spectrums*, *15*(2), 79-94. https://doi.org/10.1017/S1092852900027334

Stark, A., Kaduszkiewicz, H., Stein, J., Maier, W., Heser, K., Weyerer, S., ... & Scherer, M. (2018). A qualitative study on older primary care patients' perspectives on depression and its treatments-potential barriers to and opportunities for managing depression. *BMC Family Practice*, *19*(1), 1-10. https://doi.org/10.1186/s12875-017-0684-3

Steffens, D. C. (2017). Late-life depression and the prodromes of dementia. *JAMA Psychiatry*, *74*(7), 673-674. https://doi.org/10.1001/jamapsychiatry.2017.0658

Stetler, C., & Miller, G. E. (2011). Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Psychosomatic Medicine*, *73*(2), 114-126. https://doi.org/10.1097/PSY.0b013e31820ad12b

Stephens, J. A., Jones, K. T., & Berryhill, M. E. (2017). Task demands, tDCS intensity, and the COMT val158met polymorphism impact tDCS-linked working memory training gains. *Scientific reports*, *7*(1), 1-11. https://doi.org/10.1038/s41598-017-14030-7

Stewart, G. B., Altman, D. G., Askie, L. M., Duley, L., Simmonds, M. C., & Stewart, L. A. (2012). Statistical Analysis of Individual Participant Data Meta-Analyses: A Comparison of Methods and Recommendations for Practice. *PLoS ONE*, *7*(10). https://doi.org/10.1371/journal.pone.0046042

Stewart, L. A., Clarke, M., Rovers, M., Riley, R. D., Simmonds, M., Stewart, G., & Tierney, J. F. (2015). Preferred reporting items for a systematic review and meta-analysis of individual participant data: the PRISMA-IPD statement. *JAMA*, *313*(16), 1657-1665. https://doi.org/10.1001/jama.2015.3656

Stewart, R., Prince, M., Richards, M., Brayne, C., & Mann, A. (2001). Stroke, vascular risk factors and depression: cross-sectional study in a UK Caribbean-born population. *The British Journal of Psychiatry*, *178*(1), 23-28. https://doi.org/10.1192/bjp.178.1.23

Strauss, E., Sherman, E. M., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary*. American chemical society.

Stuart, S. A., Butler, P., Munafò, M. R., Nutt, D. J., & Robinson, E. S. (2015). Distinct neuropsychological mechanisms may explain delayed-versus rapid-onset antidepressant efficacy. *Neuropsychopharmacology*, *40*(9), 2165-2174. https://doi.org/10.1038/npp.2015.59

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: review and meta-analysis. *American Journal of Psychiatry*, *157*(10), 1552-1562. https://doi.org/10.1176/appi.ajp.157.10.1552

Summers, J. J., Kang, N., & Cauraugh, J. H. (2016). Does transcranial direct current stimulation enhance cognitive and motor functions in the ageing brain? A systematic review and meta-analysis. *Ageing Research Reviews*, *25*, 42-54. https://doi.org/10.1016/j.arr.2015.11.004

Sutin, A. R., Terracciano, A., Milaneschi, Y., An, Y., Ferrucci, L., & Zonderman, A. B. (2013). The trajectory of depressive symptoms across the adult life span. *JAMA Psychiatry*, *70*(8), 803-811. https://doi.org/10.1001/jamapsychiatry.2013.193

Swift, J. K., Callahan, J. L., & Vollmer, B. M. (2011). Preferences. *Journal of Clinical Psychology*, *67*(2), 155-165. https://doi.org/10.1002/jclp.20759

Szanto, K., Galfalvy, H., Kenneally, L., Almasi, R., & Dombrovski, A. Y. (2020). Predictors of serious suicidal behavior in late-life depression. *European Neuropsychopharmacology*, *40*, 85-98. https://doi.org/10.1016/j.euroneuro.2020.06.005

Tadayonnejad, R., Yang, S., Kumar, A., & Ajilore, O. (2014). Multimodal brain connectivity analysis in unmedicated late-life depression. *PloS ONE*, *9*(4), e96033. https://doi.org/10.1371/journal.pone.0096033

Tarricone, I., Stivanello, E., Poggi, F., Castorini, V., Marseglia, M. V., Fantini, M. P., & Berardi, D. (2012). Ethnic variation in the prevalence of depression and anxiety in primary care: a systematic

review and meta-analysis. *Psychiatry Research*, *195*(3), 91-106. https://doi.org/10.1016/j.psychres.2011.05.020

Taylor, D. (2008). Psychoanalytic and psychodynamic therapies for depression: The evidence base. *Advances in Psychiatric Treatment*, *14*(6), 401-413. https://doi.org/10.1192/apt.bp.107.004382

Taylor, E. M. (2013). Psychological appraisal of children with cerebral defects. In *Psychological Appraisal of Children with Cerebral Defects*. Harvard University Press.

Taylor, G. J., & Wainwright, P. (2005). Open label extension studies: research or marketing?. *BMJ*, *331*(7516), 572-574. https://doi.org/10.1136/bmj.331.7516.572

Taylor, W. D., Aizenstein, H. J., & Alexopoulos, G. S. (2013). The vascular depression hypothesis: mechanisms linking vascular disease with depression. *Molecular Psychiatry*, *18*(9), 963-974. https://doi.org/10.1038/mp.2013.20

Teagarden, J. R. (1989). Meta-analysis: whither narrative review?. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *9*(5), 274-284. https://doi.org/10.1002/j.1875-9114.1989.tb04139.x

Teasdale, J. D. (1988). Cognitive vulnerability to persistent depression. *Cognition & Emotion*, *2*(3), 247-274. https://doi.org/10.1080/02699938808410927

Tedeschini, E., Levkovitz, Y., Iovieno, N., Ameral, V. E., Nelson, J. C., & Papakostas, G. I. (2011). Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. *The Journal of Clinical Psychiatry*, *72*(12), 0-0. https://doi.org/10.4088/JCP.10r06531

Tedesco Triccas, L., Burridge, J. H., Hughes, A. M., Meadmore, K. L., Donovan-Hall, M., Rothwell, J. C., & Verheyden, G. (2018). A qualitative study exploring views and experiences of people with stroke undergoing transcranial direct current stimulation and upper limb robot therapy. *Topics in Stroke Rehabilitation*, *25*(7). https://doi.org/10.1080/10749357.2018.1493072

Thabane, L., Ma, J., Chu, R., Cheng, J., Ismaila, A., Rios, L. P., ... & Goldsmith, C. H. (2010). A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology*, *10*(1), 1-10. https://doi.org/10.1186/1471-2288-10-1

Tham, A., Jonsson, U., Andersson, G., Söderlund, A., Allard, P., & Bertilsson, G. (2016). Efficacy and tolerability of antidepressants in people aged 65 years or older with major depressive disorder–a systematic review and a meta-analysis. *Journal of Affective Disorders*, *205*, 1-12. https://doi.org/10.1016/j.jad.2016.06.013

Thase, M. E. (2011). Treatment-resistant depression: prevalence, risk factors, and treatment strategies. *The Journal of Clinical Psychiatry*, *72*(5), 26550. https://doi.org/10.4088/JCP.8133tx4c

Thauvoye, E., Vanhooren, S., Vandenhoeck, A., & Dezutter, J. (2018). Spirituality and well-being in old age: exploring the dimensions of spirituality in relation to late-life functioning. *Journal of Religion and Health*, *57*(6), 2167-2181. https://doi.org/10.1007/s10943-017-0515-9

Thomas, C., Datta, A., & Woods, A. (2017). Effect of aging on current flow due to transcranial direct current stimulation. *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *10*(2), 469. https://doi.org/10.1016/j.brs.2017.01.374

Thomas, W. J., Hauson, A. O., Lambert, J. E., Stern, M. J., Gamboa, J. M., Allen, K. E., ... & Newton, H. (2018). A Meta-Analysis of the Effectiveness of Cognitive-Behavioural Therapies for Late-Life Depression. *Canadian Journal of Counselling and Psychotherapy*, *52*(1).

Thomas, L., Kessler, D., Campbell, J., Morrison, J., Peters, T. J., Williams, C., ... & Wiles, N. (2013). Prevalence of treatment-resistant depression in primary care: cross-sectional data. *British Journal of General Practice*, *63*(617), e852-e858. https://doi.org/10.3399/bjgp13X675430

Thorlby, R., Gardner, T., & Turton, C. (2019). NHS performance and waiting times. *The Health Foundation*.

Tortella, G., ML Selingardi, P., L Moreno, M., P Veronezi, B., & R Brunoni, A. (2014). Does non-invasive brain stimulation improve cognition in major depressive disorder? A systematic review. *CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders)*, *13*(10), 1759-1769. https://doi.org/10.2174/1871527313666141130224431

Toye, F., Williamson, E., Williams, M. A., Fairbank, J., & Lamb, S. E. (2016). What value can qualitative research add to quantitative research design? An example from an adolescent idiopathic scoliosis trial feasibility study. *Qualitative Health Research*, *26*(13), 1838-1850. https://doi.org/10.1177/1049732316662446

Trusler, K., Doherty, C., Mullin, T., Grant, S., & McBride, J. (2006). Waiting times for primary care psychological therapy and counselling services. *Counselling and Psychotherapy Research*, *6*(1), 23-32. https://doi.org/10.1080/14733140600581358

Tsai, S. Y., Chi, L. Y., Lee, C. H., & Chou, P. (2007). Health-related quality of life as a predictor of mortality among community-dwelling older persons. *European Journal of Epidemiology*, *22*(1), 19-26. https://doi.org/10.1007/s10654-006-9092-z

Tsang, R. S., Mather, K. A., Sachdev, P. S., & Reppermund, S. (2017). Systematic review and meta-analysis of genetic studies of late-life depression. *Neuroscience & Biobehavioral Reviews*, *75*, 129-139. https://doi.org/10.1016/j.neubiorev.2017.01.028

Tsopelas, C., Stewart, R., Savva, G. M., Brayne, C., Ince, P., Thomas, A., & Matthews, F. E. (2011). Neuropathological correlates of late-life depression in older people. *The British Journal of Psychiatry*, *198*(2), 109-114. https://doi.org/10.1192/bjp.bp.110.078816

Tulving, E., & Madigan, S. A. (1970). Memory and Verbal Learning. *Annual Review of Psychology*, *21*(1), 437-484. https://doi.org/10.1146/annurev.ps.21.020170.002253

Tunvirachaisakul, C., Gould, R. L., Coulson, M. C., Ward, E. V., Reynolds, G., Gathercole, R. L., ... & Howard, R. J. (2018). Predictors of treatment outcome in depression in later life: a systematic review and meta-analysis. *Journal of Affective Disorders*, *227*, 164-182. https://doi.org/10.1016/j.jad.2017.10.008

Turi, Z., Ambrus, G. G., Ho, K. A., Sengupta, T., Paulus, W., & Antal, A. (2014). When size matters: large electrodes induce greater stimulation-related cutaneous discomfort than smaller electrodes at equivalent current density. *Brain Stimulation*, *7*(3), 460-467. https://doi.org/10.1016/j.brs.2014.01.059

Turnbull, A. V., & Rivier, C. L. (1999). Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. *Physiological Reviews*, *79*(1), 1-71. https://doi.org/10.1152/physrev.1999.79.1.1

Turner, M. D., Nedjai, B., Hurst, T., & Pennington, D. J. (2014). Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research*, *1843*(11), 2563-2582. https://doi.org/10.1016/j.bbamcr.2014.05.014

Turner, R. M., Omar, R. Z., Yang, M., Goldstein, H., & Thompson, S. G. (2000). A multilevel model framework for meta-analysis of clinical trials with binary outcomes. *Statistics in Medicine*, *19*(24), 3417-3432. https://doi.org/10.1002/1097-0258(20001230)19:24<3417::AID-SIM614>3.0.CO;2-L

Uchiyama, C. L., D'Elia, L. F., Dellinger, A. M., Becker, J. T., Selnes, O. A., Wesch, J. E., ... & Miller, E. N. (1995). Alternate forms of the Auditory-Verbal Learning Test: Issues of test comparability, longitudinal reliability, and moderating demographic variables. *Archives of Clinical Neuropsychology*, *10*(2), 133-145. https://doi.org/10.1093/arclin/10.2.133

Uher, R., & McGuffin, P. (2010). The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. *Molecular Psychiatry*, *15*(1), 18-22. https://doi.org/10.1038/mp.2009.123

Unützer, J., Katon, W., Callahan, C. M., Williams Jr, J. W., Hunkeler, E., Harpole, L., ... & Oishi, S. (2003). Depression treatment in a sample of 1,801 depressed older adults in primary care. *Journal of the American Geriatrics Society*, *51*(4), 505-514. https://doi.org/10.1046/j.1532-5415.2003.51159.x

Vaismoradi, M., Turunen, H., & Bondas, T. (2013). Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. *Nursing & Health Sciences*, *15*(3), 398-405. https://doi.org/10.1111/nhs.12048

Vakil, E. (2012). Neuropsychological assessment: Principles, rationale, and challenges. *Journal of Clinical and Experimental Neuropsychology*, *34*(2), 135-150. https://doi.org/10.1080/13803395.2011.623121

Valkanova, V., & Ebmeier, K. P. (2013). Vascular risk factors and depression in later life: a systematic review and meta-analysis. *Biological Psychiatry*, *73*(5), 406-413. https://doi.org/10.1016/j.biopsych.2012.10.028

Van Aert, R. C., Wicherts, J. M., & Van Assen, M. A. (2019). Publication bias examined in meta-analyses from psychology and medicine: A meta-meta-analysis. *PloS One*, *14*(4), e0215052. https://doi.org/10.1371/journal.pone.0215052

van Agtmaal, M. J., Houben, A. J., Pouwer, F., Stehouwer, C. D., & Schram, M. T. (2017). Association of microvascular dysfunction with late-life depression: a systematic review and meta-analysis. *JAMA psychiatry*, *74*(7), 729-739. https://doi.org/10.1001/jamapsychiatry.2017.0984

van den Berg, S. M., & de Moor, M. H. (2020). Molecular genetic research on personality. In *Behavior Genetics of Temperament and Personality* (pp. 99-121). Springer, New York, NY. https://doi.org/10.1007/978-1-0716-0933-0_4

Van den Berg, M. D., Oldehinkel, A. J., Bouhuys, A. L., Brilman, E. I., Beekman, A. T., & Ormel, J. (2001). Depression in later life: three etiologically different subgroups. *Journal of Affective Disorders*, *65*(1), 19-26. https://doi.org/10.1016/S0165-0327(00)00263-9

Van Den Noortgate, W., & Onghena, P. (2003). Hierarchical linear models for the quantitative integration of effect sizes in single-case research. *Behavior Research Methods, Instruments, & Computers*, *35*(1), 1-10. https://doi.org/10.3758/BF03195492

Van Der Elst, W. I. M., Van Boxtel, M. P., Van Breukelen, G. J., & Jolles, J. (2005). Rey's verbal learning test: normative data for 1855 healthy participants aged 24–81 years and the influence of age, sex, education, and mode of presentation. *Journal of the International Neuropsychological Society*, *11*(3), 290-302. https://doi.org/10.1017/S1355617705050344

Van de Schoot, R., Kaplan, D., Denissen, J., Asendorpf, J. B., Neyer, F. J., & Van Aken, M. A. (2014). A gentle introduction to Bayesian analysis: Applications to developmental research. *Child Development*, *85*(3), 842-860. https://doi.org/10.1111/cdev.12169

van Rooij, S. J., Riva-Posse, P., & McDonald, W. M. (2020). The efficacy and safety of neuromodulation treatments in late-life depression. *Current Treatment Options in Psychiatry*, *7*(3), 337-348. https://doi.org/10.1007/s40501-020-00216-w

Vanderhorst, R. K., & McLaren, S. (2005). Social relationships as predictors of depression and suicidal ideation in older adults. *Aging & Mental Health*, *9*(6), 517-525. https://doi.org/10.1080/13607860500193062

Vanhoutte, B. (2014). The multidimensional structure of subjective well-being in later life. *Journal of Population Ageing*, *7*(1), 1-20. https://doi.org/10.1007/s12062-014-9092-9

Vanlessen, N., De Raedt, R., Koster, E. H., & Pourtois, G. (2016). Happy heart, smiling eyes: A systematic review of positive mood effects on broadening of visuospatial attention. *Neuroscience & Biobehavioral Reviews*, *68*, 816-837. https://doi.org/10.1016/j.neubiorev.2016.07.001

Vaughn, V. M., Saint, S., Krein, S. L., Forman, J. H., Meddings, J., Ameling, J., ... & Chopra, V. (2019). Characteristics of healthcare organisations struggling to improve quality: results from a systematic review of qualitative studies. *BMJ Quality & Safety*, *28*(1), 74-84. https://doi.org/10.1136/bmjqs-2017-007573

Venkatesh, V., Morris, M. G., Davis, G. B., & Davis, F. D. (2003). User acceptance of information technology: Toward a unified view. *MIS Quarterly*, 425-478. https://doi.org/10.2307/30036540

Videbech, P., & Ravnkilde, B. (2004). Hippocampal volume and depression: a meta-analysis of MRI studies. *American Journal of Psychiatry*, *161*(11), 1957-1966. https://doi.org/10.1176/appi.ajp.161.11.1957

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. In *Journal of Statistical Software* (Vol. 36, Issue 3, pp. 1–48). Available from: https://www.jstatsoft.org/v36/i03/ https://doi.org/10.18637/jss.v036.i03

Vinkers, C. H., Joëls, M., Milaneschi, Y., Kahn, R. S., Penninx, B. W., & Boks, M. P. (2014). Stress exposure across the life span cumulatively increases depression risk and is moderated by neuroticism. *Depression and Anxiety*, *31*(9), 737-745. https://doi.org/10.1002/da.22262

Volkert, J., Schulz, H., Härter, M., Wlodarczyk, O., & Andreas, S. (2013). The prevalence of mental disorders in older people in Western countries–a meta-analysis. *Ageing Research Reviews*, *12*(1), 339-353. https://doi.org/10.1016/j.arr.2012.09.004

Vöröslakos, M., Takeuchi, Y., Brinyiczki, K., Zombori, T., Oliva, A., Fernández-Ruiz, A., ... & Berényi, A. (2018). Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nature Communications*, *9*(1), 1-17. https://doi.org/10.1038/s41467-018-02928-3

Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A., Biryukov, S., Bolliger, I., ... & Brugha, T. S. (2015). Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*, *386*(9995), 743-800.

Vyas, C. M., Donneyong, M., Mischoulon, D., Chang, G., Gibson, H., Cook, N. R., ... & Okereke, O. I. (2020). Association of race and ethnicity with late-life depression severity, symptom burden, and care. *JAMA Network Open*, *3*(3), e201606-e201606. https://doi.org/10.1001/jamanetworkopen.2020.1606

Wampold, B. E., Minami, T., Baskin, T. W., & Tierney, S. C. (2002). A meta-(re) analysis of the effects of cognitive therapy versus 'other therapies' for depression. *Journal of Affective Disorders*, *68*(2-3), 159-165. https://doi.org/10.1016/S0165-0327(00)00287-1

Wang, T., Guo, Z., Du, Y., Xiong, M., Yang, Z., Ren, L., ... & Mu, Q. (2021). Effects of Noninvasive Brain Stimulation (NIBS) on Cognitive Impairment in Mild Cognitive Impairment and Alzheimer Disease: A Meta-analysis. *Alzheimer Disease & Associated Disorders*, *35*(3), 278-288. https://doi.org/10.1097/WAD.0000000000000464

Wang, L., Leonards, C. O., Sterzer, P., & Ebinger, M. (2014). White matter lesions and depression: a systematic review and meta-analysis. *Journal of Psychiatric Research*, *56*, 56-64. https://doi.org/10.1016/j.jpsychires.2014.05.005

Watt, D. (2007). On becoming a qualitative researcher: the value of reflexivity. *Qualitative Report*, *12*(1), 82-101.

Werner-Seidler, A., Afzali, M. H., Chapman, C., Sunderland, M., & Slade, T. (2017). The relationship between social support networks and depression in the 2007 National Survey of Mental Health and Well-being. *Social Psychiatry and Psychiatric Epidemiology*, *52*(12), 1463-1473. https://doi.org/10.1007/s00127-017-1440-7

Wechsler, D. (1955). Manual for the Wechsler Adult Intelligence Scale. New York: Psychological Corporation.

Wexler, A. (2018). Who uses direct-to-consumer brain stimulation products, and why? A study of home users of tDCS devices. *Journal of Cognitive Enhancement*, *2*(1), 114-134. https://doi.org/10.1007/s41465-017-0062-z

Whitmer, A. J., & Gotlib, I. H. (2013). An attentional scope model of rumination. *Psychological Bulletin*, *139*(5), 1036. https://doi.org/10.1037/a0030923

Whyte, E. M., Basinski, J., Farhi, P., Dew, M. A., Begley, A., Mulsant, B. H., & Reynolds III, C. F. (2004). Geriatric depression treatment in non-responders to selective serotonin reuptake inhibitors. *The Journal of Clinical Psychiatry*, *65*(12), 0-0. https://doi.org/10.4088/JCP.v65n1208

Wiegand, A., Nieratschker, V., & Plewnia, C. (2016). Genetic modulation of transcranial direct current stimulation effects on cognition. *Frontiers in Human Neuroscience*, *10*, 651. https://doi.org/10.3389/fnhum.2016.00651

Wielaard, I., Hoyer, M., Rhebergen, D., Stek, M. L., & Comijs, H. C. (2018). Childhood abuse and late-life depression: Mediating effects of psychosocial factors for early-and late-onset depression. *International Journal of Geriatric Psychiatry*, *33*(3), 537-545. https://doi.org/10.1002/gps.4828

Willig, C. (2019). What can qualitative psychology contribute to psychological knowledge?. *Psychological Methods*, *24*(6), 796. https://doi.org/10.1037/met0000218

Willig, C. (2016). Constructivism and 'the real world': Can they co-exist?. *QMiP Bulletin*, (21). Available from: https://openaccess.city.ac.uk/id/eprint/13576/1/Wilson, I., Duszynski, K., & Mant, A. (2003). A 5-year follow-up of general practice patients experiencing depression. *Family Practice*, *20*(6), 685-689. https://doi.org/10.1093/fampra/cmg611

Witt, J. C., & Martens, B. K. (1983). Assessing the acceptability of behavioral interventions used in classrooms. *Psychology in the Schools*, *20*(4), 510-517. https://doi.org/10.1002/1520-6807(198310)20:4<510::AID-PITS2310200420>3.0.CO;2-1

Wittenberg, G. F. (2010). Experience, cortical remapping, and recovery in brain disease. *Neurobiology of Disease*, *37*(2), 252-258. https://doi.org/10.1016/j.nbd.2009.09.007

Wolf, M. M. (1978). Social validity: the case for subjective measurement or how applied behavior analysis is finding its heart 1. *Journal of Applied Behavior Analysis*, *11*(2), 203-214. https://doi.org/10.1901/jaba.1978.11-203

Wolf, E. J., Harrington, K. M., Clark, S. L., & Miller, M. W. (2013). Sample size requirements for structural equation models: An evaluation of power, bias, and solution propriety. *Educational and Psychological Measurement*, *73*(6), 913-934. https://doi.org/10.1177/0013164413495237

Wolkenstein, L., & Plewnia, C. (2013). Amelioration of cognitive control in depression by transcranial direct current stimulation. *Biological Psychiatry*, *73*(7), 646-651. https://doi.org/10.1016/j.biopsych.2012.10.010

Wong, H. L., Chan, W. C., Wong, Y. L., Wong, S. N., Yung, H. Y., Wong, S. M. C., & Cheng, P. W. C. (2019). High-definition transcranial direct current stimulation—An open-label pilot intervention in alleviating depressive symptoms and cognitive deficits in late-life depression. *CNS Neuroscience & Therapeutics*, *25*(11), 1244-1253. https://doi.org/10.1111/cns.13253

Woodham, R. D., Rimmer, R. M., Young, A. H., & Fu, C. H. (2022). Adjunctive home-based transcranial direct current stimulation treatment for major depression with real-time remote supervision: An open-label, single-arm feasibility study with long term outcomes. *Journal of Psychiatric Research*. https://doi.org/10.1016/j.jpsychires.2022.07.026

Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., ... & Nitsche, M. A. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology*, *127*(2), 1031-1048. https://doi.org/10.1016/j.clinph.2015.11.012

Woods, A. J., Bryant, V., Sacchetti, D., Gervits, F., & Hamilton, R. (2015). Effects of electrode drift in transcranial direct current stimulation. *Brain Stimulation*, *8*(3), 515-519. https://doi.org/10.1016/j.brs.2014.12.007

World Health Organization. (2018). *International classification of diseases for mortality and morbidity statistics* (11th Revision). Retrieved from https://icd.who.int/browse11/l-m/en

World Health Organization (2018). Global Health Estimates 2016: Deaths by cause, age, sex, by country and by region, 2000-2016. World Health Organization, Geneva. Retrieved from: https://apps.who.int/iris/rest/bitstreams/1244794/retrieve

Wray, N. R., Pergadia, M. L., Blackwood, D. H. R., Penninx, B. W. J. H., Gordon, S. D., Nyholt, D. R., ... & Sullivan, P. F. (2012). Genome-wide association study of major depressive disorder: new results, meta-analysis, and lessons learned. *Molecular Psychiatry*, *17*(1), 36-48. https://doi.org/10.1038/mp.2010.109

Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., ... & Viktorin, A. (2018). Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics*, *50*(5), 668-681. https://doi.org/10.1038/s41588-018-0090-3

Wu, Z., Schimmele, C. M., & Chappell, N. L. (2012). Aging and late-life depression. *Journal of Aging and Health*, *24*(1), 3-28. https://doi.org/10.1177/0898264311422599

Yardley, L. (2000). Dilemmas in qualitative health research. *Psychology and Health*, *15*(2), 215-228. https://doi.org/10.1080/08870440008400302

Yang, L., Liu, S., Liu, J., Zhang, Z., Wan, X., Huang, B., ... & Zhang, Y. (2020). COVID-19: immunopathogenesis and Immunotherapeutics. *Signal Transduction and Targeted Therapy*, *5*(1), 1-8. https://doi.org/10.1038/s41392-020-00243-2

York, M. K., Farace, E., Pollak, L., Floden, D., Lin, G., Wyman-Chick, K., ... & Parkinson Study Group Functional Neurosurgical Working Group. (2021). The global pandemic has permanently changed the state of practice for pre-DBS neuropsychological evaluations. *Parkinsonism & Related Disorders*, *86*, 135-138. https://doi.org/10.1016/j.parkreldis.2021.04.029

Yosephi, M. H., Ehsani, F., Zoghi, M., & Jaberzadeh, S. (2018). Multi-session anodal tDCS enhances the effects of postural training on balance and postural stability in older adults with high fall risk: primary motor cortex versus cerebellar stimulation. *Brain Stimulation*, *11*(6), 1239-1250. https://doi.org/10.1016/j.brs.2018.07.044Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British journal of psychiatry*, *133*(5), 429-435.

Yu, C. L., Liang, C. S., Yang, F. C., Tu, Y. K., Hsu, C. W., Carvalho, A. F., ... & Su, K. P. (2022). Trajectory of antidepressant effects after single-or two-dose administration of psilocybin: a systematic review and multivariate meta-analysis. *Journal of Clinical Medicine*, *11*(4), 938. https://doi.org/10.3390/jcm11040938

Zajecka, J. M. (2013). Residual symptoms and relapse: mood, cognitive symptoms, and sleep disturbances. *The Journal of Clinical Psychiatry*, *74*(suppl 2), 18130. https://doi.org/10.4088/JCP.12084su1c.02

Zaninotto, L., Solmi, M., Veronese, N., Guglielmo, R., Ioime, L., Camardese, G., & Serretti, A. (2016). A meta-analysis of cognitive performance in melancholic versus non-melancholic unipolar depression. *Journal of Affective Disorders*, *201*, 15-24. https://doi.org/10.1016/j.jad.2016.04.039

Zhang, R., Lam, C. L., Peng, X., Zhang, D., Zhang, C., Huang, R., & Lee, T. M. (2021). Efficacy and acceptability of transcranial direct current stimulation for treating depression: A meta-analysis of randomized controlled trials. *Neuroscience & Biobehavioral Reviews*, *126*, 481-490. https://doi.org/10.1016/j.neubiorev.2021.03.026

Zimmerman, M., McGlinchey, J. B., Posternak, M. A., Friedman, M., Attiullah, N., & Boerescu, D. (2006). How should remission from depression be defined? The depressed patient's perspective. *American Journal of Psychiatry*, *163*(1), 148-150. https://doi.org/10.1176/appi.ajp.163.1.148

Zimmerman, M., Posternak, M. A., & Chelminski, I. (2004). Derivation of a definition of remission on the Montgomery–Åsberg depression rating scale corresponding to the definition of remission on the Hamilton rating scale for depression. *Journal of Psychiatric Research*, *38*(6), 577-582. https://doi.org/10.1016/j.jpsychires.2004.03.007

Zisook, S., & Kendler, K. S. (2007). Is bereavement-related depression different than non-bereavement-related depression?. *Psychological Medicine*, *37*(6), 779-794. https://doi.org/10.1017/S0033291707009865

Zisook, S., & Shuchter, S. R. (1991). Depression through the first year after the death of a spouse. *The American Journal of Psychiatry*, *148*(10), 1346-1352. https://doi.org/10.1176/ajp.148.10.1346

Appendices

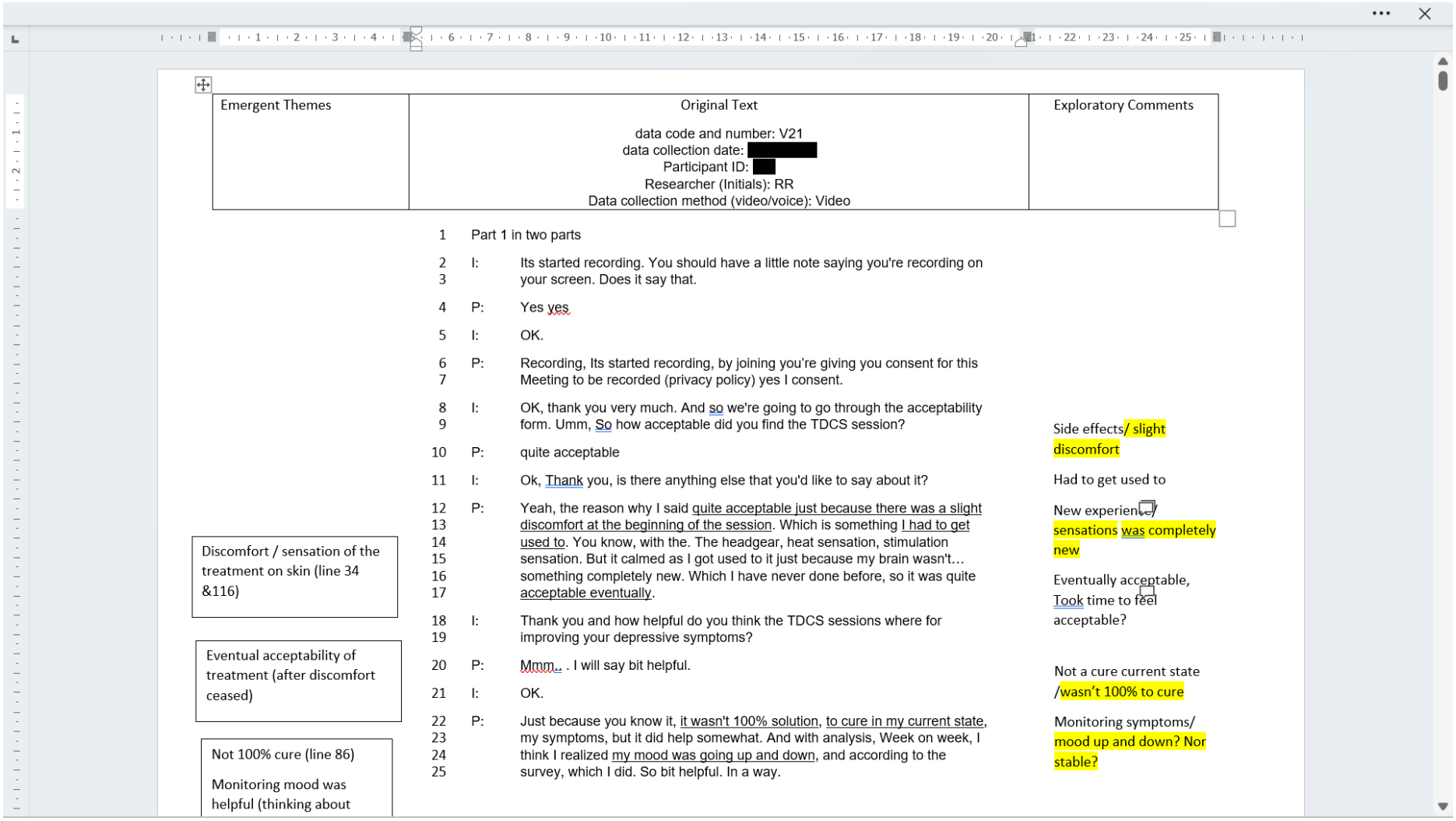
Appendix 1. - *Transcription example*

Part of stage 1 is transcription. Below is an example of the transcription coding template used.

Transcription convention		
(.)		Indicates a short pause (0.5 – 5) seconds
::	reca::ll	Colons used to signal elongation added by the speaker
italics	*recall*	Text in italics shows emphasis added by the speaker
:: & italics	*recall::*	Indicates elongation & emphasis added by the speaker
[…]		Indicates text omitted by the author due to bad quality of the recording
[text]	[recall]	Indicates information added by the author for the purpose of clarity

Appendix 2. *Stage 2 Exploratory codes*

Stage 2 involves initial coding. Below is a visual of initial codes and the initial emerging themes



Emergent Themes	Original Text	Exploratory Comments
	data code and number: V21 data collection date: [redacted] Participant ID: [redacted] Researcher (Initials): RR Data collection method (video/voice): Video	
	1 Part 1 in two parts	
	2 I: Its started recording. You should have a little note saying you're recording on 3 your screen. Does it say that.	
	4 P: Yes yes	
	5 I: OK.	
	6 P: Recording, Its started recording, by joining you're giving you consent for this 7 Meeting to be recorded (privacy policy) yes I consent.	
	8 I: OK, thank you very much. And so we're going to go through the acceptability 9 form. Umm, So how acceptable did you find the TDCS session?	Side effects/ slight discomfort
	10 P: quite acceptable	
	11 I: Ok, Thank you, is there anything else that you'd like to say about it?	Had to get used to
Discomfort / sensation of the treatment on skin (line 34 &116)	12 P: Yeah, the reason why I said quite acceptable just because there was a slight 13 discomfort at the beginning of the session. Which is something I had to get 14 used to. You know, with the. The headgear, heat sensation, stimulation 15 sensation. But it calmed as I got used to it just because my brain wasn't… 16 something completely new. Which I have never done before, so it was quite 17 acceptable eventually.	New experience/ sensations was completely new Eventually acceptable, Took time to feel acceptable?
Eventual acceptability of treatment (after discomfort ceased)	18 I: Thank you and how helpful do you think the TDCS sessions where for 19 improving your depressive symptoms?	
	20 P: Mmm.. . I will say bit helpful.	Not a cure current state /wasn't 100% to cure
	21 I: OK.	
Not 100% cure (line 86) Monitoring mood was helpful (thinking about	22 P: Just because you know it, it wasn't 100% solution, to cure in my current state, 23 my symptoms, but it did help somewhat. And with analysis, Week on week, I 24 think I realized my mood was going up and down, and according to the 25 survey, which I did. So bit helpful. In a way.	Monitoring symptoms/ mood up and down? Nor stable?

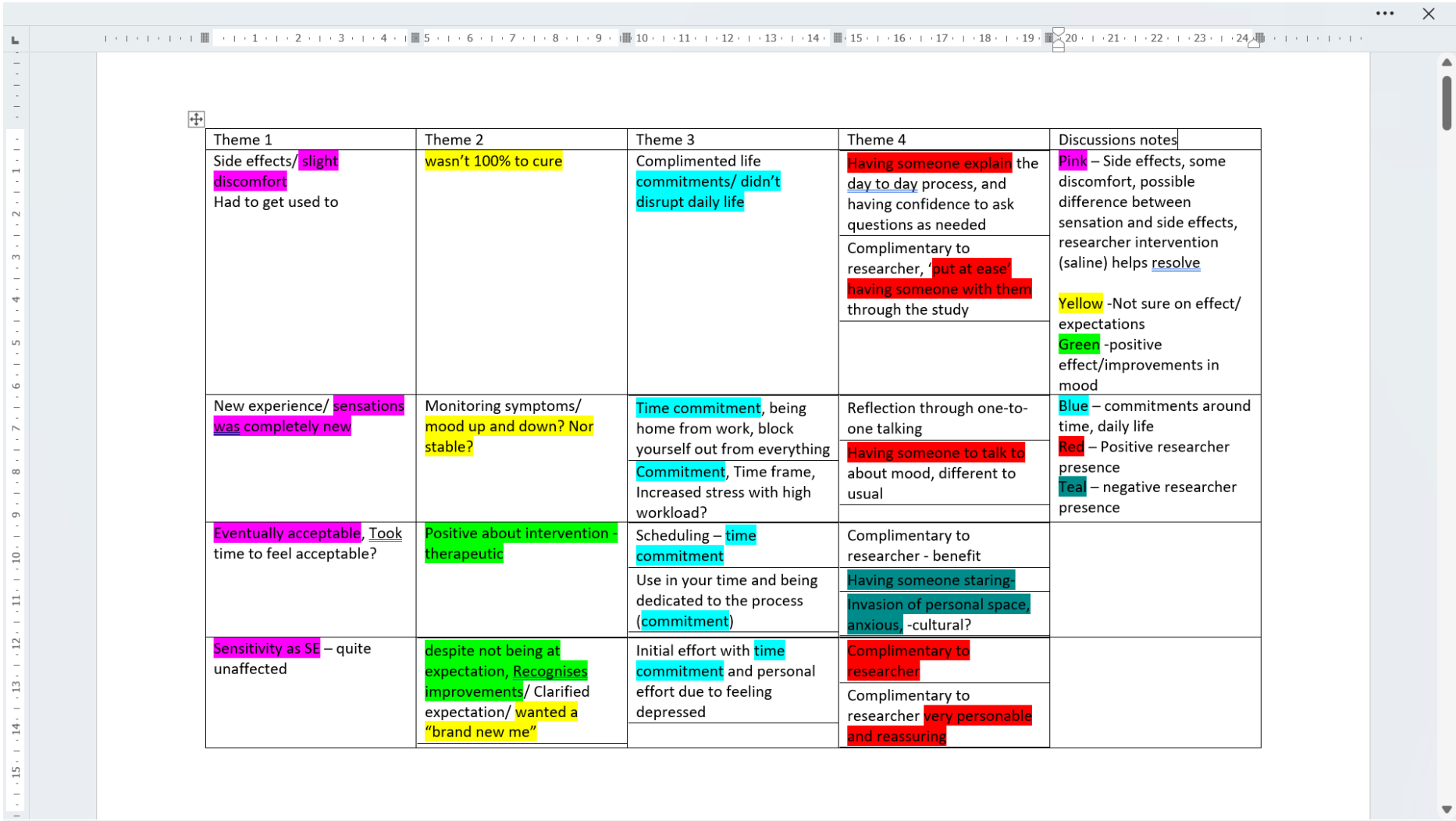
Appendix 3. *Stage 3 Emerging Themes*

Emerging themes were discussed collated (example below) and discussed with the project supervisors to develop the themes and subthemes.

Theme 1	Theme 2	Theme 3	Theme 4	Theme 5
Side effects/ slight discomfort Had to get used to	wasn't 100% to cure	Complimented life commitments/ didn't disrupt daily life	Having someone explain the day to day process, and having confidence to ask questions as needed Complimentary to researcher, 'put at ease' having someone with them through the study	
New experience/ sensations was completely new	Monitoring symptoms/ mood up and down? Nor stable?	Time commitment, being home from work, block yourself out from everything Commitment, Time frame, Increased stress with high workload?	Reflection through one-to-one talking Having someone to talk to about mood, different to usual	
Eventually acceptable, Took time to feel acceptable?	Positive about intervention - therapeutic	Scheduling – time commitment Use in your time and being dedicated to the process (commitment)	Complimentary to researcher - benefit Having someone staring- Invasion of personal space, anxious, -cultural?	
Sensitivity as SE – quite unaffected	despite not being at expectation, Recognises improvements/ Clarified expectation/ wanted a "brand new me"	Initial effort with time commitment and personal effort due to feeling depressed	Complimentary to researcher Having someone/counsellor to do CBT with	

Version 2

After discussion with supervisors, novice researcher entered notes until themes were developed as in Appendix 4.



Theme 1	Theme 2	Theme 3	Theme 4	Discussions notes
Side effects/ slight discomfort Had to get used to	wasn't 100% to cure	Complimented life commitments/ didn't disrupt daily life	Having someone explain the day to day process, and having confidence to ask questions as needed Complimentary to researcher, 'but at ease' having someone with them through the study	Pink – Side effects, some discomfort, possible difference between sensation and side effects, researcher intervention (saline) helps resolve Yellow -Not sure on effect/ expectations Green -positive effect/improvements in mood
New experience/ sensations was completely new	Monitoring symptoms/ mood up and down? Nor stable?	Time commitment, being home from work, block yourself out from everything Commitment, Time frame, Increased stress with high workload?	Reflection through one-to-one talking Having someone to talk to about mood, different to usual	Blue – commitments around time, daily life Red – Positive researcher presence Teal – negative researcher presence
Eventually acceptable, Took time to feel acceptable?	Positive about intervention - therapeutic	Scheduling – time commitment Use in your time and being dedicated to the process (commitment)	Complimentary to researcher - benefit Having someone staring- Invasion of personal space, anxious, -cultural?	
Sensitivity as SE – quite unaffected	despite not being at expectation, Recognises improvements/ Clarified expectation/ wanted a "brand new me"	Initial effort with time commitment and personal effort due to feeling depressed	Complimentary to researcher Complimentary to researcher very personable and reassuring	

Appendix 4. *Themes and Subthemes*

Version 1 Themes and subthemes were developed during a team meeting and coded into the table below.

Themes	Subthemes
Theme 1: Side Effects	Subtheme 1.1: Sensation of the treatment
	Subtheme 1.2: Side-effects from the treatment
Theme 2: Effectiveness	Subtheme 2.1: Expectation of tDCS as a treatment
	Subtheme 2.2: Recovery, enhancement; the extent of the effectiveness
	Subtheme 2.3: Uncertainty, novelty
Theme 3: Time commitment	Subtheme 3.1: Everyday commitment
	Subtheme 3.2: Convenience of having sessions at home, improving acceptability (gaining time)
Theme 4: Support, feeling held, contained	Subtheme 4.1: daily visits, interaction, felt connected, having the same person
	Subtheme 4.2: being observed i) for most was positive, felt safe
	Subtheme 4.3: being observed and ii) for some was anxiety.

After reviewing the themes together with the supervisory team they were edits and refined to the below table.

Version 2 (final)

Themes	Subthemes
Theme 1: Side Effects	Subtheme 1.1: Physical Sensation of the treatment
	Subtheme 1.2: Side-effects from the treatment
Theme 2: Effectiveness	Subtheme 2.1: Expectation of tDCS as a treatment
	Subtheme 2.2: Recovery & enhancement: the extent of the effectiveness
	Subtheme 2.3: Un/certainty & novelty
Theme 3: Time commitment	Subtheme 3.1: An everyday commitment
	Subtheme 3.2: Convenience of having sessions at home, improving acceptability (gaining time)
Theme 4: Support, feeling held, contained	Subtheme 4.1: Feeling connected by daily visits by the same person
	Subtheme 4.2: Being observed feels safe versus feels anxiety provoking

Appendix 5. *Publication 1* - Woodham, R., Rimmer, R. M., Mutz, J., & Fu, C. H. (2021). Is tDCS a potential first line treatment for major depression?. *International Review of Psychiatry*, *33*(3), 250-265.

Title:

Is transcranial direct current stimulation (tDCS) a potential first line treatment for major depression?

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Abstract

Transcranial direct current stimulation (tDCS) is a novel treatment option for major depression which could be provided as a first-line treatment. tDCS is a non-invasive form of transcranial stimulation which changes cortical tissue excitability by applying a weak (0.5-2 mA) direct current via scalp electrodes. Anodal and cathodal stimulation leads to depolarisation and hyperpolarisation, respectively, and cumulative effects are observed with repeated sessions. The montage in depression most often involves anodal stimulation to the left dorsolateral prefrontal cortex. Rates of clinical response, remission, and improvements in depressive symptoms following a course of active tDCS are greater in comparison to a course of placebo sham-controlled tDCS. In particular, the largest treatment effects are evident in first episode and recurrent major depression, while minimal effects have been observed in treatment-resistant depression. The proposed mechanism is neuroplasticity at the cellular and molecular level. Alterations in neural responses have been found at the stimulation site as well as subcortically in prefrontal-amygdala connectivity. A possible mediating effect could be cognitive control in emotion dysregulation. Additional beneficial effects on cognitive impairments have been reported, which would address an important unmet need. The tDCS device is portable and can be used at home. Clinical trials are required to establish the efficacy, feasibility and acceptability of home-based tDCS treatment and mechanisms.

Keywords

transcranial direct current stimulation, tDCS, major depression, neuroplasticity, neuropsychology, biomarkers

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Disclosure Statement

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Introduction

Major depression is a common mental health disorder, affecting about 350 million people worldwide with a lifetime prevalence of about 1 in 7 adults, and is predicted to be the leading contributor to the global burden of disease (Kessler and Bromet, 2013; Vos et al., 2015; Whiteford et al., 2013). The disorder is the largest contributor to non-fatal health loss and the most significant precursor for suicide (Vos et al., 2015; World Health Organization [WHO] 2015). There is a significant socio-economic challenge with the cost being about £9 billion in the UK in 2000 (Thomas and Morris, 2003) and expected to be as much as £12 billion by 2026 in England (McCrone et al., 2008).

The most common forms of treatments are antidepressant medication and psychotherapy. However, clinical response to antidepressant medication (Rush et al., 2006) or to psychotherapy (Cuijpers et al., 2014) is less than 50% following a full course of either treatment. Side effects from antidepressant medications are common, such as sexual dysfunction, sleepiness, and weight gain (Cascade et al., 2009; Ferguson, 2001), yet are often under-reported and can lead to discontinuation (Cipriani et al., 2018; Sinyor et al., 2020). Onset of clinically noticeable effects can take several weeks for antidepressant medication as well as psychotherapy, and access to treatment can be limited, in particular for psychotherapy (Cipriani et al., 2018; Pence et al., 2012). Providing another treatment option would be benefit patients who are unable to take current treatments or who prefer an alternative form of treatment. Transcranial direct current stimulation is a novel, non-invasive form of neurostimulation that is a potential first line treatment option for major depression.

The present review evaluates the current evidence for the efficacy and adverse events associated with a course of tDCS treatment in major depression, potential mechanisms, neuropsychological effects, and initial studies of predictive biomarkers of clinical outcome.

What is transcranial direct current stimulation (tDCS)?

The application of electrical stimulation for therapeutic effect has been reported since the first century. Placing a live electric torpedo fish over the scalp, which generates a strong electric current, was found to create a brief stupor and to alleviate pain from headache. In 1804, Aldini reported that applying electric currents to the scalp could improve melancholia (Priori, 2003).

Non-invasive brain stimulation (NIBS) refers to stimulation that can be given without the need of an implant. tDCS applies a weak direct electric current through electrodes placed on the scalp, which modulates neuronal resting membrane potential but does not directly lead to neuronal discharge (Nitsche & Paulus, 2000). Transcranial alternating current stimulation (tACS) is similar to tDCS, but consists of a sinusoidal alternating current which can be provided at a selected frequency to entrain intrinsic oscillation patterns (Matsumoto & Ugawa, 2017), and transcranial random noise stimulation (tRNS) consists of an alternating current with a random frequency and amplitude (Terney et al., 2008).

Transcranial magnetic stimulation (TMS) is another form of non-invasive brain stimulation. TMS uses a magnetic coil to generate a local electric current through electromagnetic induction. This is applied to a focal brain region leading to depolarization or hyperpolarization, neuronal excitation or inhibition, respectively (Hallet, 2000). In clinical practice, repetitive TMS (rTMS) that can be high frequency or low frequency is most common, while theta-burst TMS (TBS) is demonstrating potential efficacy (Mutz et al., 2019).

Vagus nerve stimulation (VNS) and deep brain stimulation (DBS) are forms of invasive brain stimulation techniques. In VNS, an electrical stimulation is delivered to the vagus nerve via a

stimulator implanted under the skin, and DBS involves the implantation of electrodes in specific areas in the brain.

Electroconvulsive therapy (ECT) is applied through electrodes placed on the scalp, which induce general convulsive activity leading to a seizure and is provided under a general anaesthetic. While it could be considered to be a non-invasive form of brain stimulation, ECT is usually placed in between categories as it does not require a surgical procedure but is more invasive than tDCS and TMS, leads to a seizure, and is applied under anaesthesia.

All of these methods can be grouped within the umbrella term of transcranial electric stimulation (TES). tDCS has benefits in cost-effectiveness, portability, and a low side effect profile (Tortella et al., 2015).

How doe tDCS affect neuronal activity?

The current is typically in the range 0.5 – 2 mA and is applied through electrodes placed on the scalp with a conductive substance such as a saline solution or gel. The current flows from the anode electrode to the cathode electrode (and electrons flow from the cathode to the anode). The stimulation is non-focal. The surface area of the sponge-electrode used in studies in depression are typically large, approximately 25 – 35 cm^2, and sponge-electrode size can range from 3.5 – 100 cm^2 (Dedoncker et al., 2016; Turi et al., 2014).

The current passes through the skin, subcutaneous tissue and skull with high impedance. It is estimated that 25 – 50 % of the given current reaches through the cerebrospinal fluid (CSF) to gray matter (Rush & Driscoll 1968; Vöröslakos et al., 2018). Factors such as area of stimulation, electrode size, distance between electrodes, as well as individual differences contribute to the final current intensity (Dedoncker et al., 2016; Rush & Driscoll 1968; Turi et al., 2014; Woods et al., 2015).

Anodal stimulation typically leads to depolarisation of the neuronal resting membrane potential and to increased potential firing of cells. Cathodal stimulation tends to inhibit cortical excitability through hyperpolarisation to decreased potential cell firing (Creutzfeldt et al., 1962). tDCS changes neural activity by modulating the resting membrane potential, rather than directly stimulating an action potential. However, factors including orientation of the neuronal axon to the current and neuron type impact on the activity and directionality (Jefferys, 1981).

Does tDCS affect neuroplasticity?

Neuroplasticity is a general term that refers to our ability to learn as a result of cellular and molecular changes in neurons leading to alterations in regional brain activity or structure. Synaptic plasticity includes synaptogenesis, forming and fitting new synapses together, and non-synaptic plasticity includes neural migration and neurogenesis. In brain imaging, this can be observed by persistent changes in regional neurofunction or neuroanatomy (Zatorre et al., 2012). While neuroplasticity has typically been described in rehabilitation following brain injury, it is also seen as a mechanism for treatments, such as antidepressant medication, psychotherapy, and mindfulness (Davidson & McEwen, 2012; Lomas et al., 2015; Fu et al., 2020).

The neurophysiological effects of tDCS typically last beyond the immediate stimulation period (Nitsche et al., 2003). Long-term potentiation (LTP) describes the sustained increase in synaptic transmission that is the cellular correlate of learning and memory, first described in neuronal cells in the hippocampus (Bliss & Lømo, 1973). Cortical LTP and long-term depression (LTD)-like changes are modulated by glutamatergic and GABAergic neurons (Trepel & Racine, 2000). Anodal tDCS-

enhanced excitability in the primary motor cortex is LTP-like, which is dependent on N-methyl-D-aspartate (NMDA) receptor and calcium channel activity (Leibetanz et al., 2002; Monte-Silva et al., 2013). Stimulation strength, duration and direction have a non-linear relationship impact on whether excitatory or inhibitory effects are generated (Batsikadze et al., 2013; Jamil et al., 2017; Monte-Silva et al., 2013).

Anodal tDCS stimulation to the primary motor cortex (M1) results in a significant decrease in gamma-aminobutyric acid (GABA) concentration in the stimulated region as measured by magnetic resonance spectroscopy (MRS), suggesting a mediating effect that is in part due to reduced GABAergic inhibition, while cathodal tDCS stimulation is associated with a significant decrease in glutamate with a seemingly counterintuitive correlated decrease in GABA, indicating a mediating effect of a reduction in excitatory glutamatergic function. Effects on GABA levels have been observed in the stimulated primary motor cortex as well as in the non-stimulated but functionally connected contralateral motor cortex demonstrating that neurochemical changes are also evident outside of the targeted region during plasticity induction (Bachtier et al., 2018).

LTP is further dependent on the neurotrophin, brain-derived neurotrophic factor (BDNF), in motor skill learning (Fritsch et al., 2010). Anodal tDCS applied to the primary motor cortex enhanced motor learning as long as activity-dependent BDNF secretion was present, which was evident in animal studies and behaviourally in human participants with the BDNF Val66Met polymorphism.

In neuroimaging studies, effects have been observed as changes in brain function, for example tDCS modulates distinct resting state networks as measured by functional magnetic resonance imaging (fMRI) (Keeser et al., 2011). Active anodal tDCS applied to the left dorsolateral prefrontal cortex has been associated with significant changes in connectivity in the default mode network, self-referential network and frontal-parietal networks in comparison with sham tDCS.

Does tDCS treatment improve depressive symptoms?

Meta-analyses of sham placebo controlled RCTs

In our meta-analysis, we examined the efficacy and acceptability of non-invasive brain stimulation in adults with major depressive disorder or bipolar depression (Mutz et al., 2018). We obtained data from 56 randomised sham-controlled trials which included a total of 131 treatment arms and 66 treatment comparisons, consisting of tDCS, TMS (repetitive TMS, deep TMS, and synchronised TMS) and theta-burst stimulation (TBS), without co-initiation of another treatment.

3,058 participants (mean age = 45.0 years; 61.7 % female) had been randomly assigned to active treatment (n = 1,598) or sham therapy (n = 1,460). In our main analysis of response rates, defined as a minimum of 50% reduction in symptom scores, at the primary study endpoint, we found evidence of antidepressant efficacy for high frequency rTMS over the left dorsolateral prefrontal cortex (OR = 3.75, 95% CI 2.44 to 5.75), right-sided low frequency rTMS (OR = 7.44, 95% CI 2.06 to 26.83), bilateral rTMS (OR = 3.68, 95% CI 1.66 to 8.13), deep TMS (OR = 1.69, 95% CI 1.003 to 2.85), intermittent TBS (OR = 4.70, 95% CI 1.14 to 19.38) and tDCS (OR = 4.17, 95% CI 2.25 to 7.74). We did not find evidence that continuous TBS, bilateral TBS or synchronised TMS were more efficacious than sham. We also did not find evidence of differences in all-cause discontinuation rates between active and sham treatment for any of the protocols.

tDCS was associated with higher response rates (k = 9, OR = 4.17, 95% CI 2.25 to 7.74), higher remission rates (k = 8, OR = 2.88, 95% CI 1.65 to 5.04), and lower post-treatment depression severity scores (k = 7, Hedge's g = -0.76, 95% CI −1.31 to −0.21) relative to sham therapy. The overall number

of patients included in the tDCS trials was n = 456 (n = 246 participants randomised to active treatment and n = 210 participants randomised to receive sham therapy). Sample sizes of the trials varied substantially, ranging from 10 to 151 participants (median = 35 participants, IQR = 30.25). Most trials (80%) recruited only participants with major depressive disorder, although one trial recruited exclusively participants with bipolar depression. tDCS was applied in an outpatient setting, and trials had excluded patients who had reported psychotic symptoms. In 7 out of 10 trials, tDCS was applied as monotherapy; in 1 trial, tDCS was added to stable pharmacotherapy, and in 2 trials, tDCS was given as monotherapy or augmentation treatment.

The number of tDCS treatment sessions ranged from 5 – 22 (median = 10, IQR = 5.75), applied over the course of 1.5 – 10 weeks (median = 2, IQR = 3.63). Treatment duration was 20 minutes in 6 out of 10 trials and 30 minutes in the remaining 4 trials. The anode was applied over F3 (according to the EEG 10/20 coordinate system), generally referred to as left dorsolateral prefrontal cortex, while the cathode/reference electrode was located over F4 (6/10 trials), FP2 (3/10 trials) or F8 (1 trial). tDCS was most frequently applied with a current strength of 2 mA (in 70% of trials), although 3 trials applied tDCS at 1 mA. 70% of trials used an electrode size of 35 cm^2 and three trials used an electrode size of 25 cm^2. Current density ranged from 0.028 – 0.080.

In subgroup analyses, we found evidence that tDCS was associated with higher response rates only in trials which had recruited participants with a non-treatment resistant form of depression or which had recruited patients with either treatment resistant or non-treatment resistant depression. We did not find evidence of differences in all-cause discontinuation rates between active treatment and sham treatment in any of the treatment protocols.

In a subsequent meta-analysis, we estimated the comparative clinical efficacy and acceptability of non-surgical brain stimulation treatments more broadly, using network meta-analysis (Mutz et al., 2019). We included clinical trials in which adult patients with major depressive disorder or bipolar depression were randomly assigned to ECT, TMS (repetitive, accelerated, priming, deep, and synchronised), TBS, magnetic seizure therapy, tDCS, or sham therapy.

113 trials (262 treatment arms) that randomised n = 6,750 patients (mean age = 47.9 years, 59% women) met our inclusion criteria. The most studied treatment comparisons were high frequency left rTMS and tDCS compared to sham therapy (40 and 11 treatment comparisons, respectively). In our primary analysis of response rates, 10 out of 18 treatment protocols were associated with higher response rates relative to sham therapy: bitemporal ECT (OR = 8.91, 95% CI 2.57 to 30.91), high dose right unilateral ECT (OR = 7.27, 95% CI 1.90 to 27.78), priming TMS (OR = 6.02, 95% CI 2.21 to 16.38), magnetic seizure therapy (OR = 5.55, 95% CI 1.06 to 28.99), bilateral rTMS (OR = 4.92, 95% CI 2.93 to 8.25), bilateral TBS (OR = 4.44, 95% CI 1.47 to 13.41), low frequency right rTMS (OR = 3.65, 95% CI 2.13 to 6.24), intermittent theta-burst stimulation (OR = 3.20, 95% CI 1.45 to 7.08), high frequency left rTMS (OR = 3.17, 95% CI 2.29 to 4.37), and tDCS (OR = 2.65, 95% CI 1.55 to 4.55).

Active tDCS treatment was also associated higher remission rates (OR = 2.18, 95% CI 1.18 to 4.04) and lower post-treatment depression severity scores (SMD = -0.55, 95% CI -0.96 to -0.14) relative to sham treatment. All treatment protocols included in this study were at least as acceptable as sham treatment, estimated from all-cause discontinuation (i.e. discontinuation of treatment for any reason). We did not examine specific undesired and adverse effects in this study, and future research should systematically evaluate specific cognitive and adverse effects associated with these treatment modalities (Kiebs et al., 2019).

There is a suggestion of a synergistic potential of tDCS with antidepressant medication (Brunoni et al., 2013; Shiozawa et al., 2013). Combination of tDCS with an antidepressant medication, sertraline, demonstrated a significantly greater early improvement in depressive symptoms following 2 weeks of treatment in comparison with placebo only, sertraline only, and tDCS only treatment arms. Factor analysis revealed a main effect of tDCS, indicating that this was driving the initial antidepressant effect (Brunoni et al., 2013). Meron et al. (2015) meta-analysis similarly found active tDCS to be superior to sham tDCS in the treatment of depression, ranging from 1 – 4 weeks of treatment. However, an overall benefit of tDCS combined with antidepressant medication was not observed. The observation of an early improvement in depressive symptoms is an important potential advantage of tDCS relative to current treatment options for depression.

Recent clinical trials

Brunoni et al. (2017a) investigated the efficacy of the antidepressant medication, escitalopram (a selective serotonin-reuptake inhibitor), and tDCS, in patients with major depressive disorder. Participants were enrolled into a non-inferiority, parallel, placebo-controlled trial. There was random allocation to one of three treatment arms for 10 weeks: 1) tDCS group: active tDCS and placebo medication (n=91), 2) escitalopram group: sham tDCS and escitalopram (n=94), and 3) placebo group: sham tDCS and placebo medication (n=60). Active anodal tDCS was administered to the left DLPFC at 2 mA for 30 minutes per session, with sessions on five consecutive weekdays in the first three weeks, and one session per week for the remaining seven weeks. Escitalopram was prescribed daily at 10 mg for the first three weeks and then increased to maximum dose of 20 mg daily until week 10. Clinical improvements were highest for escitalopram, followed by tDCS and then placebo. As the improvement in depressive symptoms in the tDCS group was not 50% or less than in the escitalopram group compared to placebo, the findings failed to show non-inferiority of tDCS as compared with escitalopram.

Loo et al. (2018) conducted a two-arm, parallel, randomised, sham-controlled trial to compare the efficacy of tDCS as treatment for unipolar and bipolar depression. All patients were in a current depressive episode and had a diagnosis of recurrent depression, with historic treatment profiles indicating that many had a form of depression approaching treatment resistance. Participants in both unipolar and bipolar samples were randomised to receive either active or sham tDCS for 5 consecutive weekdays over a 4-week period. tDCS was administered for 30 minutes with the anode centered over the left DLPFC. Active tDCS was delivered at 2.5 mA, whilst sham tDCS was set at 0.034 mA for the majority of the session (a current strength thought to be a negligible) with a 10 second ramp up to 1 mA at the start of the session, followed by a 60 second ramp down; this was reversed at the end of the session. However, there was no significant difference in the rates of response or remission in the sham and active tDCS treatment groups. Loo et al. (2018) suggested that the low current of the sham tDCS was sufficient to lead to an improvement in depressive symptoms, however the clinical history of participants seemed to be approaching a treatment-resistant form of depression, which could have contributed to the low response rates.

What are the adverse effects of tDCS?

Brunoni et al. meta-analysis (2011a) reported that the most common adverse effects are itching (39.3% vs. 32.9%, p>0.05) and tingling (22.2% vs. 18.3%, p>0.05) followed by headache (14.8% vs. 16.2%, p>0.05), burning sensation (8.7% vs. 10%, p>0.05) and discomfort (10.4% vs. 13.4%, p>0.05) in active tDCS as compared to sham tDCS, respectively. The summary is from 209 studies, consisting of 3,836 participants, in which about 117 studies (56%) had reported side effect symptoms in some form, reflecting also how limited reporting of adverse effects had been in early studies (Brunoni et

al., 2011a). Additional side effects also include headache after a tDCS session (11.8%), nausea (2.9%) and insomnia (0.98%) found in a study of 102 patients. Those with a history of migraines appeared to experience this side effect to a significantly higher degree though (55.6%) and could be considered an exclusionary consideration in future studies (Poreisz et al., 2007). Mild skin redness at the site of the electrode, which resolves following stimulation, is commonly reported as an issue that affects blinding in sham placebo-controlled trials (Brunoni et al., 2011a; Guarienti et al., 2014. Ezquerro et al., 2016).

Erythema or redness is likely related to local vasodilatory skin changes rather than damage (Durand et al., 2002). In rare cases, skin lesions have been produced following poor electrode skin contact (Palm et al., 2014; Rodríguez et al., 2014). Diminishing electrode density, such as by increasing the size of the electrode, and reducing electrical resistance, such as by using rubber electrodes covered with sponge and conductive substance, e.g. saline, at the site can improve contact (Woods et al., 2015). MRI studies have not detected oedema or injury in the blood-brain barrier or cerebral tissue following tDCS (Nitsche et al., 2004b). Surface skin lesions are not attributable to brain injury as electrochemical reactions produced at the skin are not expected to diffuse into the brain (Bikson et al., 2009).

A potentially serious adverse event is treatment-emergent mania or hypomania. From a sample of 231 participants, 14 participants were observed to develop hypomania (n = 11) or mania (n = 3), following either active (n=13) or sham (n=1) tDCS in participants with bipolar depression (n=4) or unipolar depression (n=10) (Brunoni et al., 2017b). Most had also been taking adjunctive medication (n=13), namely antidepressant medication and mood stabilisers, whereby symptoms resolved through withholding treatment for a few days, medication dosage adjustment, additional pharmacotherapy or by themselves (Brunoni et al., 2011a, 2017b).

Charge densities applied in most human clinical studies (range: 171 C/m² - 480 C/m²) are well below the threshold shown to cause tissue damage in rats (above 52,400 C/m²), which is at least 100 times higher (Liebetanz et al., 2009). The threshold might be even higher, as no tissue damage or changes in cerebral temperature were found when cathodal tDCS was applied at a greater charge density (128,571 C/m^2) than the determined threshold (85,714 C/m^2) (Liebetanz et al., 2009; Rueger et al., 2012; Zhang et al., 2019).

Overall, adverse effects have been described as being mild and there have not been any significant differences in discontinuation rates between active and sham tDCS treatment groups due to adverse events, (Aparício et al., 2016; Brunoni et al., 2016; Moffa et al., 2017; Alonzo et al., 2019). Standardised scales though would aid in documenting and reporting adverse effects (Brunoni et al., 2011a).

Ethical concerns include how and who will deliver tDCS, necessity of regulation, particularly in light of a growing ‘do-it-yourself’ community in which there are no current regulatory requirements, and the potential of inducing maladaptive long-term neuroplastic changes.

What are the potential mechanisms of tDCS in depression?

Neuroplasticity

Growing evidence implicates impaired neuroplasticity in major depression (Fossati et al., 2004; Pittenger & Duman, 2008; Player et al., 2013). Current treatments are associated with neuroplastic changes in the brain (Arnone et al., 2012; Joshi et al., 2016; Tendolkar et al., 2013; Fu et al., 2020).

tDCS can enhance neuroplasticity (Stagg et al., 2018), however there has been limited direct evidence as to whether this mechanism contributes to the improvement in depressive symptoms following tDCS.

The glutamatergic system, in particular NMDA receptors, have an important role in LTP, and impairments in glutamatergic neurotransmission are evident in major depression (Valentine & Sanacora, 2009). LTP is the neural basis for memory (Bliss & Collingridge, 1993). Learning and memory impairments in depression may reflect impaired neuroplasticity (Pittenger & Duman, 2008), and LTP is instrumental to recovery in depression, in which upregulation of biomarkers such as BDNF are associated with increased long-term potentiation and neuroplasticity (Martinowich et al., 2007, Brunoni et al., 2008). As a potential mechanism by which tDCS contributes to recovery from depression, effects in the glutamatergic system and BDNF measures would be expected.

Widespread functional and structural abnormalities are observed in major depression (Wise et al., 2018). In particular, bilateral reductions in hippocampal volume are one of the most common findings (Cole et al., 2011; Schmaal et al., 2016). Located within the limbic system in the medial temporal lobe, the hippocampus plays a central role in learning and memory. It is a plastic brain structure, in which excitatory amino acids neurotransmitters and NMDA receptors are involved in the damaging effects of stress and trauma effects on function and structure (McEwen, 1999). Neuroplastic changes in the hippocampus are associated with changes in mood, and hippocampal grey matter volume is state dependent (Arnone et al., 2012). Clinical efficacy of antidepressant medication is proposed to be mediated through neural plasticity (Castrén & Hen, 2013; Santarelli et al., 2003; Warner-Schmidt & Duman, 2006; Fu et al., 2020). Treatment with antidepressant drugs can stimulate neurogenesis in the hippocampus and restore grey matter to a volume similar to that in both healthy participants and patients in remission (Arnone et al., 2012; Warner-Schmidt & Duman, 2006). At the cellular level, animal models show increased postsynaptic spine density and enhanced synaptic plasticity following treatment with fluoxetine (Ampuero et al., 2010). Increases BDNF serum levels, indicating increased neuroplasticity, are observed following treatment with antidepressant medication which are associated with improvements in depressive symptoms (Brunoni et al., 2008; Duman & Monteggia, 2006).

Clinical studies of the treatment resistant form of major depression have reported increases in hippocampal connectivity and volume following ECT treatment (Abbott et al., 2014; Gbyl & Videbech, 2018; Joshi et al., 2016; Nordanskog et al., 2010; Sartorius et al., 2016; Tendolkar et al., 2013)**.** ECT treatment modulates alterations in white matter microstructure in pathways connecting frontal and limbic areas in major depression (Lyden et al., 2014). In animal models, ECT has been found to stimulate neurogenesis in frontal regions (Inta et al., 2013). Moreover, an increase in a range of plasticity-associated transcripts, including BDNF, have been found after ECT (Conti et al., 2006). However, Brunoni et al. (2008) meta-analysis found that BDNF levels did not tend to increase following a course of ECT or TMS, suggesting that this may be due to an BDNF increase prior to brain stimulation as a majority of patients receiving these treatments had already been taking antidepressant medication.

Relative to healthy participants, patients in a current depressive episode show reduced paired-associative stimulation (PAS)-induced neuroplasticity in the motor cortex (Player et al., 2013; 2014) implicating reduced neuroplasticity in major depression. Anodal tDCS to the left dorsolateral prefrontal cortex has been associated with increased PAS-induced neuroplasticity in the motor cortex of currently depressed patients in comparison to sham tDCS (Player et al., 2014), suggesting that tDCS induces neuroplasticity. This effect was evident in a greater proportion of patients who had received a longer course of tDCS with a minimum of 20 sessions (Player et al., 2014).

The prefrontal-limbic dysregulation model of emotion processing of major depression involves a dorsal component, which includes the dorsolateral prefrontal cortex, dorsal anterior cingulate cortex, hippocampus and middle frontal regions, implicated in attentional and cognitive qualities of the disorder, such as cognitive regulation when responding to emotional cues, and a ventral component, which includes the amygdala, subgenual anterior cingulate, anterior insula, orbitofrontal and ventrolateral prefrontal regions, that are involved in the production of emotional states (Mayberg, 1993; Phillips et al., 2003). The rostral anterior cingulate cortex is an important region in connecting these components, in which cognitive and emotion processing systems depend on coordinated interactions between these two systems, which are impaired in major depression (Mayberg, 1993; Costafreda et al., 2013).

Prefrontal-limbic dysregulation in major depression is characterised by decreased activity in prefrontal cortical regions and reduced inhibition in the amygdala (Ressler & Mayberg, 2008; Savitz & Drevets, 2009; Costafreda et al., 2013; Fidalgo et al., 2014). The amygdala shows increased responsivity to negative stimuli (Fu et al., 2004, 2008; Siegle et al., 2007; Arnone et al., 2012; Hamilton et al., 2012). Following treatment with antidepressant medication (Drevets, 2001; Fu et al., 2004, Arnone et al., 2012), rTMS (Kito et al., 2008; Ding et al., 2014; Luborzewski et al., 2006) as well as cognitive behavioural therapy (Fu et al, 2008), normalisation in amygdala activity has been observed.

Ironside et al. (2018) observed a direct relationship between prefrontal cortical and amygdala responses in participants with trait anxiety. Following anodal tDCS stimulation over the left dorsolateral prefrontal cortex, amygdala “hyper” responsivity was reduced to a similar level to that in participants with low anxiety. Behavioural data revealed that following active tDCS, accuracy on an attentional load task was improved, reflecting that fearful distractor faces had reduced attentional capture and suggesting that the fear response associated with amygdala hyperactivity was reduced. Additionally, Nord et al. (2019) reported that dorsolateral prefrontal cortical activity was increased during an emotion processing task following active tDCS stimulation combined with CBT, which was not observed in patients who had received sham tDCS and CBT, although there were not any significant changes in amygdala activity following tDCS. Anodal tDCS is associated with increased activation at the stimulation site, typically left dorsolateral prefrontal cortex in major depression which in turn could regulate prefrontal cortical-amygdala function.

Although, functional connectivity changes following tDCS treatment in major depression have not yet been reported, a recent TMS study observed increased global connectivity following active rTMS but not sham treatment, which were more in line with connectivity in healthy controls, in particular significant changes were noted in connectivity between amygdalae and contralateral dorsolateral prefrontal cortex (Eshel et al., 2020).

While the relationship between BDNF levels and tDCS treatment have so far not demonstrated significant effects, sample sizes have been small (Loo et al., 2018; Palm et al., 2013; Player et al., 2014). As LTP is mediated by activity-dependent BDNF secretion (Fritsch et al., 2010) and BDNF levels correlate with amygdala responses in major depression (Lorenzetti et al., 2020), there is a potential relationship of BDNF with prefrontal-amygdala responses in the clinical efficacy of tDCS treatment.

Neuropsychology

Anodal tDCS shows a beneficial effect on stress-related emotional reactivity, strengthening cognitive processes which modulate negative emotional states in response to stress reactions and attenuating

acute stress reactivity (Smits et al., 2020). Improved recognition in an emotional face recognition task, most notably for positive faces with anodal tDCS in healthy participants (Nitsche et al., 2012), support left dorsolateral prefrontal cortical stimulation in major depression. Anodal tDCS stimulation to the left dorsolateral prefrontal cortex increased valence ratings of negative affective images, which were perceived as being less negative, as compared to sham and cathodal stimulation (Peña-Gómez et al., 2011). Ratings of unpleasantness while viewing aversive emotional pictures were significantly decreased following anodal tDCS relative to sham tDCS of the left dorsolateral prefrontal cortex (Maeoka et al., 2012). Significant decreases in EEG alpha band power and increases in beta band power accompanied the subjective responses, reflecting modulation of affective processing networks through increased local cortical activity (Maeoka et al., 2012).

Specific biases in processing affectively negative stimuli and information are evident in major depression, including difficulties in attentional disengagement from negative stimuli and impaired cognitive control in processing negative stimuli (Mitterschiffthaler et al., 2008; Foland-Ross and Gotlib, 2012). Vanderhasselt et al., (2013) assessed the effects of tDCS on cognitive control by using a cued emotional conflict task (CECT). Participants responded to a happy or sad face by selecting the same or opposite emotion, depending on the cue they were given. In 'opposite' trials, cognitive control enables one to respond with the incongruent emotion to the presented emotional stimuli. A three-way interaction between cue, emotion and group was found in healthy participants. tDCS improved reaction times during trials that require an inhibition in responses to happy but not sad faces. Vanderhasselt et al. (2014) subsequently observed that participants with major depression demonstrated a greater response time to 'opposite-sad' than to 'opposite-happy' cue-emotion combination trials, in that response time was slower when addressed with a conflict that was negatively valenced than that of the positive conflict. This suggests patients had difficulty in overriding a habitual response to negative stimuli. Further, the contrast of 'opposite' was associated with greater activity in right middle frontal gyrus and bilateral precuneus. In comparison to cue-emotion 'actual-sad', 'opposite-sad' also led to a stronger bilateral activation of dorsal anterior cingulate cortex, reflecting enhanced conflict-detection or a compensatory process. Both depression and healthy control groups had greater response times for 'actual-sad' than 'actual-happy' trials (Vanderhassalt et al., 2014). This behavioural data support both the negative bias and reduced cognitive control in major depression, as the response was selectively slower when participants were asked to press an incongruent answer (opposite) as a response to negative stimuli (sad face).

Increased accuracy in an affective go-no go task (Boggio et al., 2007) as well as increases response rates for negative vs. neutral and positive vs. neutral words in an emotional Stroop task (Brunoni et al., 2014) have been found following tDCS. Salehinejad et al. (2017) reported improvements in working memory and attention along with improvements in depressive symptoms in participants with major depression who received 10 consecutive daily anodal tDCS sessions over the left dorsolateral prefrontal cortex as compared to participants who received sham tDCS sessions. The ability of tDCS to improve emotion processing (Peña-Gómez et al., 2011) and affective cognitive control (Boggio et al., 2007; Brunoni et al., 2014; Vanderhassalt et al., 2014) in major depression, which is associated with improved depressive symptoms, support improved prefontal-limbic regulation following tDCS treatment.

An area of unmet need is how to improve the cognitive impairments in major depression that contribute to psychosocial impairments. Impairments in executive functions, attention, memory and psychomotor speed are common in major depression, which can be seen during an acute depressive

episode and can persist into recovery and remission phases (Paelecke-Habermann et al., 2005; Hammar and Ardal, 2009; Shilyansky et al., 2016).

Preliminary evidence suggests that tDCS could uniquely improve cognitive impairments in major depression (Loo et al., 2012; Moreno et al., 2015; Oliveira et al., 2013). Improvement in acute working memory after a single session of tDCS has been reported, with (Loo et al., 2012) and without (Moreno et al., 2015; Oliveira et al., 2013) concurrent antidepressant medication. tDCS over the dorsolateral prefrontal cortex was associated with both improved discriminability and response criterion in a working memory n-back task, suggesting an increase of signal-to-noise ratio that enables responses to be fine-tuned (Oliveira et al., 2013). tDCS not only modulates affective processing but also impairments in executive functions in major depression, which might be evident following one session and also following a course of tDCS treatment. Whether the improvements endure in the long term require further investigation.

Is there potential for biomarkers to improve tDCS response?

Biomarkers are objective biological measures that indicate the underlying pathogenesis of disease, including normal biological processes, that aid in the classification of a disease and risk factors (Mayeux, 2004). The measurements could be biological media, such as physiological or biochemical measures, or brain imaging measures, which link to changes neural structure or function.

Predictive biomarkers may aid in clinical decision making for tDCS for the forms of depression most likely respond and those less likely to respond well to current tDCS montage, such as treatment resistant depression. As a predictor of clinical outcome, increased activity in the left dorsolateral prefrontal cortex at baseline (Nord et al., 2019) and volume (Bulubas et al., 2019) have been associated with improved treatment responses to tDCS. Common and distinct predictors to tDCS treatment in comparison with antidepressant medication and psychotherapy treatments (Pizzagalli, 2011; Fu et al., 2013) are continuing areas of investigation.

Summary

A course of active tDCS treatment demonstrates greater clinical efficacy as measured by rate of response, remission, and continuous symptom ratings in comparison to a course of placebo sham tDCS treatment. However, lack of inferiority to a course of treatment with antidepressant medication has not yet been established. The mechanism is proposed to be through neuroplasticity with effects observed at the neuronal level. Evidence of neuroplastic effects mediating clinical outcome in major depression has been limited to date. Identifying predictive biomarkers is important to understanding disease pathophysiology and would aid in clinical decision making. tDCS is a potential treatment for individual with major depression who are unable to or prefer not to take current first line treatments. With high levels of acceptability, portability, and cost-effectiveness, tDCS is a potential first line treatment for major depression.

References:

Abbott, C. C., Jones, T., Lemke, N. T., Gallegos, P., McClintock, S. M., Mayer, A. R., … Calhoun, V. D. (2014). Hippocampal structural and functional changes associated with electroconvulsive therapy response. *Translational Psychiatry*, *4*(11). doi: 10.1038/tp.2014.124

Al-Kaysi, A. M., Al-Ani, A., Loo, C. K., Powell, T. Y., Martin, D. M., Breakspear, M., & Boonstra, T. W. (2017). Predicting tDCS treatment outcomes of patients with major depressive disorder using automated EEG classification. *Journal of Affective Disorders*, *208*, 597-603. doi: 10.1016/j.jad.2016.10.021

Almeida, L., Kashdan, T. B., Nunes, T., Coelho, R., Albino-Teixeira, A., & Soares-da-Silva, P. (2008). Who volunteers for phase I clinical trials? Influences of anxiety, social anxiety and depressive symptoms on self-selection and the reporting of adverse events. *European journal of clinical pharmacology*, *64*(6), 575-582. doi: 10.1007/s00228-008-0468-8

Alonzo, A., Fong, J., Ball, N., Martin, D., Chand, N., & Loo, C. (2019). Pilot trial of home-administered transcranial direct current stimulation for the treatment of depression. *Journal of affective disorders*, *252*, 475-483. doi: 10.1016/j.jad.2019.04.041

Ampuero, E., Rubio, F., Falcon, R., Sandoval, M., Diaz-Veliz, G., Gonzalez, R., … Wyneken, U. (2010). Chronic fluoxetine treatment induces structural plasticity and selective changes in glutamate receptor subunits in the rat cerebral cortex. *Neuroscience,* 169(1), 98-108. doi: 10.1016/j.neuroscience.2020.04.035

Aparício, L. V., Guarienti, F., Razza, L. B., Carvalho, A. F., Fregni, F., & Brunoni, A. R. (2016). A systematic review on the acceptability and tolerability of transcranial direct current stimulation treatment in neuropsychiatry trials. *Brain stimulation*, *9*(5), 671-681. doi: 10.1016/j.brs.2016.05.004

Arnone, D. (2019). Functional MRI findings, pharmacological treatment in major depression and clinical response. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *91*, 28-37. doi: 10.1016/j.pnpbp.2018.08.004

Arnone, D., Mckie, S., Elliott, R., Juhasz, G., Thomas, E. J., Downey, D., … Anderson, I. M. (2012). State-dependent changes in hippocampal grey matter in depression. *Molecular Psychiatry*, *18*(12), 1265–1272. doi: 10.1038/mp.2012.150

Arul-Anandam, A. P., Loo, C., & Mitchell, P. (2010). Induction of hypomanic episode with transcranial direct current stimulation. *The journal of ECT*, *26*(1), 68-69. doi: 10.1097/YCT.0b013e3181a744bf

Baccaro, A., Brunoni, A. R., Bensenor, I. M., & Fregni, F. (2010). Hypomanic episode in unipolar depression during transcranial direct current stimulation. *Acta Neuropsychiatrica*, *22*(6), 316-318. doi: 10.1111/j.1601-5215.2010.00495.x

Bachtiar, V., Johnstone, A., Berrington, A., Lemke, C., Johansen-Berg, H., Emir, U., & Stagg, C. J. (2018). Modulating regional motor cortical excitability with noninvasive brain stimulation results in neurochemical changes in bilateral motor cortices. *Journal of Neuroscience*, *38*(33), 7327-7336. doi: 10.1523/JNEUROSCI.2853-17.2018

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *The Journal of physiology*, *591*(7), 1987-2000. doi: 10.1113/jphysiol.2012.249730

Benvenuti, A., Rucci, P., Miniati, M., Papasogli, A., Fagiolini, A., Cassano, G. B., ... & Frank, E. (2008). Treatment-emergent mania/hypomania in unipolar patients. *Bipolar disorders*, *10*(6), 726-732. doi: 10.1111/j.1399-5618.2008.00613.x

Bikson, M., Datta, A., & Elwassif, M. (2009). Establishing safety limits for transcranial direct current stimulation. *Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, *120*(6), 1033. doi: 10.1016/j.clinph.2009.03.018

Bliss, T. V. P., & Collingridge, G. L. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. *Nature*, *361*(6407), 31–39. doi: 10.1038/361031ª

Bliss, T. V., & Lømo, T. (1973). Long-lasting potentiation of synaptic transmission in the dentate area of the anaesthetized rabbit following stimulation of the perforant path. *The Journal of Physiology, 232*(2), 331-356. doi:10.1113/jphysiol.1973.sp010273

Boggio, P. S., Bermpohl, F., Vergara, A. O., Muniz, A. L., Nahas, F. H., Leme, P. B., ... & Fregni, F. (2007). Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression. *Journal of affective disorders*, *101*(1-3), 91-98. doi: 10.1016/j.jad.2006.10.026

Border, R., Johnson, E. C., Evans, L. M., Smolen, A., Berley, N., Sullivan, P. F., & Keller, M. C. (2019). No Support for historical candidate gene or candidate cene-by-interaction hypotheses for major depression across multiple large samples. *American Journal of Psychiatry, 176*(5), 376-387. doi:10.1176/appi.ajp.2018.18070881

Brunoni, A. R., Amadera, J., Berbel, B., Volz, M. S., Rizzerio, B. G., & Fregni, F. (2011a). A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. *International Journal of Neuropsychopharmacology*, *14*(8), 1133-1145. doi: 10.1017/S1461145710001690

Brunoni, A. R., Lopes, M., & Fregni, F. (2008). A systematic review and meta-analysis of clinical studies on major depression and BDNF levels: implications for the role of neuroplasticity in depression. *International Journal of Neuropsychopharmacology*, *11*(8), 1169–1180. doi: 10.1017/s1461145708009309

Brunoni, A. R., Moffa, A. H., Fregni, F., Palm, U., Padberg, F., Blumberger, D. M., ... & Loo, C. K. (2016). Transcranial direct current stimulation for acute major depressive episodes: meta-analysis of individual patient data. *The British Journal of Psychiatry*, *208*(6), 522-531. doi: 10.1192/bjp.bp.115.164715

Brunoni, A. R., Moffa, A. H., Sampaio-Junior, B., Borrione, L., Moreno, M. L., Fernandes, R. A., … Benseñor, I. M. (2017a). Trial of electrical direct-current therapy versus escitalopram for depression. *New England Journal of Medicine*, *376*(26), 2523–2533. doi: 10.1056/nejmoa1612999

Brunoni, A. R., Moffa, A. H., Sampaio-Júnior, B., Gálvez, V., & Loo, C. K. (2017b). Treatment-emergent mania/hypomania during antidepressant treatment with transcranial direct current stimulation (tDCS): A systematic review and meta-analysis. *Brain Stimulation, 10*(2), 260-262. doi:10.1016/j.brs.2016.11.005

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., ... & Ferrucci, R. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain stimulation*, *5*(3), 175-195. doi: 10.1016/j.brs.2011.03.002

Brunoni, A. R., Valiengo, L., Baccaro, A., Zanao, T. A., de Oliveira, J. F., Goulart, A., ... & Fregni, F. (2013). The sertraline vs electrical current therapy for treating depression clinical study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry*, *70*(4), 383-391. doi: 10.1001/2013.jamapsychiatry.32

Brunoni, A. R., Valiengo, L., Zanao, T., de Oliveira, J. F., Bensenor, I. M., & Fregni, F. (2011b). Manic psychosis after sertraline and transcranial direct-current stimulation. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *23*(3), E4-E5. doi: 10.1176/jnp.23.3.jnpe4

Brunoni, A. R., & Vanderhasselt, M. (2014). Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: A systematic review and meta-analysis. *Brain and Cognition, 86*, 1-9. doi:10.1016/j.bandc.2014.01.008

Brunoni, A. R., Zanao, T. A., Vanderhasselt, M. A., Valiengo, L., de Oliveira, J. F., Boggio, P. S., ... & Fregni, F. (2014). Enhancement of affective processing induced by bifrontal transcranial direct current stimulation in patients with major depression. *Neuromodulation: Technology at the Neural Interface*, *17*(2), 138-142. doi: 10.1111/ner.12080

Bulubas, L., Padberg, F., Bueno, P. V., Duran, F., Busatto, G., Amaro Jr, E., ... & Keeser, D. (2019). Antidepressant effects of tDCS are associated with prefrontal gray matter volumes at baseline: Evidence from the ELECT-TDCS trial. *Brain stimulation*, *12*(5), 1197-1204. doi: 10.1016/j.brs.2019.05.006

Cascade, E., Kalali, A. H., & Kennedy, S. H. (2009). Real-world data on SSRI antidepressant side effects. *Psychiatry (Edgmont)*, *6*(2), 16.

Castrén, E., & Hen, R. (2013). Neuronal plasticity and antidepressant actions. *Trends in Neurosciences*, *36*(5), 259–267. doi: 10.1016/j.tins.2012.12.010

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., Higgins, J. P. T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J. P. A., & geddes, J. R. (2018). Comparative efficacy and acceptability of antidepressant drugs in the acute treatment of major depressive disorder: A network meta-analysis. *Lancet*. doi: 10.1016/S0140-6736(17)32802-7

Cole, J., Costafreda, S. G., McGuffin, P., & Fu, C. H. (2011). Hippocampal atrophy in first episode depression: a meta-analysis of magnetic resonance imaging studies. *Journal of affective disorders*, *134*(1-3), 483-487. doi: 10.1016/j.jad.2011.05.057

Conti, B., Maier, R., Barr, A. M., Morale, M. C., Lu, X., Sanna, P. P., … Bartfai, T. (2006). Region-specific transcriptional changes following the three antidepressant treatments electro convulsive therapy, sleep deprivation and fluoxetine. *Molecular Psychiatry*, *12*(2), 167–189. doi: 10.1038/sj.mp.4001897

Costafreda, S. G., Chu, C., Ashburner, J., & Fu, C. H. (2009). Prognostic and diagnostic potential of the structural neuroanatomy of depression. *PloS one*, *4*(7). doi: 10.1371/journal.pone.0006353

Costafreda, S. G., McCann, P., Saker, P., Cole, J. H., Cohen-Woods, S., Farmer, A. E., ... & Fu, C. H. (2013). Modulation of amygdala response and connectivity in depression by serotonin transporter polymorphism and diagnosis. *Journal of affective disorders*, *150*(1), 96-103. doi: 10.1016/j.jad.2013.02.028

Creutzfeldt, O. D., Fromm, G. H., & Kapp, H. (1962). Influence of transcortical dc currents on cortical neuronal activity. *Experimental neurology*, *5*(6), 436-452. doi: 10.1016/0014-4886(62)90056-0

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S. D., & van Straten, A. (2014). The effects of psychotherapies for major depression in adults on remission, recovery and improvement: a meta-analysis. *Journal of affective disorders*, *159*, 118-126. doi: 10.1016/j.jad.2014.02.026

Davidson, R. J., & McEwen, B. S. (2012). Social influences on neuroplasticity: stress and interventions to promote well-being. *Nature neuroscience*, *15*(5), 689-695. doi: 10.1038/nn.3093

Dedoncker, J., Brunoni, A. R., Baeken, C., & Vanderhasselt, M. A. (2016). A systematic review and meta-analysis of the effects of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex in healthy and neuropsychiatric samples: influence of stimulation parameters. *Brain stimulation*, *9*(4), 501-517. doi: 10.1016/j.brs.2016.04.006

Ding, L., Shou, G., Yuan, H., Urbano, D., & Cha, Y. (2014). Lasting modulation effects of rTMS on neural activity and connectivity as revealed by resting-state EEG. *IEEE Transactions on Biomedical Engineering, 61*(7), 2070-2080. doi:10.1109/tbme.2014.2313575

Drevets, W. C. (2001). Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. *Current opinion in neurobiology*, *11*(2), 240-249. doi: 10.1016/S0959-4388(00)00203-8

Duman, R. S., & Monteggia, L. M. (2006). A neurotrophic model for stress-related mood disorders. *Biological Psychiatry*, *59*(12), 1116–1127. doi: 10.1016/j.biopsych.2006.02.013

Durand, S., Fromy, B., Bouyé, P., Saumet, J. L., & Abraham, P. (2002). Vasodilatation in response to repeated anodal current application in the human skin relies on aspirin-sensitive mechanisms. *The Journal of physiology*, *540*(1), 261-269. doi: 10.1113/jphysiol.2001.013364

Eichenbaum, H., Otto, T., & Cohen, N. J. (1992). The hippocampus—what does it do? *Behavioral and Neural Biology*, *57*(1), 2–36. doi: 10.1016/0163-1047(92)90724-i

Elliott, R., Rubinsztein, J. S., Sahakian, B. J., & Dolan, R. J. (2002). The neural basis of mood-congruent processing biases in depression. *Archives of General Psychiatry, 59*(7), 597. doi:10.1001/archpsyc.59.7.597

Eshel, N., Keller, C. J., Wu, W., Jiang, J., Mills-Finnerty, C., Huemer, J., ... & Wong, M. (2020). Global connectivity and local excitability changes underlie antidepressant effects of repetitive transcranial magnetic stimulation. *Neuropsychopharmacology*, *45*(6), 1018-1025. doi: 10.1038/s41386-020-0633-z

Eugène, F., Joormann, J., Cooney, R. E., Atlas, L. Y., & Gotlib, I. H. (2010). Neural correlates of inhibitory deficits in depression. *Psychiatry Research: Neuroimaging, 181*(1), 30-35. doi:10.1016/j.pscychresns.2009.07.010

Ezquerro, F., Moffa, A. H., Bikson, M., Khadka, N., Aparicio, L. V., de Sampaio-Junior, B., ... & Brunoni, A. R. (2017). The influence of skin redness on blinding in transcranial direct current stimulation studies: a crossover trial. *Neuromodulation: Technology at the Neural Interface*, *20*(3), 248-255.

Ferguson, J. M. (2001). SSRI antidepressant medications: adverse effects and tolerability. *Primary care companion to the Journal of clinical psychiatry*, *3*(1), 22. doi: 10.4088/pcc.v03n0105

Fidalgo, T. M., Morales-Quezada, L., Muzy, G. S., Chiavetta, N. M., Mendonca, M. E., Santana, M. V., ... & Fregni, F. (2014). Biological markers in non-invasive brain stimulation trials in major depressive disorder: a systematic review. *The journal of ECT*, *30*(1), 47. doi: 10.1097/YCT.0b013e31828b34d8

Fossati, P., Radtchenko, A., & Boyer, P. (2004). Neuroplasticity: from MRI to depressive symptoms. *European Neuropsychopharmacology*, *14*. doi: 10.1016/j.euroneuro.2004.09.001

Fritsch, B., Reis, J., Martinowich, K., Schambra, H. M., Ji, Y., Cohen, L. G., & Lu, B. (2010). Direct current stimulation promotes BDNF-dependent synaptic plasticity: potential implications for motor learning. *Neuron*, *66*(2), 198-204. doi: 10.1016/j.neuron.2010.03.035

Fu, C. H., & Costafreda, S. G. (2013). Neuroimaging-based biomarkers in psychiatry: clinical opportunities of a paradigm shift. *The Canadian Journal of Psychiatry*, *58*(9), 499-508. doi: 10.1177/070674371305800904

Fu, C. H., Fan, Y., & Davatzikos, C. (2019). Addressing heterogeneity (and homogeneity) in treatment mechanisms in depression and the potential to develop diagnostic and predictive biomarkers. *NeuroImage: Clinical*, *24*, 101997. doi: 10.1016/j.nicl.2019.101997

Fu, C. H., Fan, Y., & Davatzikos, C. (2020). Widespread Morphometric Abnormalities in Major Depression: Neuroplasticity and Potential for Biomarker Development. *Neuroimaging Clinics*, *30*(1), 85-95. doi: 10.1016/j.nic.2019.09.008

Fu, C. H., Steiner, H., & Costafreda, S. G. (2013). Predictive neural biomarkers of clinical response in depression: a meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. *Neurobiology of disease*, *52*, 75-83. doi: 10.1016/j.nbd.2012.05.008

Fu, C. H., Williams, S. C., Cleare, A. J., Brammer, M. J., Walsh, N. D., Kim, J., ... & Mitterschiffthaler, M. T. (2004). Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. *Archives of general psychiatry*, *61*(9), 877-889. doi:10.1001/archpsyc.61.9.877

Fu, C. H., Williams, S. C., Cleare, A. J., Scott, J., Mitterschiffthaler, M. T., Walsh, N. D., ... & Murray, R. M. (2008). Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. *Biological psychiatry*, *64*(6), 505-512. doi: 10.1016/j.biopsych.2008.04.033

Gálvez, V., Alonzo, A., Martin, D., Mitchell, P. B., Sachdev, P., & Loo, C. K. (2011). Hypomania induction in a patient with bipolar II disorder by transcranial direct current stimulation (tDCS). *The journal of ECT*, *27*(3), 256-258. doi: 10.1097/YCT.0b013e3182012b89

Gbyl, K., & Videbech, P. (2018). Electroconvulsive therapy increases brain volume in major depression: a systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *138*(3), 180–195. doi: 10.1111/acps.12884

Guarienti, F., Caumo, W., Shiozawa, P., Cordeiro, Q., Boggio, P. S., Benseñor, I. M., ... & Brunoni, A. R. (2015). Reducing transcranial direct current stimulation-induced erythema with skin pretreatment: Considerations for sham-controlled clinical trials. *Neuromodulation: Technology at the Neural Interface*, *18*(4), 261-265.

Hamilton, J. P., Etkin, A., Furman, D. J., Lemus, M. G., Johnson, R. F., & Gotlib, I. H. (2012). Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of baseline activation and neural response data. *American Journal of Psychiatry*, *169*(7), 693-703. doi: 10.1176/appi.ajp.2012.11071105

Hayward, G., Goodwin, G. M., & Harmer, C. J. (2004). The role of the anterior cingulate cortex in the counting Stroop task. *Experimental Brain Research, 154*(3), 355-358. doi:10.1007/s00221-003-1665-4

Hayward, G., Mehta, M. A., Harmer, C., Spinks, T. J., Grasby, P. M., & Goodwin, G. M. (2007). Exploring the physiological effects of double-cone coil TMS over the medial frontal cortex on the anterior cingulate cortex: An H215O PET study. *European Journal of Neuroscience, 25*(7), 2224-2233. doi:10.1111/j.1460-9568.2007.05430.x

Inta, D., Lima-Ojeda, J. M., Lau, T., Tang, W., Dormann, C., Sprengel, R., … Gass, P. (2013). Electroconvulsive therapy induces neurogenesis in frontal rat brain areas. *PLoS ONE*, *8*(7). doi: 10.1371/journal.pone.0069869

Ironside, M., & Perlo, S. (2018). Transcranial Direct Current Stimulation for the Treatment of Depression: a Review of the Candidate Mechanisms of Action. *Current Behavioral Neuroscience Reports*, *5*(1), 26-35. doi: 10.1007/s40473-018-0138-9

Jamil, A., Batsikadze, G., Kuo, H. I., Labruna, L., Hasan, A., Paulus, W., & Nitsche, M. A. (2017). Systematic evaluation of the impact of stimulation intensity on neuroplastic after-effects induced by transcranial direct current stimulation. *The Journal of physiology*, *595*(4), 1273-1288. doi: 10.1113/JP272738

Jefferys, J. G. (1981). Influence of electric fields on the excitability of granule cells in guinea-pig hippocampal slices. *The Journal of Physiology*, *319*(1), 143-152. doi: 10.1113/jphysiol.1981.sp013897

Joshi, S. H., Espinoza, R. T., Pirnia, T., Shi, J., Wang, Y., Ayers, B., … Narr, K. L. (2016). Structural plasticity of the hippocampus and amygdala induced by electroconvulsive therapy in major depression. *Biological Psychiatry*, *79*(4), 282–292. doi: 10.1016/j.biopsych.2015.02.029

Keeser, D., Meindl, T., Bor, J., Palm, U., Pogarell, O., Mulert, C., ... & Padberg, F. (2011). Prefrontal transcranial direct current stimulation changes connectivity of resting-state networks during fMRI. *Journal of Neuroscience*, *31*(43), 15284-15293. doi: 10.1523/JNEUROSCI.0542-11.2011

Kessler, R. C., & Bromet, E. J. (2013). The epidemiology of depression across cultures. *Annual review of public health*, *34*, 119-138. doi: 10.1146/annurev-publhealth-031912-114409

Kiebs, M., Hurlemann, R., & Mutz, J. (2019). Cognitive effects of non-surgical brain stimulation for major depressive disorder: protocol for a systematic review and meta-analysis. *BMJ open*, *9*(2), bmjopen-2018. doi: 10.1136/bmjopen-2018-023796

Kito, S., Fujita, K., & Koga, Y. (2008). Regional cerebral blood flow changes after low-frequency transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in treatment-resistant depression. *Neuropsychobiology*, *58*(1), 29-36. doi: 10.1159/000154477

Lantrip, C., Gunning, F. M., Flashman, L., Roth, R. M., & Holtzheimer, P. E. (2017). Effects of transcranial magnetic stimulation on the cognitive control of emotion. *The Journal of ECT, 33*(2), 73-80. doi:10.1097/yct.0000000000000386

Leppänen, J. M. (2006). Emotional information processing in mood disorders: A review of behavioral and neuroimaging findings. *Current Opinion in Psychiatry, 19*(1), 34-39. doi:10.1097/01.yco.0000191500.46411.00

Liebetanz, D., Koch, R., Mayenfels, S., König, F., Paulus, W., & Nitsche, M. A. (2009). Safety limits of cathodal transcranial direct current stimulation in rats. *Clinical Neurophysiology, 120*(6), 1161-1167. doi:10.1016/j.clinph.2009.01.022

Liebetanz, D., Nitsche, M. A., Tergau, F., & Paulus, W. (2002). Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain*, *125*(10), 2238-2247. doi: 10.1093/brain/awf238

Liu, W., Leng, Y. S., Zou, X. H., Cheng, Z. Q., Yang, W., & Li, B. J. (2017). Affective processing in non-invasive brain stimulation over prefrontal cortex. *Frontiers in Human Neuroscience*, *11*, 439.

Lomas, T., Ivtzan, I., & Fu, C. H.Y. (2015). A systematic review of the neurophysiology of mindfulness on EEG oscillations. *Neuroscience & Biobehavioral Reviews*, *57*, 401-410. doi: 10.1016/j.neubiorev.2015.09.018

Loo, C. K., Alonzo, A., Martin, D., Mitchell, P. B., Galvez, V., & Sachdev, P. (2012). Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *The British Journal of Psychiatry*, *200*(1), 52-59. doi: 10.1192/bjp.bp.111.097634

Loo, C., Husain, M., Mcdonald, W., Aaronson, S., O'Reardon, J., Alonzo. A., … Lisanby, S. (2018). International randomized-controlled trial of transcranial Direct Current Stimulation in depression. *Brain Stimulation*, *11* (1), 125-133. doi: 10.1016/j.brs.2017.10.011

Luborzewski, A., Schubert, F., Seifert, F., Danker-Hopfe, H., Brakemeier, E. L., Schlattmann, P., ... & Bajbouj, M. (2007). Metabolic alterations in the dorsolateral prefrontal cortex after treatment with high-frequency repetitive transcranial magnetic stimulation in patients with unipolar major depression. *Journal of Psychiatric Research*, *41*(7), 606-615. doi: 10.1016/j.jpsychires.2006.02.003

Lyden, H., Espinoza, R. T., Pirnia, T., Clark, K., Joshi, S. H., Leaver, A. M., … Narr, K. L. (2014). Electroconvulsive therapy mediates neuroplasticity of white matter microstructure in major depression. *Translational Psychiatry*, *4*(4). doi: 10.1038/tp.2014.21

Maeoka, H., Matsuo, A., Hiyamizu, M., Morioka, S., & Ando, H. (2012). Influence of transcranial direct current stimulation of the dorsolateral prefrontal cortex on pain related emotions: a study using electroencephalographic power spectrum analysis. *Neuroscience Letters*, *512*(1), 12-16. doi: 10.1016/j.neulet.2012.01.037

Martinowich, K., Manji, H., & Lu, B. (2007). New insights into BDNF function in depression and anxiety. *Nature Neuroscience*, *10*(9), 1089–1093. doi: 10.1038/nn1971

Matsumoto, H., & Ugawa, Y. (2017). Adverse events of tDCS and tACS: a review. *Clinical Neurophysiology Practice*, *2*, 19-25. doi: 10.1016/j.cnp.2016.12.003

Mayberg, H. S. (1997). Limbic-cortical dysregulation: A proposed model of depression. *Journal of Neuropsychiatry and Clinical Neurosciences, 9*(3), 471-481. doi:10.1176/jnp.9.3.471

McCrone, P. R., Dhanasiri, S., Patel, A., Knapp, M., & Lawton-Smith, S. (2008). *Paying the price: the cost of mental health care in England to 2026*. King's Fund, London, UK. ISBN 9781857175714

McEwen, B. S. (1999). Stress and hippocampal plasticity. *Annual Review of Neuroscience*, *22*(1), 105–122. doi: 10.1146/annurev.neuro.22.1.105

Meron, D., Hedger, N., Garner, M., & Baldwin, D. S. (2015). Transcranial direct current stimulation (tDCS) in the treatment of depression: systematic review and meta-analysis of efficacy and tolerability. *Neuroscience & Biobehavioral Reviews, 57*, 46-62. doi:10.1016/j.neubiorev.2015.07.012

Mitterschiffthaler, M. T., Williams, S. C. R., Walsh, N. D., Cleare, A. J., Donaldson, C., Scott, J., & Fu, C. H. Y. (2008). Neural basis of the emotional Stroop interference effect in major depression. *Psychological Medicine*, *38*(2), 247-256. doi: 10.1017/S0033291707001523

Moffa, A. H., Brunoni, A. R., Fregni, F., Palm, U., Padberg, F., Blumberger, D. M., ... & Loo, C. K. (2017). Safety and acceptability of transcranial direct current stimulation for the acute treatment of major depressive episodes: Analysis of individual patient data. *Journal of affective disorders*, *221*, 1-5. doi: 10.1016/j.jad.2017.06.021

Monte-Silva, K., Kuo, M. F., Hessenthaler, S., Fresnoza, S., Liebetanz, D., Paulus, W., & Nitsche, M. A. (2013). Induction of late LTP-like plasticity in the human motor cortex by repeated non-invasive brain stimulation. *Brain stimulation*, *6*(3), 424-432. doi: 10.1016/j.brs.2012.04.011

Moreno, M. L., Vanderhasselt, M., Carvalho, A. F., Moffa, A. H., Lotufo, P. A., Benseñor, I. M., & Brunoni, A. R. (2015). Effects of acute transcranial direct current stimulation in hot and

cold working memory tasks in healthy and depressed subjects. *Neuroscience Letters, 591*, 126-131. doi:10.1016/j.neulet.2015.02.036

Mutz, J., Edgcumbe, D. R., Brunoni, A. R., & Fu, C. H.Y. (2018). Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a systematic review and meta-analysis of randomised sham-controlled trials. *Neuroscience & Biobehavioral Reviews*, *92*, 291-303. doi: 10.1016/j.neubiorev.2018.05.015

Mutz, J., Vipulananthan, V., Carter, B., Hurlemann, R., Fu, C. H.Y., & Young, A. H. (2019). Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: systematic review and network meta-analysis. *British Medical Journl*, *364*, l1079. doi: 10.1136/bmj.l1079

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

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*(10), 1899-1901. doi: 10.1212/WNL.57.10.1899

Nitsche, M. A., Fricke, K., Henschke, U., Schlitterlau, A., Liebetanz, D., Lang, N., ... & Paulus, W. (2003a). Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *The Journal of Physiology*, *553*(1), 293-301. doi: 10.1113/jphysiol.2003.049916

Nitsche, M. A., Jaussi, W., Liebetanz, D., Lang, N., Tergau, F., & Paulus, W. (2004a). Consolidation of human motor cortical neuroplasticity by D-cycloserine. *Neuropsychopharmacology*, *29*(8), 1573-1578. doi: 10.1038/sj.npp.1300517

Nitsche, M. A., Koschack, J., Pohlers, H., Hullemann, S., Paulus, W., & Happe, S. (2012). Effects of frontal transcranial direct current stimulation on emotional state and processing in healthy humans. *Frontiers in Psychiatry*, *3*, 58. doi: 10.3389/fpsyt.2012.00058

Nitsche, M. A., Niehaus, L., Hoffmann, K. T., Hengst, S., Liebetanz, D., Paulus, W., & Meyer, B. U. 2004b). MRI study of human brain exposed to weak direct current stimulation of the frontal cortex. *Clinical Neurophysiology*, *115*(10), 2419-2423. doi: 10.1016/j.clinph.2004.05.001

Nitsche, M. A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., & Tergau, F. (2003b). Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *Journal of Cognitive Neuroscience*, *15*(4), 619-626. doi: 10.1162/089892903321662994

Nord, C. L., Halahakoon, D. C., Limbachya, T., Charpentier, C., Lally, N., Walsh, V., ... & Roiser, J. P. (2019). Neural predictors of treatment response to brain stimulation and psychological therapy in depression: a double-blind randomized controlled trial. *Neuropsychopharmacology*, *44*(9), 1613-1622. doi: 10.1038/s41386-019-0401-0

Nordanskog, P., Dahlstrand, U., Larsson, M. R., Larsson, E.-M., Knutsson, L., & Johanson, A. (2010). Increase in hippocampal volume after electroconvulsive therapy in patients with depression. *Journal of ECT*, *26*(1), 62–67. doi: 10.1097/yct.0b013e3181a95da8

Oliveira, J. F., Zanão, T. A., Valiengo, L., Lotufo, P. A., Benseñor, I. M., Fregni, F., & Brunoni, A. R. (2013). Acute working memory improvement after tDCS in antidepressant-free patients with major depressive disorder. *Neuroscience Letters, 537*, 60-64. doi:10.1016/j.neulet.2013.01.023

Paelecke-Habermann, Y., Pohl, J., & Leplow, B. (2005). Attention and executive functions in remitted major depression patients. *Journal of Affective Disorders, 89*(1-3), 125-135. doi:10.1016/j.jad.2005.09.006

Palm, U., Feichtner, K. B., Hasan, A., Gauglitz, G., Langguth, B., Nitsche, M. A., ... & Padberg, F. (2014). The role of contact media at the skin-electrode interface during transcranial direct current stimulation (tDCS). *Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation*, *7*(5), 762-764. doi: 10.1016/j.brs.2014.06.006

Palm, U., Fintescu, Z., Obermeier, M., Schiller, C., Reisinger, E., Keeser, D., … Padberg, F. (2013). Serum levels of brain-derived neurotrophic factor are unchanged after transcranial direct current stimulation in treatment-resistant depression. *Journal of Affective Disorders*, *150*(2), 659–663. doi: 10.1016/j.jad.2013.03.015

Peña-Gómez, C., Vidal-Pineiro, D., Clemente, I. C., Pascual-Leone, A., & Bartres-Faz, D. (2011). Down-regulation of negative emotional processing by transcranial direct current stimulation: effects of personality characteristics. *PloS One*, *6*(7). doi: 10.1371/journal.pone.0022812

Pence, B. W., O'Donnell, J. K., & Gaynes, B. N. (2012). The depression treatment cascade in primary care: a public health perspective. *Current Psychiatry Reports*, *14*(4), 328-335. doi: 10.1007/s11920-012-0274-y

Phillips, M. L., Drevets, W. C., Rauch, S. L., & Lane, R. (2003). Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biological Psychiatry, 54*(5), 515-528. doi:10.1016/s0006-3223(03)00171-9

Pittenger, C., & Duman, R. S. (2007). Stress, depression, and neuroplasticity: a convergence of mechanisms. *Neuropsychopharmacology*, *33*(1), 88–109. doi: 10.1038/sj.npp.1301574

Pizzagalli, D. A. (2011). Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology*, *36*(1), 183-206. doi: 10.1038/npp.2010.166

Player, M. J., Taylor, J. L., Weickert, C. S., Alonzo, A., Sachdev, P., Martin, D., … Loo, C. K. (2013). Neuroplasticity in depressed individuals compared with healthy controls. *Neuropsychopharmacology*, *38*(11), 2101–2108. doi: 10.1038/npp.2013.126

Player, M. J., Taylor, J. L., Weickert, C. S., Alonzo, A., Sachdev, P. S., Martin, D., … Loo, C. K. (2014). Increase in PAS-induced neuroplasticity after a treatment course of transcranial direct current stimulation for depression. *Journal of Affective Disorders*, *167*, 140–147. doi: 10.1016/j.jad.2014.05.063

Priori, A. (2003). Brain polarization in humans: a reappraisal of an old tool for prolonged non-invasive modulation of brain excitability. *Clinical Neurophysiology*, *114*(4), 589-595. doi: 10.1016/S1388-2457(02)00437-6

Reinhart, R. M., Cosman, J. D., Fukuda, K., & Woodman, G. F. (2017). Using transcranial direct-current stimulation (tDCS) to understand cognitive processing. *Attention, Perception, & Psychophysics*, *79*(1), 3-23. doi: 10.3758/s13414-016-1224-2

Ressler, K. J., & Mayberg, H. S. (2007). Targeting abnormal neural circuits in mood and anxiety disorders: from the laboratory to the clinic. *Nature Neuroscience*, *10*(9), 1116-1124. doi: 10.1038/nn1944

Rodríguez, N., Opisso, E., Pascual-Leone, Á., & Soler, M. D. (2014). Skin lesions induced by transcranial direct current stimulation (tDCS). *Brain Stimulation*, *7*(5), 765-767. doi: 10.1016/j.brs.2014.06.005

Rueger, M. A., Keuters, M. H., Walberer, M., Braun, R., Klein, R., Sparing, R., . . . Schroeter, M. (2012). Multi-Session Transcranial Direct Current Stimulation (tDCS) Elicits Inflammatory and Regenerative Processes in the Rat Brain. *PLoS One, 7*(8). doi:10.1371/journal.pone.0043776

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., ... & McGrath, P. J. (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. *American Journal of Psychiatry*, *163*(11), 1905-1917. doi: 10.1176/ajp.2006.163.11.1905

Rush, S., & Driscoll, D. A. (1968). Current distribution in the brain from surface electrodes. *Anesthesia and Analgesia*, *47*(6), 717-723.

Salehinejad, M. A., Ghanavai, E., Rostami, R., & Nejati, V. (2017). Cognitive control dysfunction in emotion dysregulation and psychopathology of major depression (MD): Evidence from transcranial brain stimulation of the dorsolateral prefrontal cortex (DLPFC). *Journal of Affective Disorders*, *210*, 241-248. doi: 10.1016/j.jad.2016.12.036

Santarelli, L., Saxe, M., Gross, C., Surger, A., Battaglia, F., Dulawa, S., … Hen, R. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science*, *301*(5634), 805–809. doi: 10.1126/science.1083328

Sartorius, A., Demirakca, T., Böhringer, A., Hohenberg, C. C. V., Aksay, S. S., Bumb, J. M., … Ende, G. (2016). Electroconvulsive therapy increases temporal gray matter volume and cortical thickness. *European Neuropsychopharmacology*, *26*(3), 506–517. doi: 10.1016/j.euroneuro.2015.12.036

Savitz, J. B., & Drevets, W. C. (2009). Imaging phenotypes of major depressive disorder: genetic correlates. *Neuroscience*, *164*(1), 300-330. doi: 10.1016/j.neuroscience.2009.03.082

Schmaal, L., Veltman, D. J., van Erp, T. G., Sämann, P. G., Frodl, T., Jahanshad, N., ... & Vernooij, M. W. (2016). Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Molecular Pychiatry*, *21*(6), 806-812. doi: 10.1038/mp.2015.69

Shilyansky, C., Williams, L. M., Gyurak, A., Harris, A., Usherwood, T., & Etkin, A. (2016). Effect of antidepressant treatment on cognitive impairments associated with depression: A randomised longitudinal study. *Lancet Psychiatry, 3*(5), 425-435. doi:10.1016/s2215-0366(16)00012-2

Shiozawa, P., Cordeiro, Q., Fregni, F., & Brunoni, A. R. (2013). Is sertraline plus transcranial direct current stimulation the future of effective depression treatment? *Journal of Comparative Effectiveness Research*, *2*(3), 213-215. doi: 10.2217/cer.13.28

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: related and independent features. *Biological Psychiatry*, *61*(2), 198-209. doi: 10.1016/j.biopsych.2006.05.048

Sinyor, M., Cheung, C. P., Abraha, H. Y., Lanctôt, K. L., Saleem, M., Liu, C. S., ... & Schaffer, A. (2020). Antidepressant-placebo differences for specific adverse events in major depressive disorder: A systematic review. *Journal of Affective Disorders*, *267*, 185-190. doi: 10.1016/j.jad.2020.02.013

Smits, F.M., Schutter, D.J.L.G., van Honk, J., Geuze, E. (2020). Does non-invasive brain stimulation modulate emotional stress reactivity*? Social Cognitive and Affective Neuroscience, 15*(1), 23–51. doi: 10.1093/scan/nsaa011

Stagg, C. J., Antal, A., & Nitsche, M. A. (2018). Physiology of transcranial direct current stimulation. *Journal of ECT*, *34*(3), 144-152. doi: 10.1097/YCT.0000000000000510

Stagg, C. J., Best, J. G., Stephenson, M. C., O'Shea, J., Wylezinska, M., Kincses, Z. T., ... & Johansen-Berg, H. (2009). Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *Journal of Neuroscience*, *29*(16), 5202-5206. doi: 10.1523/JNEUROSCI.4432-08.2009

Tendolkar, I., Beek, M. V., Oostrom, I. V., Mulder, M., Janzing, J., Voshaar, R. O., & Eijndhoven, P. V. (2013). Electroconvulsive therapy increases hippocampal and amygdala volume in therapy refractory depression: A longitudinal pilot study. *Psychiatry Research: Neuroimaging*, *214*(3), 197–203. doi: 10.1016/j.pscychresns.2013.09.004

Terney, D., Chaieb, L., Moliadze, V., Antal, A., & Paulus, W. (2008). Increasing human brain excitability by transcranial high-frequency random noise stimulation. *Journal of Neuroscience*, *28*(52), 14147-14155. doi: 10.1523/JNEUROSCI.4248-08.2008

Trepel, C., & Racine, R. J. (2000). GABAergic modulation of neocortical long-term potentiation in the freely moving rat. *Synapse*, *35*(2), 120-128. doi: 10.1002/(SICI)1098-2396(200002)35:2<120::AID-SYN4>3.0.CO;2-6

Turi, Z., Ambrus, G. G., Ho, K. A., Sengupta, T., Paulus, W., & Antal, A. (2014). When size matters: large electrodes induce greater stimulation-related cutaneous discomfort than smaller electrodes at equivalent current density. *Brain stimulation*, *7*(3), 460-467. doi: 10.1016/j.brs.2014.01.059

Valentine, G. W., & Sanacora, G. (2009). Targeting glial physiology and glutamate cycling in the treatment of depression. *Biochemical Pharmacology*, *78*(5), 431–439. doi: 10.1016/j.bcp.2009.04.008

Vanderhasselt, M., De Raedt, R., Brunoni, A. R., Campanhã, C., Baeken, C., Remue, J., & Boggio, P. S. (2013). TDCS over the left prefrontal cortex enhances cognitive control for positive affective stimuli. *PLoS ONE, 8*(5). doi:10.1371/journal.pone.0062219

Vanderhasselt, M. A., De Raedt, R., De Paepe, A., Aarts, K., Otte, G., Van Dorpe, J., & Pourtois, G. (2014). Abnormal proactive and reactive cognitive control during conflict processing in major depression. *Journal of abnormal psychology*, *123*(1), 68. doi: 10.1037/a0035816

Vöröslakos, M., Takeuchi, Y., Brinyiczki, K., Zombori, T., Oliva, A., Fernández-Ruiz, A., ... & Berényi, A. (2018). Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nature communications*, *9*(1), 1-17. doi: 10.1038/s41467-018-02928-3

Vos, T., Allen, C., Arora, M., Barber, R. M., Bhutta, Z. A., Brown, A., ... & Coggeshall, M. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, *388*(10053), 1545-1602. doi: 10.1016/S0140-6736(16)31678-6

Warner-Schmidt, J. L., & Duman, R. S. (2006). Hippocampal neurogenesis: Opposing effects of stress and antidepressant treatment. *Hippocampus*, *16*(3), 239–249. doi: 10.1002/hipo.20156

Warren, M. B., Pringle, A., & Harmer, C. J. (2015). A neurocognitive model for understanding treatment action in depression. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *370*(1677), 20140213. doi: 10.1098/rstb.2014.0213

Whiteford HA, Degenhardt L, Rehm J, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; 382(9904):1575–86

Wise, T., Radua, J., Via, E., Cardoner, N., Abe, O., Adams, T. M., ... & Dickstein, D. P. (2017). Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. *Molecular psychiatry*, *22*(10), 1455-1463. doi: 10.1038/mp.2016.72

Woods, A. J., Bryant, V., Sacchetti, D., Gervits, F., & Hamilton, R. (2015). Effects of electrode drift in transcranial direct current stimulation. *Brain stimulation*, *8*(3), 515-519. doi: 10.1016/j.brs.2014.12.007

World Health Organization. (2017). *Depression and other common mental disorders: global health estimates* (No. WHO/MSD/MER/2017.2). World Health Organization. [Accessed on: https://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf]

Zatorre, R. J., Fields, R. D., & Johansen-Berg, H. (2012). Plasticity in gray and white: neuroimaging changes in brain structure during learning. *Nature neuroscience*, *15*(4), 528-536. doi: 10.1038/nn.3045

Zhang, K., Guo, L., Zhang, J., An, G., Zhou, Y., Lin, J., . . . Ding, G. (2019). A safety study of 500 μA cathodal transcranial direct current stimulation in rat. *BMC Neuroscience, 20*(1). doi:10.1186/s12868-019-0523-7

Appendix 6. *Publication 2* - Woodham, R. D., Rimmer, R. M., Young, A. H., & Fu, C. H. (2022). Adjunctive home-based transcranial direct current stimulation treatment for major depression with real-time remote supervision: An open-label, single-arm feasibility study with long term outcomes. *Journal of Psychiatric Research*.

Title:

Adjunctive home-based transcranial direct current stimulation treatment for major depression with real-time remote supervision: an open-label, single-arm feasibility study with long term outcomes

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Abstract:

Current treatments for major depressive disorder (MDD) have limited effectiveness and acceptability. Transcranial direct current stimulation (tDCS) is a novel non-invasive brain stimulation method that has demonstrated treatment efficacy in MDD. tDCS requires daily sessions, however clinical trials have been conducted in research centers requiring repeated visits. As tDCS is portable and safe, it could be provided at home. We developed a home-based protocol with real-time supervision, and we examined the clinical outcomes, acceptability and feasibility. Participants were 26 MDD (19 women), mean age 40.9 ± 14.2 years, in current depressive episode of moderate to severe severity (mean 17-item Hamilton Rating Scale for Depression (HAMD) score 19.12 ± 2.12). tDCS was provided in a bilateral frontal montage, F3 anode, F4 cathode, 2mA, each session 30 minutes, in a 6-week trial, for a total 21 sessions. Participants maintained their current treatment (antidepressant medication, psychotherapy, or were enrolled in online CBT). Two tDCS device brands were used, and a research team member was present in person or by real-time video call at each session. 92.3% MDD participants (n=24) completed the 6-week treatment. Attrition rate was 7.7%. There was a significant improvement in depressive symptoms following treatment (mean HAMD 5.33 ± 2.33), which was maintained at 6 months (mean HAMD 5.43 ± 2.73). Acceptability was endorsed as “very acceptable” or “quite acceptable” by all participants. Due to the open-label feasibility design, efficacy findings are preliminary. In summary, home-based tDCS with real-time supervision was associated with significant clinical improvements and high acceptability which were maintained in the long term.

Keywords:

transcranial direct current stimulation, neuromodulation, non-invasive, major depression, long term outcome

1. Introduction:

Major depressive disorder (MDD) is a leading cause of disability worldwide and is the most significant precursor in suicide (James et al., 2018). MDD is characterised by low mood or loss of enjoyment for a prolonged period that is associated with impairments in sleep, appetite, and cognition, as well as low energy and often feelings of guilt. MDD is often expressed in impaired interpersonal, school or workplace functioning (Wittchen et al., 2011), with a socioeconomic cost of over $326 million in the USA (Greenberg et al., 2021) and £9 billion in the UK (Thomas and Morris, 2003).

The most common treatments for MDD are pharmacological and psychological therapies. However, the clinical response to a full course of either treatment is usually achieved in less than 50% of patients (Cuijpers et al., 2014; Rush et al., 2006). Even after multiple treatment trials, over a third of patients do not achieve remission (Rush et al., 2006). Residual symptoms increase the risk of another episode and, in turn, repeated episodes, resulting in cycles of more frequent recurrences (Kessing et al., 2004). Moreover, up to 40% of patients are not accessing treatment, despite having severe depressive symptoms (McManus et al., 2016), and patient preference is an important determinant of engagement and clinical outcomes (Windle et al., 2020).

Transcranial direct current stimulation (tDCS) is a non-invasive form of brain stimulation, which is a potential novel treatment for depression (Woodham et al., 2021). tDCS delivers a weak direct current (0.5-2.5mA), in which electrode placement is typically with the anode over the left dorsolateral prefrontal cortex (DLPFC) and cathode over either the right DLPFC, suborbital or frontotemporal region (Brunoni et al., 2016b; Fregni et al., 2021). The current changes neuronal membrane potential and facilitates discharge. In contrast to rTMS and ECT, tDCS does not directly trigger an action

potential. The most common side effects are tingling, itching, burning sensation, skin redness or headache, with no differences reported in active relative to sham tDCS (Brunoni et al., 2011).

A course of active tDCS treatment is associated with significant improvements in depressive symptoms, clinical response and remission relative to placebo sham stimulation (Brunoni et al., 2016b; Fregni et al., 2021). Meta-analyses of randomised sham-controlled trials show that a course of tDCS treatment is associated with a fourfold increased rate of clinical response and a threefold increased rate of clinical remission (Mutz et al., 2019, 2018). Moreover, the onset of improvement might be seen in the first 2 weeks of treatment (Brunoni et al., 2016b; Meron et al., 2015), and the strongest efficacy has been observed in first episode and recurrent MDD (Mutz et al., 2019, 2018).

However, tDCS requires daily sessions for several weeks, which are time consuming and potentially costly for travel requirements. As tDCS devices are low cost and portable, providing the treatment at home could improve availability and engagement. In an open label 4-week trial, Alonzo et al. (2018) found a response rate of 38% in 33 MDD patients, and in an open label 6-week trial, Borrione et al. (2021) found a response rate of 80% in 5 MDD using a tDCS protocol combined with app-based psychological intervention. While treatment effects seem to be evident, long term clinical outcomes have not been investigated. We sought to investigate the long term effects, acceptability and feasibility of a home-based protocol with clinical assessments at 3 and 6 months.

2. Materials and Methods:

2.1. Study design and tDCS protocol

Ethical approval was provided by the London Fulham Research Ethics Committee. All participants provided informed written consent. The study was an open-label acceptability and feasibility trial of home-based tDCS treatment for MDD (ClinicalTrials.gov ID: NCT03632434). The protocol consisted of a 6-week treatment period of active tDCS, consisting of 5 sessions per week for 3 weeks and then 2 sessions a week for 3 weeks, for a total of 21 sessions. A minimum of 15 sessions was required for study completion. Given the novelty of the treatment, ethical approval required that all participants receive active tDCS in addition to their current treatment e.g. antidepressant medication, psychotherapy, or an online course of cognitive behaviour therapy (CBT), Living Life to The Full (www.llttf.com). Long term clinical assessments were conducted at 3 and 6 months by telephone or video call.

The anode was positioned over the left dorsolateral prefrontal cortex (DLPFC) (position F3 on the international 10/20 EEG system) and cathode over the right DLPFC (position F4). Conductive rubber electrodes covered by saline soaked sponges were 35cm^2 in diameter. Stimulation was 2mA for 30 minutes with a gradual ramp up and ramp down of 10 seconds. A research team member was present at each session. In person, the research member provided a discreet presence, remaining in the same room as the participant. By Microsoft Teams video call, the research member would have their camera on and the participant would have their camera and microphone on, so they could easily communicate with the researcher. The researcher would ensure that the participant was visible at the side of the screen. The participant and team member did not interact unless the participant required support.

Two tDCS devices were used: Neuroelectrics Starstim 8 system (3 participants) and Flow Neuroscience tDCS device (23 participants). The Neuroelectrics tDCS device was initially used, which required in person administration as electrodes are placed within a neoprene cap. During the Covid-19 pandemic, the Flow tDCS device was used which in a fully remote protocol with real-time remote supervision.

The participant would put on the tDCS device with a research team member present by video call. All additional study activities were conducted by video call. Written informed consent was provided electronically. Neuropsychological assessments were mailed to participants and necessary sections were completed by pen and paper. A screenshot of the completed assessment was taken by the researcher following completion.

2.2. Inclusion and exclusion criteria

Participants were recruited from online advertisements and GP referrals. Inclusion criteria: (1) adults aged 18 or older; (2) current major depressive episode, without psychotic features, defined by Diagnostic Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association, 2013), determined by a structured assessment using the Mini-International Neuropsychiatric Interview (MINI; Version 7.0.2) (Sheehan et al., 1998); (3) having at least a moderate severity of depressive symptoms, as measured by a minimum score of 16 on the 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960); and (4) taking antidepressant medication or engaging in psychological therapy, including online CBT. Exclusion criteria: (1) treatment resistant depression as defined by poor clinical response to 2 or more antidepressant trials; (2) any concurrent DSM-5 comorbid Axis I or II disorder within the previous 6 months; (3) history of bipolar disorder, obsessive compulsive disorder, or primary psychotic disorder; (4) significant risk of suicide or self-harm; (5) pregnant women or women who were breastfeeding; (6) history of ECT, TMS or VNS; (7) any exclusion criteria for receiving tDCS, including having a scalp or skin condition (e.g. psoriasis or eczema), contact with the scalp is not possible, having metallic implants, including intracranial electrodes or a pacemaker, history of epilepsy or seizure resulting in loss of consciousness, neurological disorder or history of migraine.

2.3. Clinical assessments

Clinical assessments were conducted at baseline and at weeks 1, 2, 3, 4, 5, 6, 18 and 30, following initiation of tDCS sessions. The following rating scales were used: 17-item Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), Hamilton Anxiety Rating Scale (HAMA) (Hamilton, 1959), Sheehan Disability Scale (SDS) (Sheehan, 1893), Patient Health Questionnaire-9 (PHQ-9) (Kroenke et al., 2001) and Young Mania Rating Scale (YMRS) (Young et al., 1978). Clinical response was defined as an improvement of 50% or greater in HAMD, and clinical remission was defined as a HAMD score of less than 8. Each participant was rated by the same researcher throughout the study with clinical supervision.

2.4. Safety, tolerability and acceptability

Safety and tolerability were assessed with monitoring of any adverse events before and after each treatment session at the same timepoints, using the tDCS Adverse Events Questionnaire (AEQ) (Brunoni et al., 2011). We devised an acceptability questionnaire based on Sekhon et al. (2017) framework model, consisting of five questions: (1) general acceptability: 'How acceptable do you consider the tDCS sessions to be?'; (2) perceived effectiveness: 'How helpful do you think the tDCS sessions may be for improving your depressive symptoms?'; (3) side effects: 'How likely do you think that there will be negative side effects from the tDCS sessions?'; (4) ethicality: 'How ethical do you think the tDCS sessions are?'; (5) burden: How much effort do you think you need to put in for the tDCS sessions?'. Responses were rated on a 7-point anchored Likert scale, ranging from e.g. "very acceptable" to "very unacceptable", with the opportunity for open-ended responses (Table 1). Responses were acquired at baseline, 6-week end of treatment and at the 6-month follow up.

At the end of treatment and at follow up, the acceptability questionnaire consisted of the same questions written in the past tense, with the addition of a sixth question: (6) affective attitude: 'Would you recommend the tDCS sessions to others?', and questions related to the study design: (7) 'Please explain, in your view, what were the most successful parts of the study?'; (8) 'Please explain in your view what were the least successful parts of the study?'; (9) 'Are there any ways in which the study can be improved?'; (10) 'Do you have any other comments?' Participants completed the questionnaires in writing or in a video recorded semi-structured interview conducted via Microsoft Teams.

2.5. Neuropsychological assessments

IQ was evaluated with Weschler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) in person or Ammons Quick Test (Ammons and Ammons, 1962) by video call. Neuropsychological functioning was assessed at baseline and after sessions 1, 10 and 21, using the Symbol Digit Modalities Test (SDMT) (Smith, 1991), to assess psychomotor processing speed and visuospatial attention, and the Rey Auditory Veral Learning Test (RAVLT) (Rey, 1964) to assess memory and verbal learning. Different versions of each test were used at each session and the administration order was counterbalanced.

2.6. Statistical analysis

An intention to treat analysis was completed, using a last observation carried forward (LOCF) method for missing data on clinical assessments. Four within-subject ANOVAS were conducted, with HAMD, HAMA, PHQ-9 and SDS total scores were the dependant variables and assessment time-point was the within-subjects factor, with four levels including baseline (*t*0), end of treatment period (*t*1), 3-month follow-up (*t*2) and 6-month follow-up (*t*3). Statistical analyses were conducted using IBM SPSS

Statistics for MacOS, version 26.0. All analyses were two tailed and a significance value of $p = 0.05$ was set. Greenhouse-Geisser correction was applied if Mauchley's assumption of sphericity was violated. An analysis was also conducted for participants who completed the course of treatment and both follow up sessions. Post hoc pairwise comparisons with Bonferroni corrections were conducted. Neuropsychological test scores were analysed with within-subject ANCOVA, examining a main effect of time with baseline HAMD scores as a covariate. For the acceptability questionnaire, median and interquartile range were calculated at each time point for each response. Nonparametric Friedman's ANOVA was performed to assess the repeated measures for each response for participants with data at all three timepoints (n=18), and nonparametric Wilcoxon signed-rank test was used to assess significance given the Likert scale, uncertain differences between anchors, and small range of response choices.

3. Results

3.1. Participants

26 MDD participants were enrolled (19 women), mean age 40.9 ± 14.2 years, mean HAMD 19.12 ± 2.12 (Table 2). Mean duration of the current episode was 17.0 ± 11.4 weeks. 12 participants were taking antidepressant medication, range 1 week - 10 years prior to starting the study. 13 participants had online CBT (Living Life to the Full), and 1 participant had telephone CBT. 92.8% participants (n=24) completed the 6-week course of treatment, mean number of tDCS sessions 19.8 ± 1.6 (range 15 – 21). One participant declined the follow-up sessions and was not included in the completers analysis. In person sessions using the Neuroelectrics device was stopped for 2 participants due to the Covid-19 pandemic, and remote sessions could not continue for one participant due to a broken device, but all participants had completed at least 15 sessions. One participant discontinued after 3 sessions due to

physical health and one participant after 12 sessions for personal reasons. Five participants continued with tDCS treatment on their own during the 6-month follow up period, 4 continuing twice weekly sessions and 1 reporting occasional use.

3.2. Clinical assessments

For all four time points (weeks 0, 6, and months 3, 6), 88.5% of participants (n=23) completed clinical assessments at all time points in the completers analysis. Data was missing for 7.7% of participants (n=2) at the end of treatment (week 6) and 11.5% (n=3) at 3- and 6- month follow up.

At week 6, mean HAMD score was 5.33 $\pm$ 2.33, in which 22 participants (91.7%) show a clinical response and 21 participants (87.5%) achieved clinical remission. At the 3-month follow up, mean HAMD score was 5.65 $\pm$ 3.02, clinical response was 20 out of 23 participants (87.0%) and clinical remission was 18 out of 23 participants (78.2%). At the 6-month follow up, mean HAMD score was 5.43 $\pm$ 2.73, clinical response was 21 out of 23 participants (91.3%) and remission was 17 out of 23 participants (73.9%). Four participants (16.7%) showed an early response following 2 weeks of treatment (10 tDCS sessions); 3 participants were in remission (12.5%). Significant clinical improvements from baseline were maintained at the 6-month follow up in the intention to treat analysis (Table 3) as well as completers analysis (Table 4).

HAMA, PHQ-9 and SDS scores showed significant improvements from baseline which were maintained from the end of the trial to the 6-month follow up (Table 3, Table 4). Mean HAMA score at baseline was 15.13 $\pm$ 1.70 (range = 12 - 19), reflecting mild to moderate severity of anxiety. Following treatment, the mean score was 6.17 $\pm$ 2.86 which was maintained at 6 months. Mean PHQ-9 score at baseline was 16.04 $\pm$ 3.81, which improved following treatment (mean 9.00 $\pm$ 4.28) and was maintained at 6 months (mean 7.8 $\pm$ 4.17) follow up. SDS ratings of functional impairment were high at baseline (mean

19.09 ± 5.57), in which the maximum score is 30. Functional impairment was significantly improved at the end of treatment (mean 9.57 ± 6.86) and maintained at 6 months (mean 11.85 ± 8.15).

3.3. Safety, tolerability and acceptability

The most common side effects were skin redness, tingling, itching or mild burning sensation and headache (Supplementary Materials Table 1). 84.9% of reports were rated as mild, 14.5% were rated as moderate, and 0.6% were rated as severe, which were for sleepiness (2 reports) and for a positive change in mood (1 report). There were no episodes of hypomania or mania as measured by the YMRS.

Acceptability was endorsed as being “very acceptable” at each timepoint with no significant changes over time (t1 Mdn=7, IQR=1; t2 Mdn=7, IQR=1; t3 Mdn=7, IQR=1) (X^2_F (2) = 2.0, p = 0.368). Ethicality remained high at “very ethical” with no significant changes over time (t1 Mdn=7, IQR=1, t2 Mdn=7, IQR=1, t3 Mdn=7, IQR=2) (X^2_F (2) = 071, p = 0.965). The effort required remained consistent at “little bit more than usual” with no significant changes over time (t1 Mdn=3, IQR=2, t2 Mdn=3, IQR=3, t3 Mdn=3, IQR=1) (X^2_F (2) = 3.796, p = 0.150).

There was a significant increase in endorsements from “would recommend” tDCS at the end of treatment to “would strongly recommend” at follow up (t2 Mdn=6, IQR=1; t3 Mdn=7, IQR=1; T = 4.5, p < 0.01) with a moderate effect size (r = -0.44). 20.8% of participants chose "would very strongly recommend" tDCS which increased to 55.6% at follow up (Figure 1). Ratings for perceived effectiveness showed an increase from “quite helpful” at baseline to “quite helpful” / “very helpful” at follow up, which approached significance (t1: Mdn=6, IQR=1, t2; Mdn=6, IQR=2, t3; Mdn=6.5, IQR=1) (X^2_F (2) = 5.42, p = 0.067). The impact of side effects showed a decrease from being “a bit

unlikely" at baseline to being "very much unaffected" / "quite unaffected" at follow up, which approached significance (t1; Mdn=3., IQR=2, t2; Mdn=2, IQR=4, t3; Mdn=1.5, IQR=4) (X^2_F (2) = 5.48, p = 0.065).

3.4. Neuropsychological assessments

No significant changes in performance were observed in SDMT or AVLT following the initial tDCS session, at 10 sessions, or at the end of treatment (Supplementary Material Table 2). Data from one participant was not included in the SDMT analysis as they were unable to follow the task instructions.

4. Discussion

Home-based tDCS with real-time remote supervision was associated with significant clinical improvements, which were maintained over a 6-month follow up. There was high participant retention, high acceptability for the treatment, and adverse effects were transient and mild. Significant improvements were also observed in anxiety, self-reported depressive symptoms and in interpersonal, social and work functioning. The high rates of remission were maintained at 6 months, reflecting the long term effects of the treatment, and participants reported a noticeable impact in their lives. While the present is a home-based study, participants had been experiencing a depressive episode of at least a moderate severity for an average of 5 months and the majority had a history of multiple previous episodes.

tDCS parameters were based on meta-analyses which demonstrated that treatment effects are most evident at 2 mA current of 30 minute stimulus duration for at least 20 sessions in recurrent MDD

(Brunoni et al., 2016b; Meron et al., 2015; Mutz et al., 2018). While there is no firm consensus on the optimal tDCS dosage, meta-analyses indicate that increased session numbers may be associated with improved clinical outcomes (Brunoni et al., 2016b; Moffa et al., 2020; Shiozawa et al., 2014). tDCS and rTMS have demonstrated efficacy in treating anxiety disorders (Matza et al., 2010; Vergallito et al., 2021), and we observed a further long term maintenance of the improvements in the present study.

In the present study, participants had a concurrent treatment, which included online CBT, while larger treatment effects have been observed for tDCS as a stand-alone treatment (Brunoni et al., 2016b; Meron et al., 2015).

A significant benefit of a home-based protocol is the flexibility to have regular treatment sessions at a suitable time. In the present study, a research team member was present, and participants were asked to sit quietly during each session. The presence of an observer is a unique experience which could have provided additional treatment effects, which may have contributed to the high rates of symptom improvement (Papoutsi and Fu, 2021).

The rate of attrition was 7.7%, which appears to be lower than clinic-based studies with rates of 10.1% (Brunoni et al., 2016b) and 14.7% (Moffa et al., 2020) and lower than rates for pharmacological and psychological therapies, which range from 11-15% within 8 weeks (Amick et al., 2015; DeRubeis et al., 2005). Most participants had experienced skin redness after tDCS at some point during the treatment period, although they were generally rated as being mild. Having a research team member present allowed for detailed safety monitoring and clinical assessments at each session. Patients may have difficulty in managing side effects adequately without regular supervision, which could result in worsening adverse effects and in turn discontinuation. Monitoring of daily side effects through completion of an online entry though might be sufficient (Alonzo et al., 2019).

Overall acceptability was high prior to the start of treatment and remained high at the end of treatment and at the 6-month follow up, indicating that anticipated beliefs about the treatment were experienced. The low attrition rate seemed also to reflect the high overall acceptability. Perceived effectiveness was anticipated to be “quite helpful” and was then experienced to be “quite helpful” immediately following the course of treatment, increasing to “very helpful” at follow up. High perceived effectiveness paralleled the high response and remission rates in the present study. Expecting that a treatment will be beneficial can enhance treatment effects (Bystad et al., 2015; Krell et al., 2004). Furthermore, the increase in perceived effectiveness ratings at the 6-month follow up reflected greater certainty in beliefs about effectiveness, likely due to the long term sustained improvements. Moreover, there was a significant increase in personal endorsement from “would strongly recommend” at the end of the treatment to “would very strongly recommend” at follow up.

There was a wide range of ratings for side effects, with equal numbers endorsing being “unaffected” and being “affected”. Acceptability has usually been measured by tolerability and adverse effect attrition (Brunoni et al., 2016a), yet being affected by expected side effects did not appear to impact on acceptability ratings. The full range of responses were selected to the question about effort, ranging from “very much more [effort] than usual” to “very much less [effort] than usual”. Alongside patient beliefs about a treatment, self-efficacy and ease of administration can reduce the likelihood of nonadherence to treatment (Bandura, 1978; Horne et al., 2013) and should be considered for future community-based tDCS protocols. Ratings for ethicality remained high, ranging from “neither ethical or unethical” to “very ethical” with the majority of participants rating the tDCS treatment as “very ethical”, perhaps reflecting participants’ informed consent to take part in the study and might suggest that the information they had received about treatment was a good representation of the treatment.

In the present study, pregnant and breastfeeding women had not been included, although rTMS in both pregnant women and breastfeeding women has not shown any additional side effects or harm compared to other adult populations (Al-Shamali et al., 2022; Cole et al., 2019). In fact, non-invasive brain stimulation, including tDCS could potentially be an important alternative treatment in peripartum depression (Cole et al., 2019; Pacheco et al., 2021). Future studies should consider researching tDCS within these populations and carefully consider if these exclusion criteria are necessary.

Limitations of the present study include the lack of a sham tDCS treatment arm as all participants received active tDCS treatment in an open-label design. Moreover, having real-time supervision for each session likely contributed to symptom improvement. As the protocol was not designed to establish efficacy, the findings should be considered as preliminary, and a placebo sham treatment control group is required to investigate efficacy. The acceptability questionnaire that we developed was based on Sekhon (2017) framework to assess participant views but there we had not measured validity or reliability prior to using the questionnaire, which is required in the early stages of a technology intervention cycle (International Test Commission (ITC), 2014). Further feasibility assessment should include access to the technology required for app-based devices as lower socioeconomic status is associated with higher rates of depression and reduced life expectancy, but internet non-usage is higher amongst people who are economically inactive or on a low income (Lorant et al., 2003; Strategic Review of Health Inequalities in England post-2010, 2010; Stringhini et al., 2017). It is important to consider potential barriers when assessing access to treatment.

In summary, home-based tDCS with real-time remote supervision was associated with significant improvements in depressive symptoms in moderate to severe severity of MDD, which were maintained at the long term follow up. The treatment showed high acceptability, tolerability and

safety. Home-based tDCS is a potential novel treatment in first-episode MDD. As all participants had received active tDCS with real-time supervision, large-scale randomised sham-controlled trials are required to investigate efficacy.

References

Al-Shamali, H., Hussain, A., Dennett, L., Cao, B., Burback, L., Greenshaw, A., Zhang, Y., 2022. Is repetitive transcranial magnetic stimulation (rTMS) an effective and safe treatment option for postpartum and peripartum depression? A Systematic Review. J. Affect. Disord. Rep. 100356. https://doi.org/10.1016/j.jadr.2022.100356

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. ed. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425596

Amick, H.R., Gartlehner, G., Gaynes, B.N., Forneris, C., Asher, G.N., Morgan, L.C., Coker-Schwimmer, E., Boland, E., Lux, L.J., Gaylord, S., Bann, C., Pierl, C.B., Lohr, K.N., 2015. Comparative benefits and harms of second generation antidepressants and cognitive behavioral therapies in initial treatment of major depressive disorder: systematic review and meta-analysis. BMJ 351, h6019. https://doi.org/10.1136/bmj.h6019

Ammons, R.B., Ammons, C.H., 1962. The Quick Test (QT): Provisional manual. Psychol. Rep. 11, 111–161. https://doi.org/10.1177/003329416201100106

Bandura, A., 1978. Self-efficacy: Toward a unifying theory of behavioral change. Adv. Behav. Res. Ther., Perceived Self-Efficacy: Analyses of Bandura's Theory of Behavioural Change 1, 139–161. https://doi.org/10.1016/0146-6402(78)90002-4

Brunoni, A.R., Amadera, J., Berbel, B., Volz, M.S., Rizzerio, B.G., Fregni, F., 2011. A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation. Int. J. Neuropsychopharmacol. 14, 1133–1145. https://doi.org/10.1017/S1461145710001690

Brunoni, A.R., Loo, C.K., Nitsche, M.A., 2016a. Safety and tolerability, in: Transcranial Direct Current Stimulation in Neuropsychiatric Disorders: Clinical Principles and Management. pp. 343–350. https://doi.org/10.1007/978-3-319-33967-2_22

Brunoni, A.R., Moffa, A.H., Fregni, F., Palm, U., Padberg, F., Blumberger, D.M., Daskalakis, Z.J., Bennabi, D., Haffen, E., Alonzo, A., Loo, C.K., 2016b. Transcranial direct current stimulation for acute major depressive episodes: Meta-analysis of individual patient data. Br. J. Psychiatry 208, 522–531. https://doi.org/10.1192/bjp.bp.115.164715

Bystad, M., Bystad, C., Wynn, R., 2015. How can placebo effects best be applied in clinical practice? A narrative review. Psychol. Res. Behav. Manag. 8, 41–45. https://doi.org/10.2147/PRBM.S75670

Cole, J., Bright, K., Gagnon, L., McGirr, A., 2019. A systematic review of the safety and effectiveness of repetitive transcranial magnetic stimulation in the treatment of peripartum depression. J. Psychiatr. Res. 115, 142–150. https://doi.org/10.1016/j.jpsychires.2019.05.015

Cuijpers, P., Karyotaki, E., Weitz, E., Andersson, G., Hollon, S.D., van Straten, A., 2014. The effects of psychotherapies for major depression in adults on remission, recovery and improvement: A meta-analysis. J. Affect. Disord. 159, 118–126. https://doi.org/10.1016/j.jad.2014.02.026

DeRubeis, R.J., Hollon, S.D., Amsterdam, J.D., Shelton, R.C., Young, P.R., Salomon, R.M., O'Reardon, J.P., Lovett, M.L., Gladis, M.M., Brown, L.L., Gallop, R., 2005. Cognitive therapy vs medications in the treatment of moderate to severe depression. Arch. Gen. Psychiatry 62, 409–416. https://doi.org/10.1001/archpsyc.62.4.409

Fregni, F., El-Hagrassy, M.M., Pacheco-Barrios, K., Carvalho, S., Leite, J., Simis, M., Brunelin, J., Nakamura-Palacios, E.M., Marangolo, P., Venkatasubramanian, G., San-Juan, D., Caumo, W., Bikson, M., Brunoni, A.R., Neuromodulation Center Working Group, 2021. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation in neurological and psychiatric disorders. Int. J. Neuropsychopharmacol. 24, 256–313. https://doi.org/10.1093/ijnp/pyaa051

Greenberg, P.E., Fournier, A.-A., Sisitsky, T., Simes, M., Berman, R., Koenigsberg, S.H., Kessler, R.C., 2021. The economic burden of adults with major depressive disorder in the United States (2010 and 2018). PharmacoEconomics 39, 653–665. https://doi.org/10.1007/s40273-021-01019-4

Hamilton, M., 1960. A rating scale for depression. J. Neurol. Neurosurg. Psychiatry 23, 56–62. https://doi.org/10.1136/jnnp.23.1.56

Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32, 50–55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x

Horne, R., Chapman, S.C.E., Parham, R., Freemantle, N., Forbes, A., Cooper, V., 2013. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: A meta-analytic review of the Necessity-Concerns Framework. PLOS ONE 8, e80633. https://doi.org/10.1371/journal.pone.0080633

International Test Commission (ITC), 2014. ITC Guidelines on Quality Control in Scoring, Test Analysis, and Reporting of Test Scores. Int. J. Test. 14, 195–217. https://doi.org/10.1080/15305058.2014.918040

James, S.L., Abate, D., Abate, K.H., Abay, S.M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R.S., Abebe, Z., Abera, S.F., Abil, O.Z., Abraha, H.N., Abu-Raddad, L.J., Abu-Rmeileh, N.M.E., Accrombessi, M.M.K., Acharya, D., Acharya, P., Ackerman, I.N., Adamu, A.A., Adebayo, O.M., Adekanmbi, V., Adetokunboh, O.O., Adib, M.G., Adsuar, J.C., Afanvi, K.A., Afarideh, M., Afshin, A., Agarwal, G., Agesa, K.M., Aggarwal, R., Aghayan, S.A., Agrawal, S., Ahmadi, A., Ahmadi, M., Ahmadieh, H., Ahmed, M.B., Aichour, A.N., Aichour, I., Aichour, M.T.E., Akinyemiju, T., Akseer, N., Al-Aly, Z., Al-Eyadhy, A., Al-Mekhlafi, H.M., Al-Raddadi, R.M., Alahdab, F., Alam, K., Alam, T., Alashi, A., Alavian, S.M., Alene, K.A., Alijanzadeh, M., Alizadeh-Navaei, R., Aljunid, S.M., Alkerwi, A., Alla, F., Allebeck, P., Alouani, M.M.L., Altirkawi, K., Alvis-Guzman, N., Amare, A.T., Aminde, L.N., Ammar, W., Amoako, Y.A., Anber, N.H., Andrei, C.L., Androudi, S., Animut, M.D.,

Anjomshoa, M., Ansha, M.G., Antonio, C.A.T., Anwari, P., Arabloo, J., Arauz, A., Aremu, O., Ariani, F., Armoon, B., Ärnlöv, J., Arora, A., Artaman, A., Aryal, K.K., Asayesh, H., Asghar, R.J., Ataro, Z., Atre, S.R., Ausloos, M., Avila-Burgos, L., Avokpaho, E.F.G.A., Awasthi, A., Ayala Quintanilla, B.P., Ayer, R., Azzopardi, P.S., Babazadeh, A., Badali, H., Badawi, A., Bali, A.G., Ballesteros, K.E., Ballew, S.H., Banach, M., Banoub, J.A.M., Banstola, A., Barac, A., Barboza, M.A., Barker-Collo, S.L., Bärnighausen, T.W., Barrero, L.H., Baune, B.T., Bazargan-Hejazi, S., Bedi, N., Beghi, E., Behzadifar, Masoud, Behzadifar, Meysam, Béjot, Y., Belachew, A.B., Belay, Y.A., Bell, M.L., Bello, A.K., Bensenor, I.M., Bernabe, E., Bernstein, R.S., Beuran, M., Beyranvand, T., Bhala, N., Bhattarai, S., Bhaumik, S., Bhutta, Z.A., Biadgo, B., Bijani, A., Bikbov, B., Bilano, V., Bililign, N., Bin Sayeed, M.S., Bisanzio, D., Blacker, B.F., Blyth, F.M., Bou-Orm, I.R., Boufous, S., Bourne, R., Brady, O.J., Brainin, M., Brant, L.C., Brazinova, A., Breitborde, N.J.K., Brenner, H., Briant, P.S., Briggs, A.M., Briko, A.N., Britton, G., Brugha, T., Buchbinder, R., Busse, R., Butt, Z.A., Cahuana-Hurtado, L., Cano, J., Cárdenas, R., Carrero, J.J., Carter, A., Carvalho, F., Castañeda-Orjuela, C.A., Castillo Rivas, J., Castro, F., Catalá-López, F., Cercy, K.M., Cerin, E., Chaiah, Y., Chang, A.R., Chang, H.-Y., Chang, J.-C., Charlson, F.J., Chattopadhyay, A., Chattu, V.K., Chaturvedi, P., Chiang, P.P.-C., Chin, K.L., Chitheer, A., Choi, J.-Y.J., Chowdhury, R., Christensen, H., Christopher, D.J., Cicuttini, F.M., Ciobanu, L.G., Cirillo, M., Claro, R.M., Collado-Mateo, D., Cooper, C., Coresh, J., Cortesi, P.A., Cortinovis, M., Costa, M., Cousin, E., Criqui, M.H., Cromwell, E.A., Cross, M., Crump, J.A., Dadi, A.F., Dandona, L., Dandona, R., Dargan, P.I., Daryani, A., Das Gupta, R., Das Neves, J., Dasa, T.T., Davey, G., Davis, A.C., Davitoiu, D.V., De Courten, B., De La Hoz, F.P., De Leo, D., De Neve, J.-W., Degefa, M.G., Degenhardt, L., Deiparine, S., Dellavalle, R.P., Demoz, G.T., Deribe, K., Dervenis, N., Des Jarlais, D.C., Dessie, G.A., Dey, S., Dharmaratne, S.D., Dinberu, M.T., Dirac, M.A., Djalalinia, S., Doan, L., Dokova, K., Doku, D.T., Dorsey, E.R., Doyle, K.E., Driscoll, T.R., Dubey, M., Dubljanin, E., Duken, E.E., Duncan, B.B., Duraes, A.R., Ebrahimi, H., Ebrahimpour, S., Echko, M.M., Edvardsson, D., Effiong, A., Ehrlich, J.R., El Bcheraoui, C., El Sayed Zaki, M., El-

Khatib, Z., Elkout, H., Elyazar, I.R.F., Enayati, A., Endries, A.Y., Er, B., Erskine, H.E., Eshrati, B., Eskandarieh, S., Esteghamati, A., Esteghamati, S., Fakhim, H., Fallah Omrani, V., Faramarzi, M., Fareed, M., Farhadi, F., Farid, T.A., Farinha, C.S.E. sá, Farioli, A., Faro, A., Farvid, M.S., Farzadfar, F., Feigin, V.L., Fentahun, N., Fereshtehnejad, S.-M., Fernandes, E., Fernandes, J.C., Ferrari, A.J., Feyissa, G.T., Filip, I., Fischer, F., Fitzmaurice, C., Foigt, N.A., Foreman, K.J., Fox, J., Frank, T.D., Fukumoto, T., Fullman, N., Fürst, T., Furtado, J.M., Futran, N.D., Gall, S., Ganji, M., Gankpe, F.G., Garcia-Basteiro, A.L., Gardner, W.M., Gebre, A.K., Gebremedhin, A.T., Gebremichael, T.G., Gelano, T.F., Geleijnse, J.M., Genova-Maleras, R., Geramo, Y.C.D., Gething, P.W., Gezae, K.E., Ghadiri, K., Ghasemi Falavarjani, K., Ghasemi-Kasman, M., Ghimire, M., Ghosh, R., Ghoshal, A.G., Giampaoli, S., Gill, P.S., Gill, T.K., Ginawi, I.A., Giussani, G., Gnedovskaya, E.V., Goldberg, E.M., Goli, S., Gómez-Dantés, H., Gona, P.N., Gopalani, S.V., Gorman, T.M., Goulart, A.C., Goulart, B.N.G., Grada, A., Grams, M.E., Grosso, G., Gugnani, H.C., Guo, Y., Gupta, P.C., Gupta, Rahul, Gupta, Rajeev, Gupta, T., Gyawali, B., Haagsma, J.A., Hachinski, V., Hafezi-Nejad, N., Haghparast Bidgoli, H., Hagos, T.B., Hailu, G.B., Haj-Mirzaian, Arvin, Haj-Mirzaian, Arya, Hamadeh, R.R., Hamidi, S., Handal, A.J., Hankey, G.J., Hao, Y., Harb, H.L., Harikrishnan, S., Haro, J.M., Hasan, M., Hassankhani, H., Hassen, H.Y., Havmoeller, R., Hawley, C.N., Hay, R.J., Hay, S.I., Hedayatizadeh-Omran, A., Heibati, B., Hendrie, D., Henok, A., Herteliu, C., Heydarpour, S., Hibstu, D.T., Hoang, H.T., Hoek, H.W., Hoffman, H.J., Hole, M.K., Homaie Rad, E., Hoogar, P., Hosgood, H.D., Hosseini, S.M., Hosseinzadeh, M., Hostiuc, M., Hostiuc, S., Hotez, P.J., Hoy, D.G., Hsairi, M., Htet, A.S., Hu, G., Huang, J.J., Huynh, C.K., Iburg, K.M., Ikeda, C.T., Ileanu, B., Ilesanmi, O.S., Iqbal, U., Irvani, S.S.N., Irvine, C.M.S., Islam, S.M.S., Islami, F., Jacobsen, K.H., Jahangiry, L., Jahanmehr, N., Jain, S.K., Jakovljevic, M., Javanbakht, M., Jayatilleke, A.U., Jeemon, P., Jha, R.P., Jha, V., Ji, J.S., Johnson, C.O., Jonas, J.B., Jozwiak, J.J., Jungari, S.B., Jürisson, M., Kabir, Z., Kadel, R., Kahsay, A., Kalani, R., Kanchan, T., Karami, M., Karami Matin, B., Karch, A., Karema, C., Karimi, N., Karimi, S.M., Kasaeian, A., Kassa, D.H., Kassa, G.M., Kassa, T.D., Kassebaum, N.J.,

Katikireddi, S.V., Kawakami, N., Karyani, A.K., Keighobadi, M.M., Keiyoro, P.N., Kemmer, L., Kemp, G.R., Kengne, A.P., Keren, A., Khader, Y.S., Khafaei, B., Khafaie, M.A., Khajavi, A., Khalil, I.A., Khan, E.A., Khan, M.S., Khan, M.A., Khang, Y.-H., Khazaei, M., Khoja, A.T., Khosravi, A., Khosravi, M.H., Kiadaliri, A.A., Kiirithio, D.N., Kim, C.-I., Kim, D., Kim, P., Kim, Y.-E., Kim, Y.J., Kimokoti, R.W., Kinfu, Y., Kisa, A., Kissimova-Skarbek, K., Kivimäki, M., Knudsen, A.K.S., Kocarnik, J.M., Kochhar, S., Kokubo, Y., Kolola, T., Kopec, J.A., Kosen, S., Kotsakis, G.A., Koul, P.A., Koyanagi, A., Kravchenko, M.A., Krishan, K., Krohn, K.J., Kuate Defo, B., Kucuk Bicer, B., Kumar, G.A., Kumar, M., Kyu, H.H., Lad, D.P., Lad, S.D., Lafranconi, A., Lalloo, R., Lallukka, T., Lami, F.H., Lansingh, V.C., Latifi, A., Lau, K.M.-M., Lazarus, J.V., Leasher, J.L., Ledesma, J.R., Lee, P.H., Leigh, J., Leung, J., Levi, M., Lewycka, S., Li, S., Li, Y., Liao, Y., Liben, M.L., Lim, L.-L., Lim, S.S., Liu, S., Lodha, R., Looker, K.J., Lopez, A.D., Lorkowski, S., Lotufo, P.A., Low, N., Lozano, R., Lucas, T.C.D., Lucchesi, L.R., Lunevicius, R., Lyons, R.A., Ma, S., Macarayan, E.R.K., Mackay, M.T., Madotto, F., Magdy Abd El Razek, H., Magdy Abd El Razek, M., Maghavani, D.P., Mahotra, N.B., Mai, H.T., Majdan, M., Majdzadeh, R., Majeed, A., Malekzadeh, R., Malta, D.C., Mamun, A.A., Manda, A.-L., Manguerra, H., Manhertz, T., Mansournia, M.A., Mantovani, L.G., Mapoma, C.C., Maravilla, J.C., Marcenes, W., Marks, A., Martins-Melo, F.R., Martopullo, I., März, W., Marzan, M.B., Mashamba-Thompson, T.P., Massenburg, B.B., Mathur, M.R., Matsushita, K., Maulik, P.K., Mazidi, M., McAlinden, C., McGrath, J.J., McKee, M., Mehndiratta, M.M., Mehrotra, R., Mehta, K.M., Mehta, V., Mejia-Rodriguez, F., Mekonen, T., Melese, A., Melku, M., Meltzer, M., Memiah, P.T.N., Memish, Z.A., Mendoza, W., Mengistu, D.T., Mengistu, G., Mensah, G.A., Mereta, S.T., Meretoja, A., Meretoja, T.J., Mestrovic, T., Mezerji, N.M.G., Miazgowski, B., Miazgowski, T., Millear, A.I., Miller, T.R., Miltz, B., Mini, G.K., Mirarefin, M., Mirrakhimov, E.M., Misganaw, A.T., Mitchell, P.B., Mitiku, H., Moazen, B., Mohajer, B., Mohammad, K.A., Mohammadifard, N., Mohammadnia-Afrouzi, M., Mohammed, M.A., Mohammed, S., Mohebi, F., Moitra, M., Mokdad, A.H., Molokhia, M., Monasta, L., Moodley, Y., Moosazadeh, M., Moradi, G.,

Moradi-Lakeh, M., Moradinazar, M., Moraga, P., Morawska, L., Moreno Velásquez, I., Morgado-Da-Costa, J., Morrison, S.D., Moschos, M.M., Mountjoy-Venning, W.C., Mousavi, S.M., Mruts, K.B., Muche, A.A., Muchie, K.F., Mueller, U.O., Muhammed, O.S., Mukhopadhyay, S., Muller, K., Mumford, J.E., Murhekar, M., Musa, J., Musa, K.I., Mustafa, G., Nabhan, A.F., Nagata, C., Naghavi, M., Naheed, A., Nahvijou, A., Naik, G., Naik, N., Najafi, F., Naldi, L., Nam, H.S., Nangia, V., Nansseu, J.R., Nascimento, B.R., Natarajan, G., Neamati, N., Negoi, I., Negoi, R.I., Neupane, S., Newton, C.R.J., Ngunjiri, J.W., Nguyen, A.Q., Nguyen, Ha Thu, Nguyen, H.L.T., Nguyen, Huong Thanh, Nguyen, L.H., Nguyen, M., Nguyen, N.B., Nguyen, S.H., Nichols, E., Ningrum, D.N.A., Nixon, M.R., Nolutshungu, N., Nomura, S., Norheim, O.F., Noroozi, M., Norrving, B., Noubiap, J.J., Nouri, H.R., Nourollahpour Shiadeh, M., Nowroozi, M.R., Nsoesie, E.O., Nyasulu, P.S., Odell, C.M., Ofori-Asenso, R., Ogbo, F.A., Oh, I.-H., Oladimeji, O., Olagunju, A.T., Olagunju, T.O., Olivares, P.R., Olsen, H.E., Olusanya, B.O., Ong, K.L., Ong, S.K., Oren, E., Ortiz, A., Ota, E., Otstavnov, S.S., Øverland, S., Owolabi, M.O., P A, M., Pacella, R., Pakpour, A.H., Pana, A., Panda-Jonas, S., Parisi, A., Park, E.-K., Parry, C.D.H., Patel, S., Pati, S., Patil, S.T., Patle, A., Patton, G.C., Paturi, V.R., Paulson, K.R., Pearce, N., Pereira, D.M., Perico, N., Pesudovs, K., Pham, H.Q., Phillips, M.R., Pigott, D.M., Pillay, J.D., Piradov, M.A., Pirsaheb, M., Pishgar, F., Plana-Ripoll, O., Plass, D., Polinder, S., Popova, S., Postma, M.J., Pourshams, A., Poustchi, H., Prabhakaran, D., Prakash, S., Prakash, V., Purcell, C.A., Purwar, M.B., Qorbani, M., Quistberg, D.A., Radfar, A., Rafay, A., Rafiei, A., Rahim, F., Rahimi, K., Rahimi-Movaghar, A., Rahimi-Movaghar, V., Rahman, M., Rahman, M.H. ur, Rahman, M.A., Rahman, S.U., Rai, R.K., Rajati, F., Ram, U., Ranjan, P., Ranta, A., Rao, P.C., Rawaf, D.L., Rawaf, S., Reddy, K.S., Reiner, R.C., Reinig, N., Reitsma, M.B., Remuzzi, G., Renzaho, A.M.N., Resnikoff, S., Rezaei, S., Rezai, M.S., Ribeiro, A.L.P., Roberts, N.L.S., Robinson, S.R., Roever, L., Ronfani, L., Roshandel, G., Rostami, A., Roth, G.A., Roy, A., Rubagotti, E., Sachdev, P.S., Sadat, N., Saddik, B., Sadeghi, E., Saeedi Moghaddam, S., Safari, H., Safari, Y., Safari-Faramani, R., Safdarian, M., Safi, S., Safiri, S., Sagar, R., Sahebkar, A.,

Sahraian, M.A., Sajadi, H.S., Salam, N., Salama, J.S., Salamati, P., Saleem, K., Saleem, Z., Salimi, Y., Salomon, J.A., Salvi, S.S., Salz, I., Samy, A.M., Sanabria, J., Sang, Y., Santomauro, D.F., Santos, I.S., Santos, J.V., Santric Milicevic, M.M., Sao Jose, B.P., Sardana, M., Sarker, A.R., Sarrafzadegan, N., Sartorius, B., Sarvi, S., Sathian, B., Satpathy, M., Sawant, A.R., Sawhney, M., Saxena, S., Saylan, M., Schaeffner, E., Schmidt, M.I., Schneider, I.J.C., Schöttker, B., Schwebel, D.C., Schwendicke, F., Scott, J.G., Sekerija, M., Sepanlou, S.G., Serván-Mori, E., Seyedmousavi, S., Shabaninejad, H., Shafieesabet, A., Shahbazi, M., Shaheen, A.A., Shaikh, M.A., Shams-Beyranvand, M., Shamsi, M., Shamsizadeh, M., Sharafi, H., Sharafi, K., Sharif, M., Sharif-Alhoseini, M., Sharma, M., Sharma, R., She, J., Sheikh, A., Shi, P., Shibuya, K., Shigematsu, M., Shiri, R., Shirkoohi, R., Shishani, K., Shiue, I., Shokraneh, F., Shoman, H., Shrime, M.G., Si, S., Siabani, S., Siddiqi, T.J., Sigfusdottir, I.D., Sigurvinsdottir, R., Silva, J.P., Silveira, D.G.A., Singam, N.S.V., Singh, J.A., Singh, N.P., Singh, V., Sinha, D.N., Skiadaresi, E., Slepak, E.L.N., Sliwa, K., Smith, D.L., Smith, M., Soares Filho, A.M., Sobaih, B.H., Sobhani, S., Sobngwi, E., Soneji, S.S., Soofi, M., Soosaraei, M., Sorensen, R.J.D., Soriano, J.B., Soyiri, I.N., Sposato, L.A., Sreeramareddy, C.T., Srinivasan, V., Stanaway, J.D., Stein, D.J., Steiner, C., Steiner, T.J., Stokes, M.A., Stovner, L.J., Subart, M.L., Sudaryanto, A., Sufiyan, M.B., Sunguya, B.F., Sur, P.J., Sutradhar, I., Sykes, B.L., Sylte, D.O., Tabarés-Seisdedos, R., Tadakamadla, S.K., Tadesse, B.T., Tandon, N., Tassew, S.G., Tavakkoli, M., Taveira, N., Taylor, H.R., Tehrani-Banihashemi, A., Tekalign, T.G., Tekelemedhin, S.W., Tekle, M.G., Temesgen, H., Temsah, M.-H., Temsah, O., Terkawi, A.S., Teweldemedhin, M., Thankappan, K.R., Thomas, N., Tilahun, B., To, Q.G., Tonelli, M., Topor-Madry, R., Topouzis, F., Torre, A.E., Tortajada-Girbés, M., Touvier, M., Tovani-Palone, M.R., Towbin, J.A., Tran, B.X., Tran, K.B., Troeger, C.E., Truelsen, T.C., Tsilimbaris, M.K., Tsoi, D., Tudor Car, L., Tuzcu, E.M., Ukwaja, K.N., Ullah, I., Undurraga, E.A., Unutzer, J., Updike, R.L., Usman, M.S., Uthman, O.A., Vaduganathan, M., Vaezi, A., Valdez, P.R., Varughese, S., Vasankari, T.J., Venketasubramanian, N., Villafaina, S., Violante, F.S., Vladimirov, S.K., Vlassov, V., Vollset,

S.E., Vosoughi, K., Vujcic, I.S., Wagnew, F.S., Waheed, Y., Waller, S.G., Wang, Y., Wang, Y.-P., Weiderpass, E., Weintraub, R.G., Weiss, D.J., Weldegebreal, F., Weldegwergs, K.G., Werdecker, A., West, T.E., Whiteford, H.A., Widecka, J., Wijeratne, T., Wilner, L.B., Wilson, S., Winkler, A.S., Wiyeh, A.B., Wiysonge, C.S., Wolfe, C.D.A., Woolf, A.D., Wu, S., Wu, Y.-C., Wyper, G.M.A., Xavier, D., Xu, G., Yadgir, S., Yadollahpour, A., Yahyazadeh Jabbari, S.H., Yamada, T., Yan, L.L., Yano, Y., Yaseri, M., Yasin, Y.J., Yeshaneh, A., Yimer, E.M., Yip, P., Yisma, E., Yonemoto, N., Yoon, S.-J., Yotebieng, M., Younis, M.Z., Yousefifard, M., Yu, C., Zadnik, V., Zaidi, Z., Zaman, S.B., Zamani, M., Zare, Z., Zeleke, A.J., Zenebe, Z.M., Zhang, K., Zhao, Z., Zhou, M., Zodpey, S., Zucker, I., Vos, T., Murray, C.J.L., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet 392, 1789–1858. https://doi.org/10.1016/S0140-6736(18)32279-7

Kessing, L.V., Hansen, M.G., Andersen, P.K., Angst, J., 2004. The predictive effect of episodes on the risk of recurrence in depressive and bipolar disorders - a life-long perspective. Acta Psychiatr. Scand. 109, 339–344. https://doi.org/10.1046/j.1600-0447.2003.00266.x

Krell, H.V., Leuchter, A.F., Morgan, M., Cook, I.A., Abrams, M., 2004. Subject expectations of treatment effectiveness and outcome of treatment with an experimental antidepressant. J. Clin. Psychiatry 65, 1174–1179. https://doi.org/10.4088/jcp.v65n0904

Kroenke, K., Spitzer, R., Williams, W., 2001. The PHQ-9: Validity of a brief depression severity measure. J. Gen. Intern. Med. 16, 606–616.

Lorant, V., Deliège, D., Eaton, W., Robert, A., Philippot, P., Ansseau, M., 2003. Socioeconomic inequalities in depression: A meta-analysis. Am. J. Epidemiol. 157, 98–112. https://doi.org/10.1093/aje/kwf182

Matza, L.S., Morlock, R., Sexton, C., Malley, K., Feltner, D., 2010. Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder: HAM-A severity ranges. Int. J. Methods Psychiatr. Res. 19, 223–232. https://doi.org/10.1002/mpr.323

McManus, S., Bebbington, P., Jenkins, R., Brugha, T., NHS Digital, UK Statistics Authority, 2016. Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014: a survey carried out for NHS Digital by NatCen Social Research and the Department of Health Sciences, University of Leicester.

Meron, D., Hedger, N., Garner, M., Baldwin, D.S., 2015. Transcranial direct current stimulation (tDCS) in the treatment of depression: Systematic review and meta-analysis of efficacy and tolerability. Neurosci. Biobehav. Rev. 57, 46–62. https://doi.org/10.1016/j.neubiorev.2015.07.012

Moffa, A.H., Martin, D., Alonzo, A., Bennabi, D., Blumberger, D.M., Benseñor, I.M., Daskalakis, Z., Fregni, F., Haffen, E., Lisanby, S.H., Padberg, F., Palm, U., Razza, L.B., Sampaio-Jr, B., Loo, C., Brunoni, A.R., 2020. Efficacy and acceptability of transcranial direct current stimulation (tDCS) for major depressive disorder: An individual patient data meta-analysis. Prog. Neuropsychopharmacol. Biol. Psychiatry 99, 109836. https://doi.org/10.1016/j.pnpbp.2019.109836

Mutz, J., Edgcumbe, D.R., Brunoni, A.R., Fu, C.H.Y., 2018. Efficacy and acceptability of non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: A systematic review and meta-analysis of randomised sham-controlled trials. Neurosci. Biobehav. Rev. 92, 291–303. https://doi.org/10.1016/j.neubiorev.2018.05.015

Mutz, J., Vipulananthan, V., Carter, B., Hurlemann, R., Fu, C.H.Y., Young, A.H., 2019. Comparative efficacy and acceptability of non-surgical brain stimulation for the acute treatment of major depressive episodes in adults: Systematic review and network meta-analysis. BMJ 1079. https://doi.org/10.1136/bmj.l1079

Pacheco, F., Guiomar, R., Brunoni, A.R., Buhagiar, R., Evagorou, O., Roca-Lecumberri, A., Poleszczyk, A., Lambregtse-van den Berg, M., Caparros-Gonzalez, R.A., Fonseca, A., Osório, A., Soliman, M., Ganho-Ávila, A., 2021. Efficacy of non-invasive brain stimulation in decreasing depression symptoms during the peripartum period: A systematic review. J. Psychiatr. Res. 140, 443–460. https://doi.org/10.1016/j.jpsychires.2021.06.005

Papoutsi, V., Fu, C.H.Y., 2021. Observing infants together: long-term experiences of observers and families. Infant Obs. 24, 4–22. https://doi.org/10.1080/13698036.2021.1952094

Rey, A., 1964. L'Examen Clinique en Psychologie. Presses Universitaires de France, Paris.

Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., McGrath, P.J., Rosenbaum, J.F., Sackeim, H.A., Kupfer, D.J., Luther, J., Fava, M., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. Am. J. Psychiatry 163, 1905–1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Sekhon, M., Cartwright, M., Francis, J.J., 2017. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv. Res. 17, 88. https://doi.org/10.1186/s12913-017-2031-8

Sheehan, D.V., 1893. The Sheehan Disability Scales, in: The Anxiety Disease and How to Overcome It. Charles Scribner and Sons, New York, p. 151.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 Suppl 20, 22-33;quiz 34-57.

Shiozawa, P., Fregni, F., Benseñor, I.M., Lotufo, P.A., Berlim, M.T., Daskalakis, J.Z., Cordeiro, Q., Brunoni, A.R., 2014. Transcranial direct current stimulation for major depression: An updated systematic review and meta-analysis. Int. J. Neuropsychopharmacol. 17, 1443–1452. https://doi.org/10.1017/S1461145714000418

Smith, A., 1991. Symbol digit modalities test. WesternPsychological Services, Los Angeles, CA.

Strategic Review of Health Inequalities in England post-2010, 2010. Fair society, healthier lives: The Marmot review. Elsevier.

Stringhini, S., Carmeli, C., Jokela, M., Avendaño, M., Muennig, P., Guida, F., Ricceri, F., d'Errico, A., Barros, H., Bochud, M., Chadeau-Hyam, M., Clavel-Chapelon, F., Costa, G., Delpierre, C., Fraga, S., Goldberg, M., Giles, G.G., Krogh, V., Kelly-Irving, M., Layte, R., Lasserre, A.M., Marmot, M.G., Preisig, M., Shipley, M.J., Vollenweider, P., Zins, M., Kawachi, I., Steptoe, A., Mackenbach, J.P., Vineis, P., Kivimäki, M., LIFEPATH consortium, 2017. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: A multicohort study and meta-analysis of 1·7 million men and women. The Lancet 389, 1229–1237. https://doi.org/10.1016/S0140-6736(16)32380-7

Thomas, C.M., Morris, S., 2003. Cost of depression among adults in England in 2000. Br. J. Psychiatry 183, 514–519. https://doi.org/10.1192/bjp.183.6.514

Vergallito, A., Gallucci, A., Pisoni, A., Punzi, M., Caselli, G., Ruggiero, G.M., Sassaroli, S., Romero Lauro, L.J., 2021. Effectiveness of noninvasive brain stimulation in the treatment of anxiety disorders: a meta-analysis of sham or behaviour-controlled studies. J. Psychiatry Neurosci. 46, E592–E614. https://doi.org/10.1503/jpn.210050

Wechsler, D., 1999. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation, San Antonio, TX.

Windle, E., Tee, H., Sabitova, A., Jovanovic, N., Priebe, S., Carr, C., 2020. Association of patient treatment preference with dropout and clinical outcomes in adult psychosocial mental health interventions: A systematic review and meta-analysis. JAMA Psychiatry 77, 294–302. https://doi.org/10.1001/jamapsychiatry.2019.3750

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R., Steinhausen, H.-C., 2011. The size and burden of mental

disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21, 655–679. https://doi.org/10.1016/j.euroneuro.2011.07.018

Woodham, R., Rimmer, R.M., Mutz, J., Fu, C.H.Y., 2021. Is tDCS a potential first line treatment for major depression? Int. Rev. Psychiatry 33, 250–265. https://doi.org/10.1080/09540261.2021.1879030

Young, R.C., Biggs, J.T., Ziegler, V.E., Meyer, D.A., 1978. A rating scale for mania: Reliability, validity and sensitivity. Br. J. Psychiatry 133, 429–435. https://doi.org/10.1192/bjp.133.5.429

Figure Legend

Figure 1. Percentage of participants who endorsed each response in the acceptability questionnaire.

Figure 2. Mean Hamilton Depression Rating Scale (HAMD) total scores in patients at every assessment time point from baseline to 6-month follow up, not including missing data. Error bars represent standard deviation. Number of participants, n=26 at week 0, n=25 at weeks 1-3, n=22 at weeks 4-6, n=23 at months 3 and 6.

Figure 3. Mean Hamilton Anxiety Rating Scale (HAMA) total scores in patients at every assessment time point from baseline to 6-month follow up, not including missing data. Error bars represent standard deviation. Number of participants, n=26 at week 0, n=25 at weeks 1-3, n=22 at weeks 4-6, n=23 at months 3 and 6.

Figure 4. Mean Patient Health Questionnaire-9 (PHQ-9) total scores in patients at every assessment time point from baseline to 6-month follow up, not including missing data. Error bars represent standard deviation. Number of participants, n=26 at week 0, n=25 at weeks 1-3, n=22 at weeks 4-6, n=23 at months 3 and 6.

Figure 5. Mean Sheehan Disability Scale (SDS) total scores in patients at every assessment time point from baseline to 6-month follow up, not including missing data. Error bars represent standard deviation. Number of participants, n=26 at week 0, n=25 at weeks 1-3, n=22 at weeks 4-6, n=23 at months 3 and 6.

Figure 1.

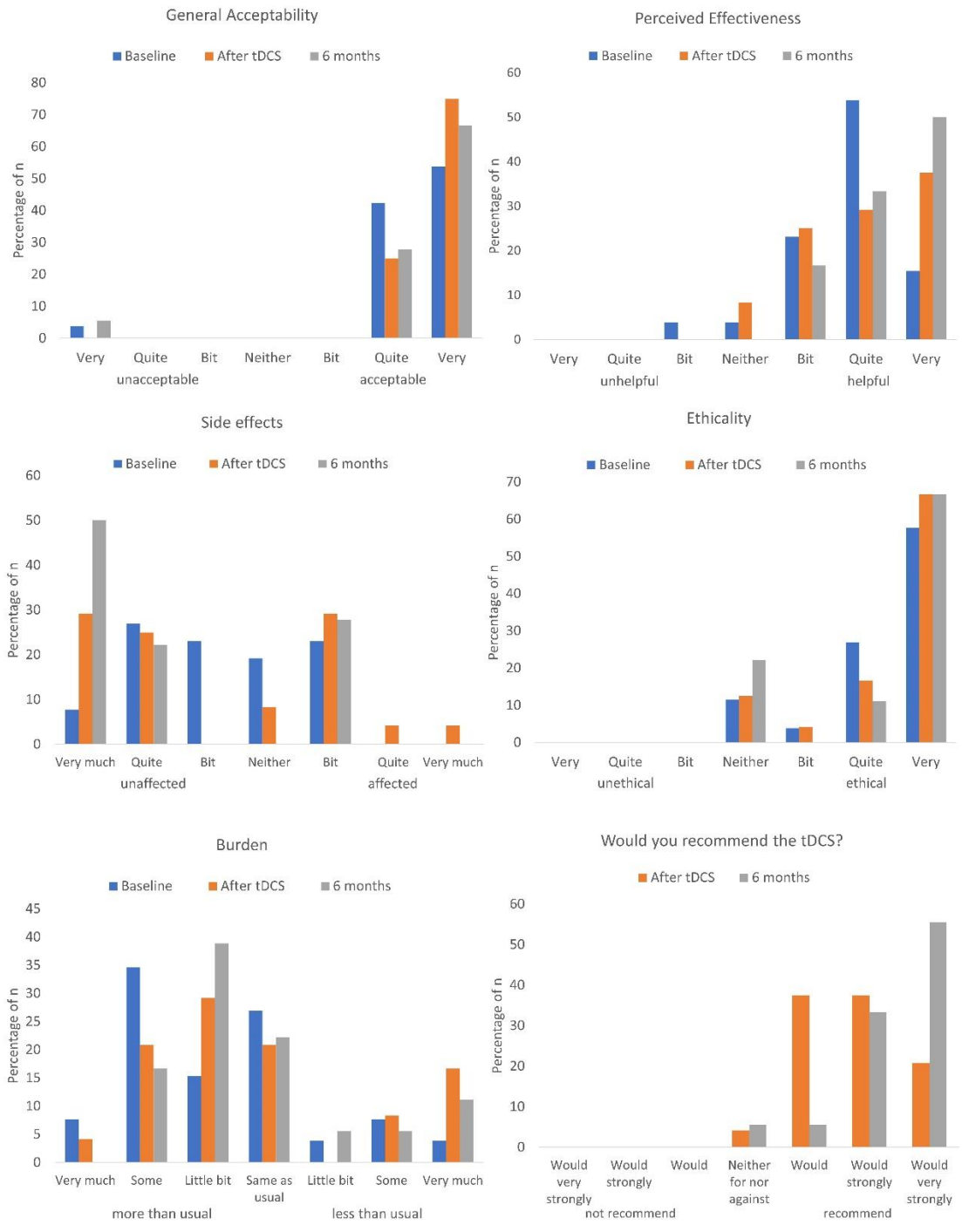

General Acceptability
Baseline
After tDCS
6 months
Percentage of n
Very
Quite unacceptable
Bit
Neither
Bit
Quite acceptable
Very
Perceived Effectiveness
Quite unhelpful
Quite helpful
Side effects
Very much
Quite unaffected
Quite affected
Very much
Ethicality
Quite unethical
Quite ethical
Burden
Some
Little bit
Same as usual
more than usual
less than usual
Would you recommend the tDCS?
Would very strongly not recommend
Would strongly not recommend
Would
Neither for nor against
Would strongly recommend
Would very strongly recommend

Figure 2.

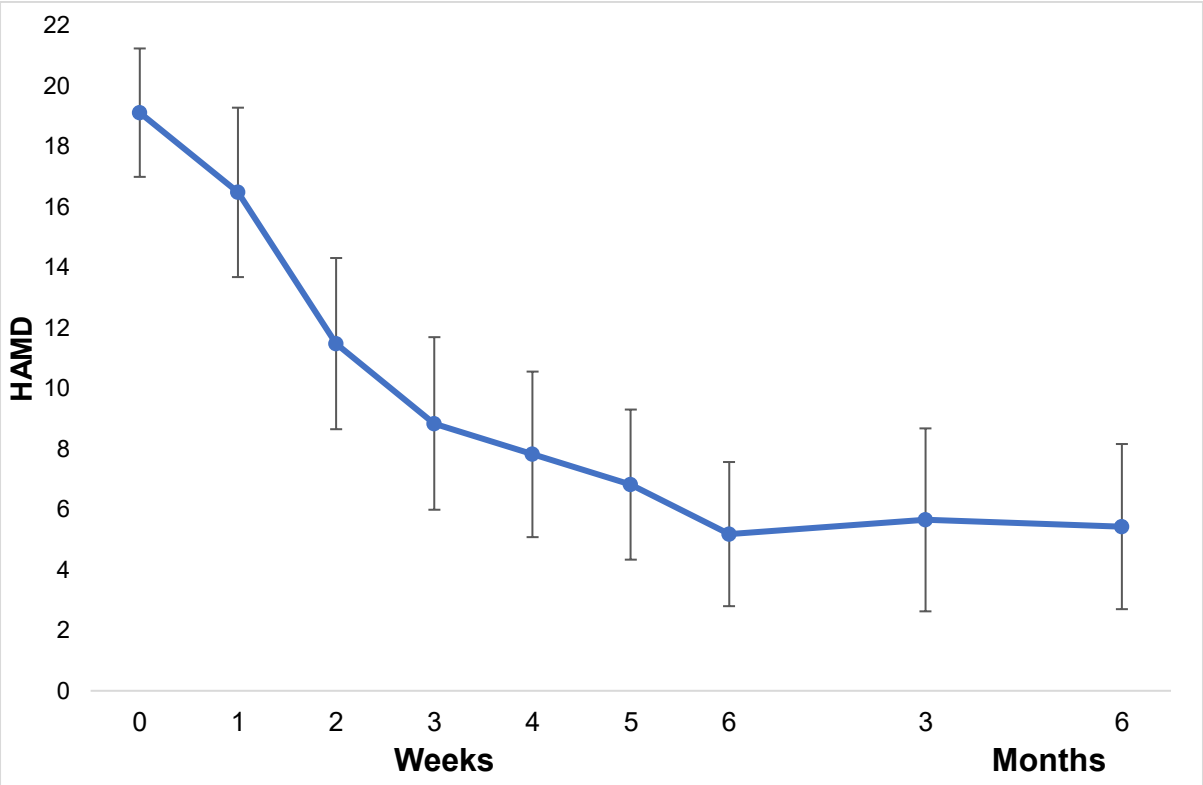


Figure 3.

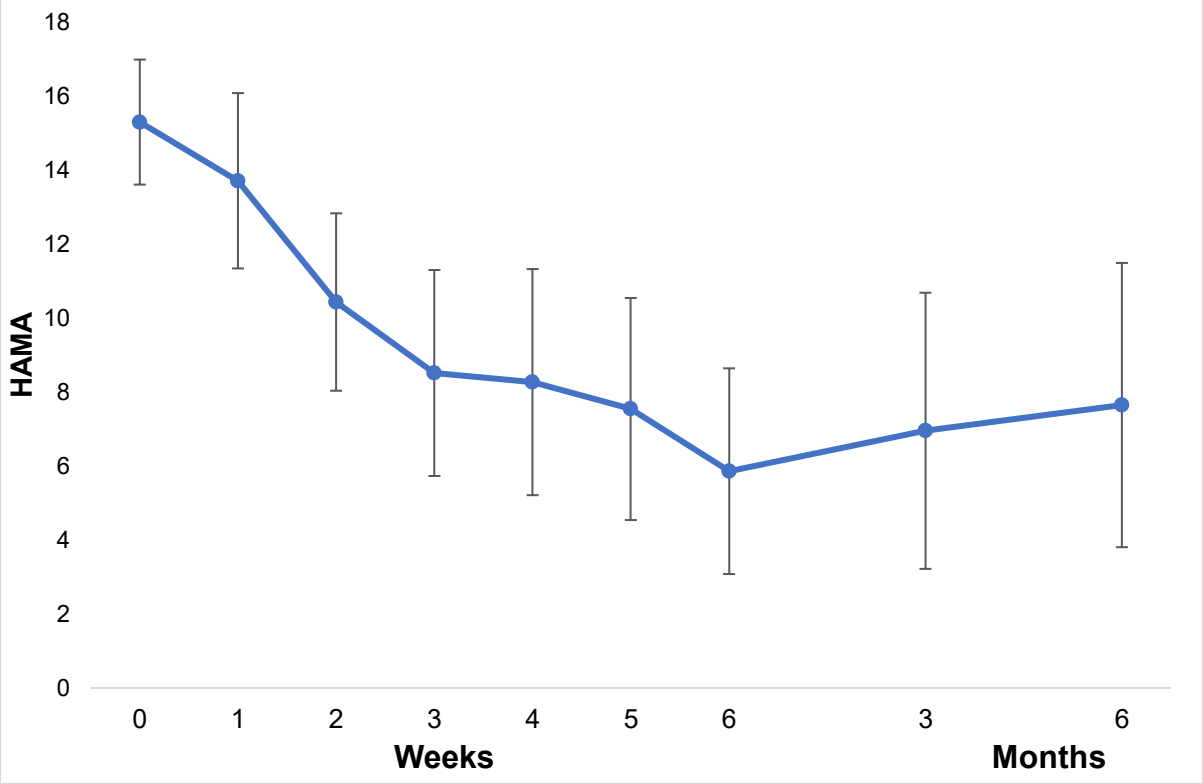


Figure 4.

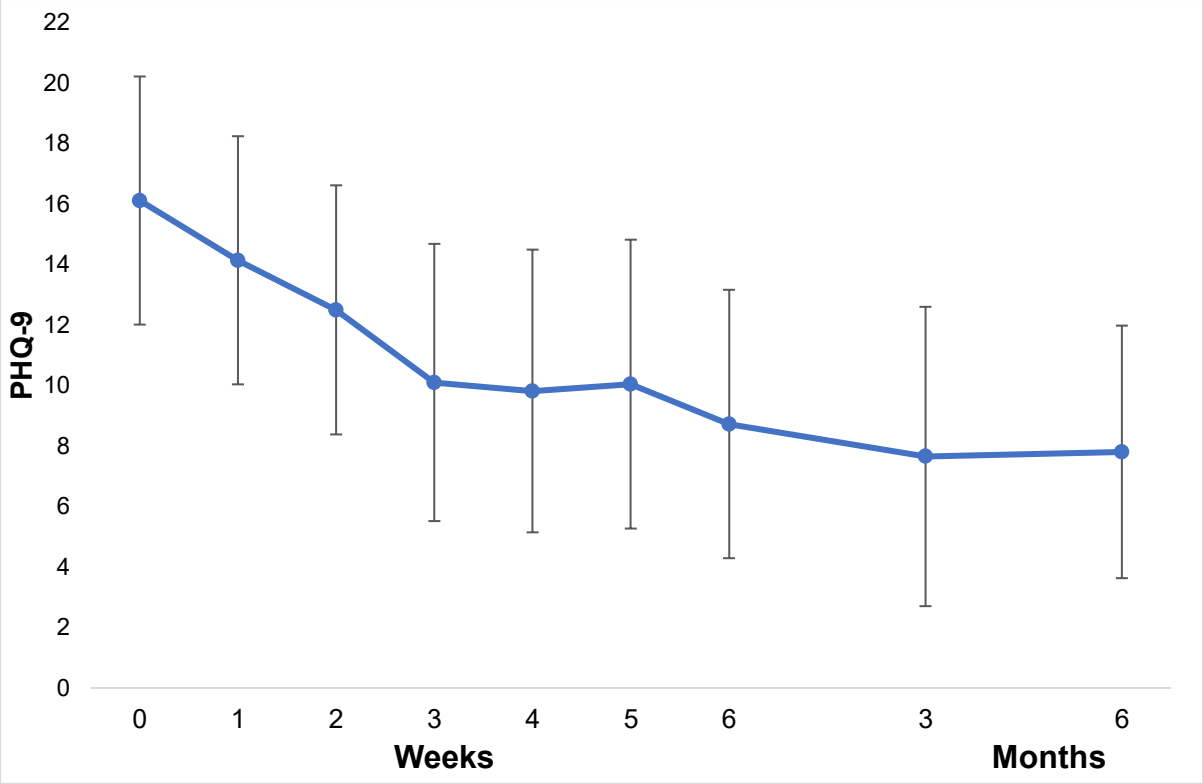
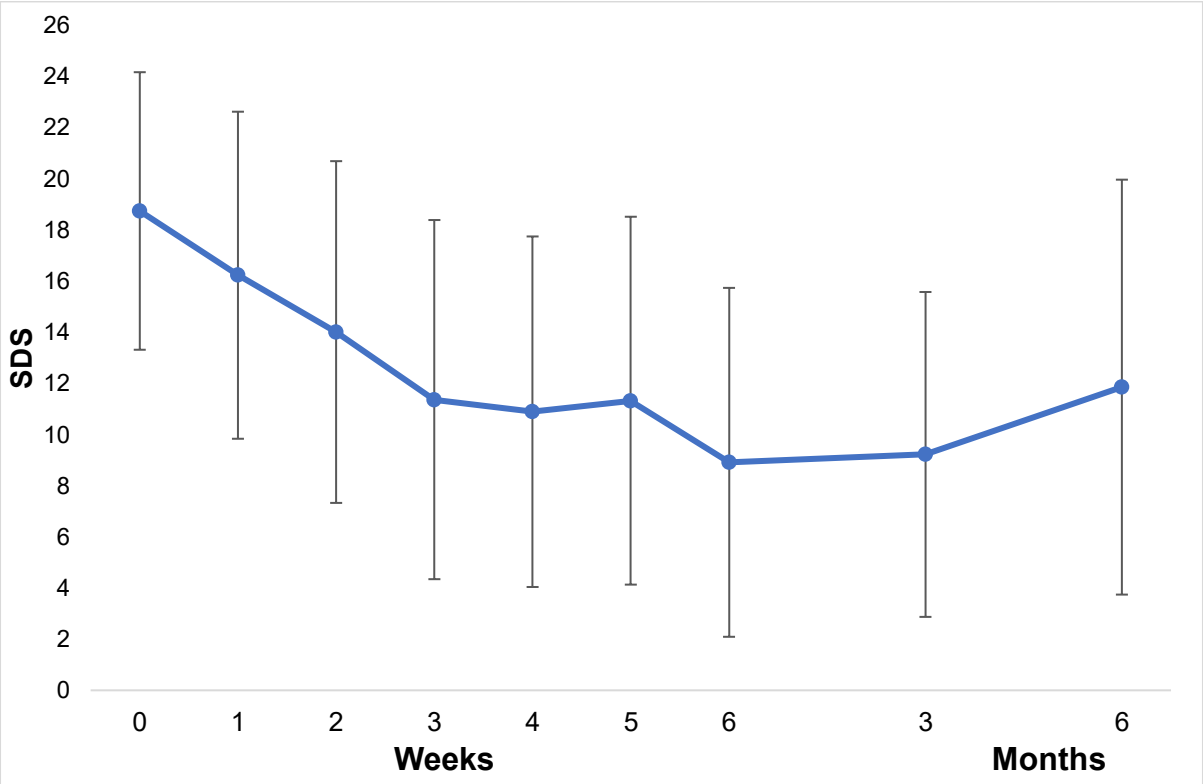

PHQ-9
22
20
18
16
14
12
10
8
6
4
2
0
0
1
2
3
4
5
6
3
6
Weeks
Months

Figure 5.


SDS
26
24
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2
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4
5
6
3
6
Weeks
Months

Table 1. Acceptability questionnaire and responses at baseline (n = 26), at the end of treatment (n = 24) and at 6-month f
treatment phrasing.

Question	Median (IQR)	Likert Ratings 1	2	3	4
How acceptable do *(did)* you consider the tDCS sessions to be?		**Very unacceptable**	**Quite unacceptable**	**Unacceptable**	**Neither**
Baseline	7 (1)	1 (3.8%)	0 (0%)	0 (0%)	0 (0%)
After 6 weeks treatment	7 (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6 months follow up	7 (1)	1 (5.6%)	0 (0%)	0 (0%)	0 (0%)
How helpful do you think the tDCS sessions may be *(were)* for improving your depressive symptoms?		**Very unhelpful**	**Quite unhelpful**	**Bit unhelpful**	**Neither**
Baseline	6 (1)	0 (0%)	0 (0%)	1 (3.8%)	1 (3.8%)
After 6 weeks treatment	6 (2)	0 (0%)	0 (0%)	0 (0%)	2 (8.3%)
6 months follow up	6.5 (1)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
How likely do you think that there will be negative side effects from the tDCS sessions? / *How were you bothered by any negative side effects from the tDCS sessions?*		**Very unlikely/ *Very much unaffected***	**Quite unlikely/ *Quite unaffected***	**Bit unlikely/ *Bit unaffected***	**Neither**
Baseline	3 (2)	2 (7.7%)	7 (26.9%)	6 (23.1%)	5 (19.2%)
After 6 weeks treatment	2 (4)	7 (29.2%)	6 (25%)	0 (0%)	2 (8.3%)
6 months follow up	1.5 (4)	9 (50%)	4 (22.2%)	0 (0%)	0 (0%)
How ethical do you think the tDCS sessions are?		**Very unethical**	**Quite unethical**	**Bit unethical**	**Neither**
Baseline	7 (1)	0 (0%)	0 (0%)	0 (0%)	3 (11.5%)
After 6 weeks treatment	7 (1)	0 (0%)	0 (0%)	0 (0%)	3(12.5%)
6 months follow up	7 (2)	0 (0%)	0 (0%)	0 (0%)	4 (22.2%)
How much effort do you think you need *(did you need)* to put in for the tDCS sessions?		**Very much more than usual**	**Some more than usual**	**Little bit more than usual**	**Same as usual**
Baseline	3 (2)	2 (7.7%)	9 (34.6%)	4 (15.4%)	7 (26.9%)
After 6 weeks treatment	3 (3)	1 (4.2%)	5 (20.8%)	7 (29.2%)	5 (20.8%)
6 months follow up	3 (1)	0 (0%)	3 (16.7%)	7 (38.9%)	4 (22.2%)
Would you recommend the tDCS sessions to others?		**Would very strongly not recommend**	**Would strongly not recommend**	**Would not recommend**	**Would not for or against**
After 6 weeks treatment	6 (1)	0 (0%)	0 (0%)	0 (0%)	1 (4.2%)
6 months follow up	7 (1)	0 (0%)	0 (0%)	0 (0%)	1 (5.6%)

Table 2. Mean baseline demographic and clinical characteristics of MDD participants

Total number (female)	26 (19)
Age (years)	40.85 (14.16)
Age range (years)	19 - 73
Age of onset (years)	22.3 (8.8)
Years of education	15.38 (2.33)
IQ	101.04 (8.43)
Duration of illness (years)	19.36 (12.47)
Duration of current episode (weeks) (range)	28.87 (32.96) (8-156)
Previous number of episodes	8 (8.45)
HAMD	19.12 (2.12)
HAMA	15.19 (1.7)
PHQ-9	16.19 (4.08)

Mean values are presented with standard deviation in parenthesis.

Table 3. Clinical rating scale scores over course of treatment and at follow up, intention to treat analysis

	Baseline	6 weeks	3 months	6 months	P-value
HAMD	19.12 (2.12)	5.92 (3.37)	6.12 (3.80)	5.92 (3.62)	*<0.001*
HAMA	15.31 (1.69)	6.81 (3.71)	7.50 (4.25)	8.12 (4.26)	*<0.001*
PHQ-9	16.12 (4.10)	9.35 (4.98)	8.15 (5.60)	8.48 (4.92)	*<0.001*
SDS	18.73 (5.42)	9.69 (6.75)	9.38 (6.30)	12.33 (7.79)	*<0.001*

Based on an intention to treat analysis, using last observation carried forward (n=26). HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; PHQ-9, Patient Health Questionnaire-9; SDS, Sheehan Disability Scale. Parentheses represent standard deviation

Table 4. Clinical rating scale scores over course of treatment and at follow up, completers analysis

	Baseline	6 weeks	3 months	6 months	P-value
HAMD	19.3 (2.14)	5.44 (2.33)	5.65 (3.02)	5.43 (2.73)	*<0.001*
HAMA	15.13 (1.7)	6.17 (2.86)	6.96 (3.73)	7.65 (3.85)	*<0.001*
PHQ-9	16.04 (3.81)	9.00 (4.28)	7.65 (4.95)	7.80 (4.17)	*<0.001*
SDS	19.09 (5.57)	9.57 (6.86)	8.78 (6.35)	11.85 (8.15)	*<0.001*

Data from participants who completed treatment and follow up (n=23). HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; PHQ-9, Patient Health Questionnaire-9; SDS, Sheehan Disability Scale. Parentheses represent standard deviation

Appendix 7. *Publication 3* - Rimmer, R. M., Costafreda, S. G., Mutz, J., Joseph, K., Brunoni, A. R., Loo, C. K., ... & Fu, C. H. (2022). Transcranial direct current stimulation effects in late life depression: A meta-analysis of individual participant data. *Journal of Affective Disorders Reports*, *10*, 100407.

Title

Transcranial direct current stimulation effects in late life depression: a meta-analysis of individual participant data

Authors

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Abstract

Background: Late life depression (LLD) refers to major depressive disorder (MDD) in adults over 65 years. LLD is associated with high morbidity and poor treatment outcomes. Transcranial direct current stimulation (tDCS) is a novel treatment for MDD. Efficacy in LLD though is unclear. Our aim was to investigate tDCS efficacy by pooling randomised controlled trials (RCT) in an individual participant data meta-analysis.

Methods: Databases were searched for sham controlled RCTs of tDCS in MDD and bipolar depression. Individual participant data (IPD) were requested. Primary outcome was change in depressive symptoms. Bayesian multilevel modelling meta-analysis was conducted with individual participants nested within studies.

Results: 6 RCTs were eligible, consisting of 43 participants (22 women), mean age 69.2 years. Active anodal tDCS over left dorsolateral prefrontal cortex (n=19) was associated with an improvement in depressive severity, effect size 0.14 (95% credible interval [-0.44;0.15]) as compared to sham tDCS, which was not statistically significant. There was an 82% probability that tDCS treatment has a modest but non-null effect in improving depressive symptoms. Acceptability was high with no significant differences in discontinuation rates between active and sham groups.

Limitations: The total sample size was small, limiting power.

Discussion: In LLD, tDCS demonstrates a modest but non-null effect in improving depressive symptoms. Acceptability was high as measured by discontinuation rates. tDCS is a potential novel treatment option in LLD, though large scale RCTs in LLD are required to investigate this important clinical application.

Keywords

transcranial direct current stimulation; late life depression; geriatric depression; major depressive disorder; individual participant data; meta-analysis

Introduction

Late life depression (LLD) refers to major depressive disorder (MDD) in adults 65 years or older (Lebowitz et al., 1997). LLD is typically associated with comorbid neurological, medical, and psychiatric disorders and shows a poorer clinical response relative to younger age groups (Tham et al., 2016). Aetiological mechanisms in LLD are multiple and complex, involving age- and disease-related processes, including immunological dysregulation, genetic liability, and cerebrovascular changes (Alexopoulos, 2019). The most common treatments are antidepressant medication and psychotherapy. Psychotherapy has demonstrated efficacy in LLD with comparable effect sizes to antidepressants (Cuijpers et al., 2006; Huang et al., 2015). However, antidepressant adherence rates are low in LLD, in which 11-21% do not start treatment and 33-38% discontinue treatment early (Holvast et al., 2019). Antidepressants are also associated with increased rates of adverse effects, including anticholinergic effects, such as diarrhoea, nausea, and dizziness, and might be contraindicated with other medications taken in this age group (Krause et al., 2019).

Transcranial direct current stimulation (tDCS) is a novel treatment for MDD (Woodham et al., 2021). tDCS applies a weak electrical current which modulates cortical tissue excitability, facilitating neuronal depolarization and leading to polarity-dependent neuroplasticity. The effect can extend beyond the site of stimulation to deeper brain structures, including anterior cingulate and amygdala, and is associated with changes in resting state networks (Palm et al., 2016). tDCS has demonstrated efficacy and acceptability in MDD with a course of active tDCS treatment is associated with a fourfold increased rate of clinical response (OR = 4.32, 95% CI [2.02; 9.29]) and a threefold increased rate of clinical remission (OR = 3.07, 95% CI [1.58; 5.99]) as compared to sham tDCS (Mutz et al., 2018). While age has not been found to have an impact on treatment effect (Razza et al., 2020), these meta-analyses had examined aggregate data. An individual participant data (IPD) meta-analysis synthesizes the raw

individual-level data from each study, which can improve quality and reliability statistically as well as clinically, and is considered the gold standard for meta-analyses (Riley et al., 2010).

We sought to investigate efficacy and acceptability of tDCS treatment in LLD in an individual participant data meta-analysis. We examined sham-controlled RCTs of tDCS in MDD and bipolar depression and approached authors to contribute their trial data in adults aged 65 years and over.

Methods

Registration

The protocol was registered with PROSPERO (No: CRD42019137488) and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Supplementary Figure S1).

Eligibility criteria

A systematic literature search was conducted using PsycINFO (EBSCO), MEDLINE (PubMed) and PsychSource (EBSCO) databases from the first available date to 20 October 2021, key words: ((“bipolar disorder” OR “bipolar depression” OR “major depression” OR “unipolar depression” OR “unipolar disorder”) AND (“transcranial direct current stimulation” OR “tDCS”)). References of reviews and included papers were checked for additional publications.

Inclusion criteria: (i) adults aged 65 years or older; (ii) current major depressive episode with diagnosis of MDD or bipolar disorder according to DSM or ICD criteria; (iii) sham-controlled tDCS RCT; (iv) clinician-administered depressive symptom rating scale, e.g., Hamilton Depression Rating Scale (HDRS) or Montgomery-Åsberg Depression Rating Scale (MADRS);

(v) being published in English. Exclusion criteria: (i) primary diagnosis other than MDD or bipolar disorder e.g., postpartum depression, psychotic depression, or secondary to a medical illness; (ii) co-initiation of any other form of treatment e.g., pharmacotherapy or cognitive control training.

Study selection and data extraction

Abstracts were independently assessed (KJ, RR), and differences were resolved by consensus with review (CF). Study level data were extracted, and authors were contacted for non-identifiable IPD and any information not available from the publication. Data consistency and completeness were checked (RR) and reviewed (CF).

Risk of bias assessment in individual studies

Methodological quality was assessed using Cochrane risk of bias tool (Higgins et al., 2021), which evaluates on basis of selection, performance, detection, attrition and reporting biases (Supplementary Figures S2-3).

Specification of outcomes

Outcome measures were: (1) continuous measure of depressive symptoms, estimated as difference in z-scaled mood scored from baseline to study end; (2) categorical measure of clinical response, defined as a 50% or greater improvement in depressive symptoms from baseline to study end; (3) categorical measure of clinical remission, defined as MADRS ≤10, 17-item HDRS ≤7, 21-item HDRS ≤8, 24-item HDRS ≤9 at study end (Keller, 2003); (4) acceptability, defined as number of participants who did not complete either active or sham tDCS treatment arms.

For studies which had used two or more depression rating scales, the scale used as the primary outcome was selected (Loo et al., 2010, Brunoni et al., 2013; Brunoni et al., 2017) (Supplementary Table S1). For studies with multiple treatment arms, only active and sham tDCS treatments arms were included. For studies with a crossover design, only the first phase parallel between-participants data were used.

Data analysis

A one-stage IPD Bayesian hierarchical model was conducted as the primary analysis. Hierarchical meta-analysis allows for modelling of individual-level covariates (age, sex, illness duration) and their potential interaction with treatment effects, while accounting for clustering of individual patients within a study (Higgins et al., 2021). One-stage Bayesian methods are recommended for meta-analysis of small trials with few participants and when heterogeneity is expected across trials, as uncertainty in estimates can be fully incorporated in the modelling (Lunn et al., 2013).

Individual study data sets were combined into a merged data set, with participants nested within studies. As studies used different rating scales (2 HDRS versions and MADRS), depression scores were standardised across studies by transforming them into z-scores. For variables of interest, 4 participants had missing follow-up mood outcome, and 1 participant had missing disease duration. To maintain the intention-to-treat nature of the analysis, we assumed data were missing at random, and we imputed missing disease duration and depression scores at follow-up using a well-established multivariate imputation algorithm (van Buuren and Groothuis-Oudshoorn, 2011), resulting in multiple (n=200) datasets with imputed missing values.

Mixed effects models with random trial-specific intercepts, treatment effects and co-variates were fitted to these data sets, with results combined into an average fitted model (Bürkner,

2017). Trial-specific treatment effects were assumed to follow a normal distribution, with the mean of this distribution representing pooled population-averaged treatment effect. We used weakly informative prior distributions so information in the dataset would be reflected in final posterior distributions. In particular, we used a weakly informative normal distribution (centred at zero and with a standard deviation of 1) as prior distribution of pooled treatment effect estimate, and similarly weakly informative half-Cauchy prior (scale parameter of 0.5) was used for between study variability. We used a Markov chain Monte Carlo algorithm to draw samples from the posterior distribution of parameters of interest (Bürkner, 2017).

Bayesian IPD meta-analysis was used to predict final depression score with adjustment for baseline score, age and sex. Additional analyses explored effect of disease duration and presence of treatment-resistant depression, defined by having persistent depressive symptoms despite at least 2 adequate treatment trials, and duration of illness. We considered fitting additional logistic regression models to predict planned categorical outcomes of treatment response and remission, however this was not possible due to the very limited number of participants with these outcomes (n=6 clinical response; n=3 remission). Further, all those who remitted were included in response outcomes.

Posterior distributions obtained from Bayesian model fitting allow for direct probability statements, and we report the probability of a beneficial treatment effect of tDCS, along with point estimates and 95% credible intervals for parameters of interest. Sensitivity analysis on average pooled tDCS treatment effect, as main parameter of interest, was conducted using a two-step approach with trial-level estimates of treatment effect estimated and pooled in a second level frequentist meta-analysis, and last observation carried forward instead of imputation of missing values (Viechtbauer, 2010). All analyses were conducted using R (R Core Team, 2018).

Results

Total of 4336 records were assessed, and 9 studies met inclusion and exclusion criteria. Present analysis consists of 6 studies, 43 participants (22 women) (mean age 69.3 ± 4.2 years, range 65 – 81 years), mean illness duration 145.33 ± 151.48 months, from total sample of 617 participants (Loo et al., 2010; Loo et al., 2012; Palm et al., 2012; Brunoni et al., 2013; Brunoni et al., 2017; Loo et al., 2018) (Supplementary Figure S1). Majority had unipolar depression 76.7% (n=33), and 62.7% met criteria for treatment resistant depression (n=27) (Table 1, Supplementary Table S1). There were no significant differences in demographics between tDCS (n=19) and sham control (n=24) treatment groups. There were no cases of treatment-emergent mania. Risk of bias was low for all studies (Supplementary Figures S2-S3). Authors from remaining studies had not replied to requests or were unable to share individual participant data.

Using Bayesian multilevel modelling for IPD meta-analysis, treatment with tDCS was associated with a reduction of SMD = -0.14 (95% credible interval [-0.44; 0.15]) in depression scores, relative to sham tDCS, which was not statistically significant.

Based on estimated posterior distribution of the average effect of tDCS across the studies, there is an 82% probability that tDCS treatment has at least a small effect (change in symptoms score < 0) in improving depressive symptoms in LLD. There was no evidence of significant main effects of age (change per year in SMD = 0.00 95% credible interval [-0.02;0.02]), sex (male sex SMD = -0.09 95% credible interval [-0.27;0.10]), or their interactions with treatment, though samples sizes were small. There was no evidence of significant main effect of treatment resistance or illness duration. Sensitivity analysis using a two-step IPD frequentist meta-analysis with last observation carried-forward showed similar results, with tDCS treatment associated with a reduction of -0.12 (95% confidence interval [-0.34; 0.12]) (Figure 1).

Most participants completed treatment (n=39; 90.7%). Discontinuation rates were 15.8% (3/19) for active tDCS and 4.2% (1/24) for sham tDCS, which was not statistically significant (OR = 4.3, 95% CI 0.41- 45.28, p=0.31).

Discussion

The present IPD meta-analysis demonstrates a modest but non-null effect for tDCS improving depressive symptoms in LLD. While the effect was low and did not reach statistical significance in the present IPD sample, the sample size was small, and many participants had a more treatment resistant form of depression, there is a need to conduct an RCT. As tolerability and acceptability are significant limitations of current treatments in LLD, tDCS offers a potential novel treatment option. tDCS efficacy has shown an overall effect size that is low to moderate across all ages (Mutz et al., 2018; Moffa et al., 2020; Zhang et al., 2021), and full efficacy might become evident over a longer term, from 3 - 6 months (Brunoni et al., 2017). In the present analysis, outcomes were assessed immediately following the treatment period, which consisted of 5 - 22 sessions (Loo et al., 2010; Loo et al., 2012; Palm et al., 2012; Brunoni et al., 2013; Brunoni et al., 2017; Loo et al., 2018), and it is possible that improved outcomes might been seen with a longer follow up. Moreover, dose has been identified as a significant and independent predictor (Brunoni et al., 2016). We also considered that treatment resistant depression might contribute to efficacy, although this was underpowered in the present sample (Moffa et al., 2020).

A limitation of this meta-analysis is the small sample size, which limited power to detect an effect. IPD were collated from large RCTs of all ages, but there has not yet been a large scale RCT in LLD. There is emerging evidence for tDCS as an adjunct treatment in hard-to-treat vascular LLD and using novel montages such as high definition-tDCS in LLD (Wong et al., 2019; Zanardi et al., 2021).

In summary, the present IPD meta-analysis demonstrates that tDCS has a modest but non-null effect in improving depressive symptoms in LLD. However, the sample was small, and large-scale RCTs are required to investigate efficacy of tDCS in LLD. Acknowledging these shortcomings and the modest statistical effects, the findings provide support for further investigation into the efficacy of tDCS as a treatment for LLD and vascular depression.

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Figure Legends

Figure 1. Standardised mean difference of depressive scores are presented for each study, with negative scores indicating a benefit from treatment and favouring tDCS over sham.

241 **References**

242 Alexopoulos, G. S. (2019). Mechanisms and treatment of late-life depression. *Translational*
243 *Psychiatry*, *9*(1), 1-16. https://doi.org/10.1038/s41398-019-0514-6
244 Brunoni, A. R., Moffa, A. H., Fregni, F., Palm, U., Padberg, F., Blumberger, D. M., ... & Loo,
245 C. K. (2016). Transcranial direct current stimulation for acute major depressive episodes:
246 meta-analysis of individual patient data. *British Journal of Psychiatry*, *208*(6), 522-531.
247 https://doi.org/10.1192/bjp.bp.115.164715
248 Brunoni, A. R., Moffa, A. H., Sampaio-Junior, B., Borrione, L., Moreno, M. L., Fernandes, R.
249 A., … Benseñor, I. M. (2017). Trial of electrical direct-current therapy versus escitalopram for
250 depression. *New England Journal of Medicine*, *376*(26), 2523–2533.
251 https://doi.org/10.1056/NEJMoa1612999
252 Brunoni, A. R., Valiengo, L., Baccaro, A., Zanao, T. A., de Oliveira, J. F., Goulart, A., ... &
253 Fregni, F. (2013). The sertraline vs electrical current therapy for treating depression clinical
254 study: results from a factorial, randomized, controlled trial. *JAMA Psychiatry*, *70*(4), 383-391.
255 https://doi.org/10.1001/2013.jamapsychiatry.32
256 Bürkner, P. C. (2017). brms: An R package for Bayesian multilevel models using
257 Stan. *Journal of Statistical Software*, *80*(1), 1-28. https://doi.org/10.18637/jss.v080.i01
258 Cuijpers, P., van Straten, A., & Smit, F. (2006). Psychological treatment of late-life
259 depression: a meta-analysis of randomized controlled trials. *International Journal of Geriatric*
260 *Psychiatry, 21*(12), 1139-1149. https://doi.org/10.1002/gps.1620
261 Higgins, J. P., Thomas, J., Chandler, J., Cumpston, M., Li T, Page, M. J., & Welch, V. A.,
262 (editors, 2021). Cochrane Handbook for Systematic Reviews of Interventions Version
263 6.2. *The Cochrane Collaboration*: 33-49. Available from:
264 www.training.cochrane.org/handbook
265 Holvast, F., Oude Voshaar, R. C., Wouters, H., Hek, K., Schellevis, F., Burger, H., &
266 Verhaak, P. F. (2019). Non-adherence to antidepressants among older patients with
267 depression: a longitudinal cohort study in primary care. *Family Practice*, *36*(1), 12-20.
268 https://doi.org/10.1093/fampra/cmy106

Huang, A. X., Delucchi, K., Dunn, L. B., & Nelson, J. C. (2015). A systematic review and meta-analysis of psychotherapy for late-life depression. *The American Journal of Geriatric Psychiatry*, *23*(3), 261-273. https://doi.org/10.1016/j.jagp.2014.04.003

Keller, M. B. (2003). Past, present, and future directions for defining optimal treatment outcome in depression: remission and beyond. *JAMA*, *289*(23), 3152-3160. https://doi.org/10.1001/jama.289.23.3152

Krause, M., Gutsmiedl, K., Bighelli, I., Schneider-Thoma, J., Chaimani, A., & Leucht, S. (2019). Efficacy and tolerability of pharmacological and non-pharmacological interventions in older patients with major depressive disorder: A systematic review, pairwise and network meta-analysis. *European Neuropsychopharmacology*, *29*(9), 1003-1022. https://doi.org/10.1016/j.euroneuro.2019.07.130

Lebowitz, B. D., Pearson, J. L., Schneider, L. S., Reynolds III, C. F., Alexopoulos, G. S., Bruce, M. L., ... & Parmelee, P. (1997). Diagnosis and Treatment of Depression in Late Life: Consensus Statement Update [Consensus Statement]. *JAMA*, *278*(14), 1186-1190. https://doi.org/10.1001/jama.1997.03550140078045

Loo, C. K., Alonzo, A., Martin, D., Mitchell, P. B., Galvez, V., & Sachdev, P. (2012). Transcranial direct current stimulation for depression: 3-week, randomised, sham-controlled trial. *British Journal of Psychiatry*, *200*(1), 52-59. https://doi.org/10.1192/bjp.bp.111.097634

Loo, C. K., Sachdev, P., Martin, D., Pigot, M., Alonzo, A., Malhi, G. S., ... & Mitchell, P. (2010). A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *International Journal of Neuropsychopharmacology*, *13*(1), 61-69. https://doi.org/10.1017/S1461145709990411

Loo, C., Husain, M., Mcdonald, W., Aaronson, S., O'Reardon, J., Alonzo. A., … Lisanby, S. (2018). International randomized-controlled trial of transcranial Direct Current Stimulation in depression. *Brain Stimulation*, *11*(1), 125-133. https://doi.org/10.1016/j.brs.2017.10.011

Lunn, D., Barrett, J., Sweeting, M., & Thompson, S. (2013). Fully Bayesian hierarchical modelling in two stages, with application to meta-analysis. *Journal of the Royal Statistical Society. Series C, Applied Statistics*, *62*(4), 551-572. https://doi.org/10.1111/rssc.12007

297 Moffa, A. H., Martin, D., Alonzo, A., Bennabi, D., Blumberger, D. M., Benseñor, I. M., ... &
298 Brunoni, A. R. (2020). Efficacy and acceptability of transcranial direct current stimulation
299 (tDCS) for major depressive disorder: an individual patient data meta-analysis. *Progress in*
300 *Neuro-Psychopharmacology and Biological Psychiatry*, *99*, 109836.
301 https://doi.org/10.1016/j.pnpbp.2019.109836
302 Mutz, J., Edgcumbe, D. R., Brunoni, A. R., & Fu, C. H. (2018). Efficacy and acceptability of
303 non-invasive brain stimulation for the treatment of adult unipolar and bipolar depression: a
304 systematic review and meta-analysis of randomised sham-controlled trials. *Neuroscience &*
305 *Biobehavioral Reviews*, *92*, 291-303. https://doi.org/10.1016/j.neubiorev.2018.05.015
306 Palm, U., Hasan, A., Strube, W., & Padberg, F. (2016). tDCS for the treatment of
307 depression: a comprehensive review. *European Archives of Psychiatry and Clinical*
308 *Neuroscience*, *266*(8), 681-694. https://doi.org/10.1007/s00406-016-0674-9
309 Palm, U., Schiller, C., Fintescu, Z., Obermeier, M., Keeser, D., Reisinger, E., ... & Padberg,
310 F. (2012). Transcranial direct current stimulation in treatment resistant depression: a
311 randomized double-blind, placebo-controlled study. *Brain Stimulation*, *5*(3), 242-251.
312 https://doi.org/10.1016/j.brs.2011.08.005
313 Razza, L. B., Palumbo, P., Moffa, A. H., Carvalho, A. F., Solmi, M., Loo, C. K., & Brunoni, A.
314 R. (2020). A systematic review and meta-analysis on the effects of transcranial direct current
315 stimulation in depressive episodes. *Depression and Anxiety*, *37*(7), 594-608.
316 https://doi.org/10.1002/da.23004
317 Riley, R. D., Lambert, P. C., & Abo-Zaid, G. (2010). Meta-analysis of individual participant
318 data: rationale, conduct, and reporting. *BMJ*, *340*(c221).https://doi.org/10.1136/bmj.c221
319 Tham, A., Jonsson, U., Andersson, G., Söderlund, A., Allard, P., & Bertilsson, G. (2016).
320 Efficacy and tolerability of antidepressants in people aged 65 years or older with major
321 depressive disorder–a systematic review and a meta-analysis. *Journal of Affective*
322 *Disorders*, *205*, 1-12. https://doi.org/10.1016/j.jad.2016.06.013

van Buuren, S., & Groothuis-Oudshoorn, K. (2011). mice: Multivariate Imputation by Chained Equations in R. *Journal of Statistical Software*, *45*(3), 1–67. https://doi.org/10.18637/jss.v045.i03

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*, *36*(3), 1-48. https://doi.org/10.18637/jss.v036.i03

Woodham, R., Rimmer, R. M., Mutz, J., & Fu, C. H. (2021). Is tDCS a potential first line treatment for major depression?. *International Review of Psychiatry*, *33*(3) 1-16. https://doi.org/10.1080/09540261.2021.1879030

Wong, H. L., Chan, W. C., Wong, Y. L., Wong, S. N., Yung, H. Y., Wong, S. M. C., & Cheng, P. W. C. (2019). High-definition transcranial direct current stimulation—An open-label pilot intervention in alleviating depressive symptoms and cognitive deficits in late-life depression. *CNS Neuroscience & Therapeutics*, *25*(11), 1244-1253. https://doi.org/10.1111/cns.13253

Zanardi, R., Poletti, S., Prestifilippo, D., Attanasio, F., Barbini, B., & Colombo, C. (2020). Transcranial direct current stimulation: A novel approach in the treatment of vascular depression. *Brain Stimulation*, *13*(6), 1559-1565. https://doi.org/10.1016/j.brs.2020.08.013

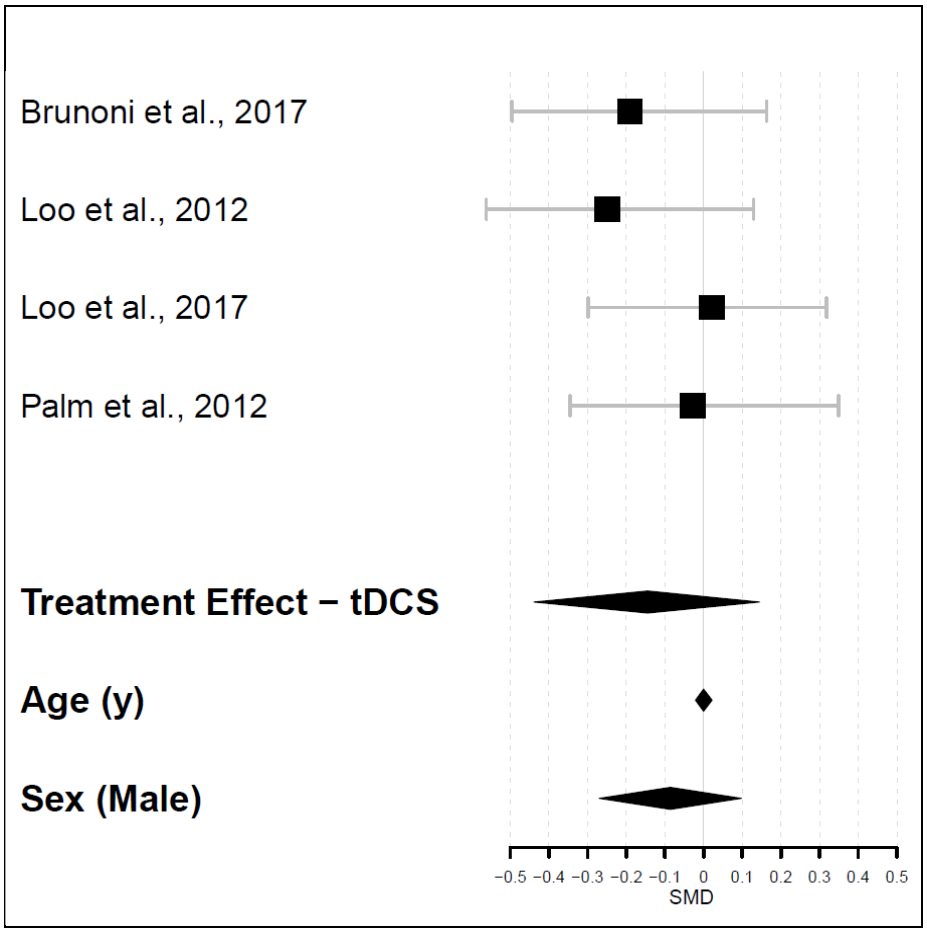
Zhang, R., Lam, C. L., Peng, X., Zhang, D., Zhang, C., Huang, R., & Lee, T. M. (2021). Efficacy and acceptability of transcranial direct current stimulation for treating depression: A meta-analysis of randomized controlled trials. *Neuroscience & Biobehavioral Reviews*, *126*, 481-490. https://doi.org/10.1016/j.neubiorev.2021.03.026

Table 1. Clinical and demographic characteristics

	Average	**Loo (2010)**	**Loo (2012)**	**Palm (2012)**	**Brunoni (2013)**	**Brunoni (2017)**	**Loo (2017)**
Total sample size	43 (22)	1 (0)	5 (2)	7 (5)	4 (2)	7 (3)	19 (10)
Age (yrs)	69.3 (4.22)	65.0	70.2 (5.17)	70 (4.83)	65.0 (0.00)	68.3 (3.45)	70.4 (4.29)
Age range	65-81	65	65-78	65-79	65	65-73	65-81
Education (yrs)	16.72 (3.57)	NR	NR	NR	NR	14.3 (3.62)	18 (2.89)
Unipolar depression	33	1	4	7	4	6	11
Medication (n)	15	0	1	7	0	2	5
Duration of illness (months)	145.33 (151.48)	6	64 (81.28)	219.4 (110.57)	11 (9.42)	87.17 (169.68)	213.89 (166.00)
Treatment resistant depression (TRD)	27	0	1	7	0	3	16

Number of participants is presented with number of female participants in parenthesis. Mean values are presented for each variable with standard deviation in parenthesis. As there was one participant from Loo et al. (2010), there is no standard deviation for age and no age range.

Figure 1.


Brunoni et al., 2017
Loo et al., 2012
Loo et al., 2017
Palm et al., 2012
Treatment Effect − tDCS
Age (y)
Sex (Male)
−0.5 −0.4 −0.3 −0.2 −0.1 0 0.1 0.2 0.3 0.4 0.5
SMD

Supplementary Table S1

Table S1. Summary of the included studies

Study	**Loo et al (2010)**	**Loo et al (2012)**	**Palm et al (2012)**	**Brunoni et al (2013)**	**Bru**
Study design	RCT	RCT	RCT, crossover	4-arm RCT	3-a
Main inclusion	MDD	MDD ≥3 years	MDD	MDD, low suicide risk, AD free	MD
Depression cut off	MADRS ≥ 20	MADRS ≥ 20	HDRS-24 ≥ 18	HDRS-17 ≥ 17	HDI
Bipolar disorder	Excluded	Allowed	Excluded	Excluded	Exc
Main exclusion criteria	Other Axis I disorders, Failure of ECT, neurological disorders	Other Axis I disorders, ECT failure, neurological disorders	Other Axis I disorders, suicidality, neurological disorders	Other Axis I disorders, Axis II disorders, neurological disorders	Oth Axis neu (An
Primary outcome measure	MADRS	MADRS	HDRS-24	MADRS	HDI
Age range, years	18-65	23-78	36-79	18-65	18-
Total Sample Size (n)	40	60	22	120	245
<u>tDCS characteristics</u>					
Device	Eldith DC	Eldith DC	Eldith DC	Chattanooga lonto	Sot
Anode	F3	pF3	F3	F3	F3
Cathode	RSO	F8	FP2	F4	F4
Frequency, No sessions	5	15	10	10	22
Weeks, stimulation	2	3	2*	4	10
Current density	0.29	0.57	0.28-0.57	0.8	0.8
Session duration (mins)	20	20	20	30	30
Total charge (mA)	1	2	1-2	2	2

AD= antidepressant, HDRS = Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale; all studies completed an intention-to-treat analysis, *crossover +2.

Figure S1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only

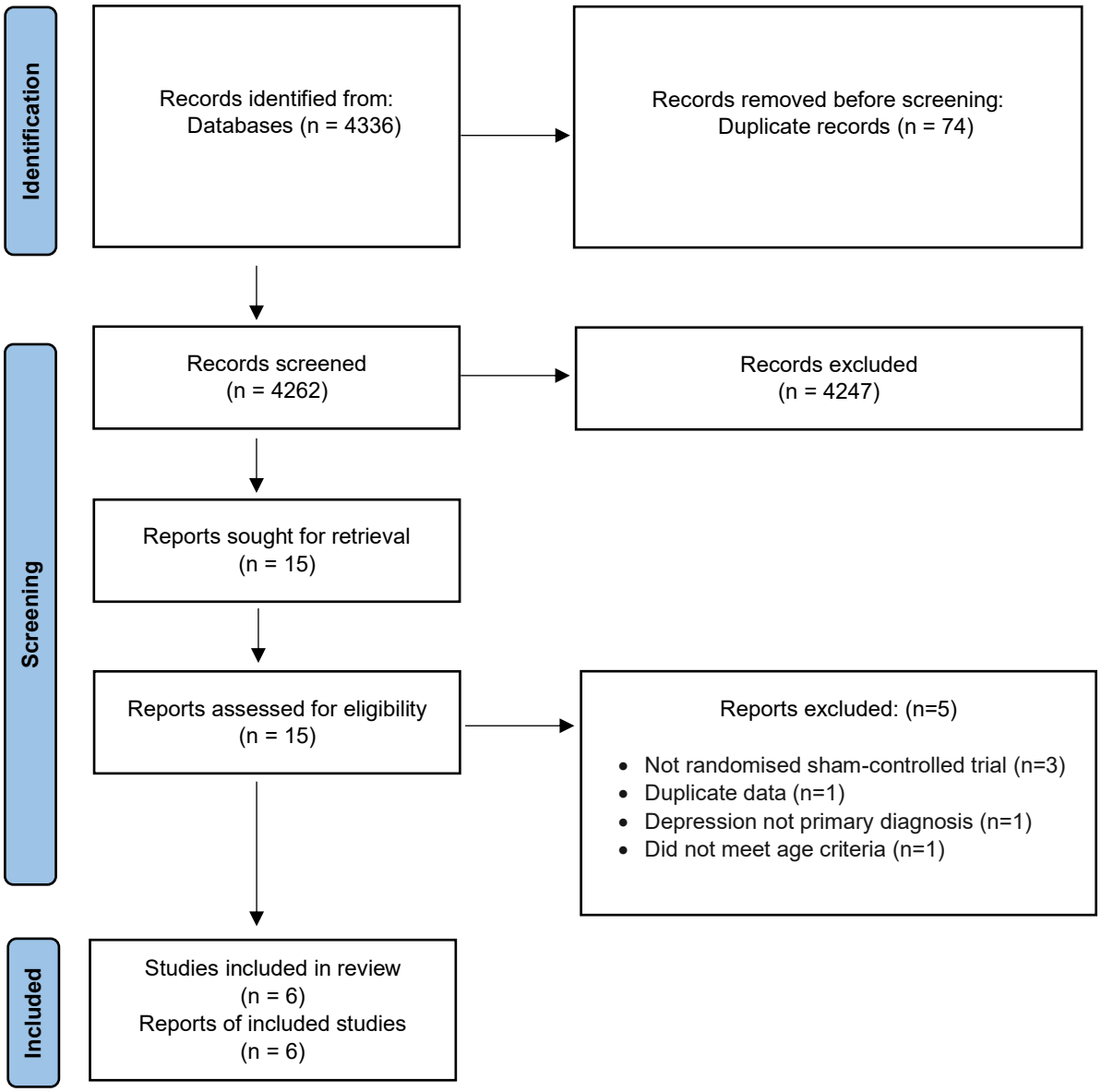


Figure S2. Cochrane Risk of Bias Graph

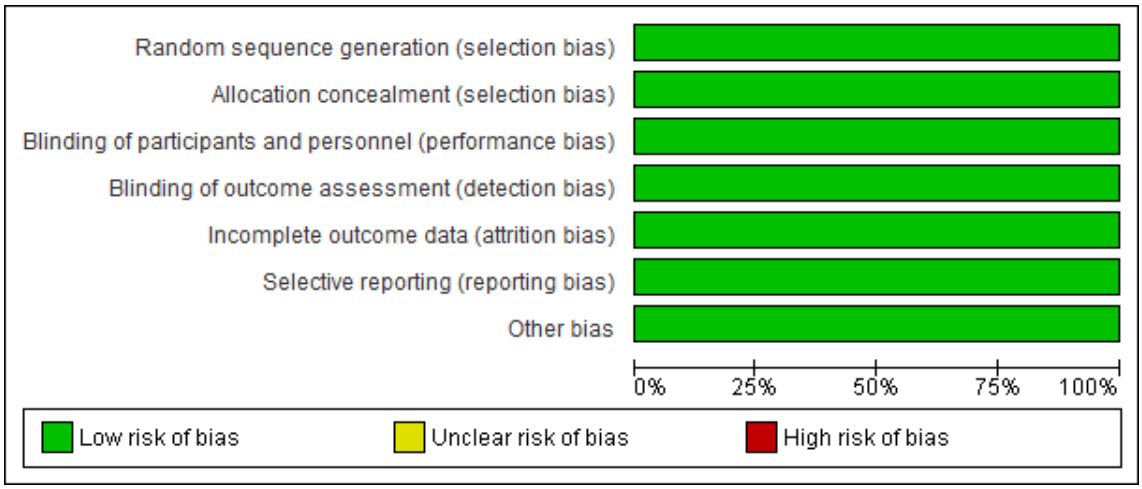
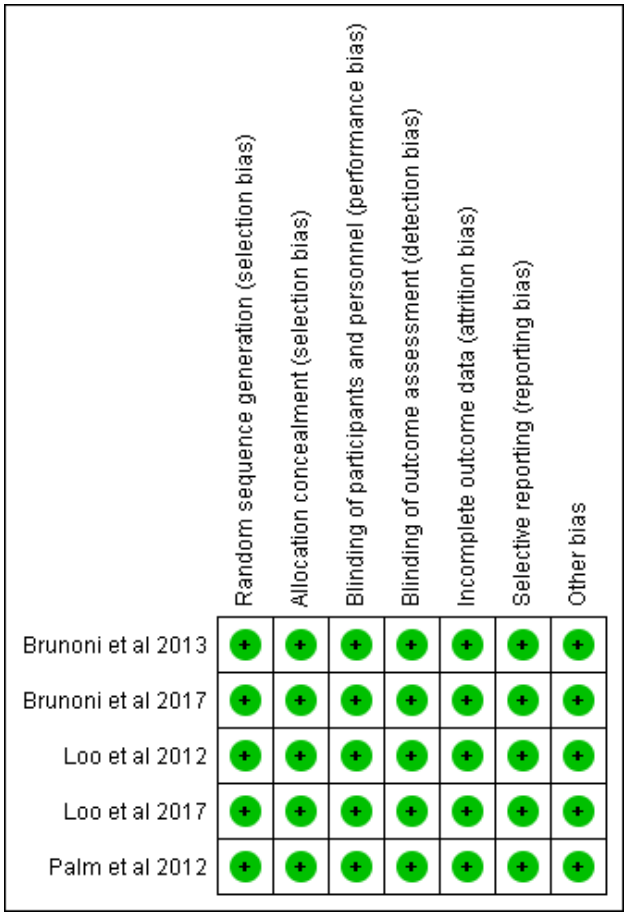


Figure S3. Risk of Bias Summary



Cochrane Risk of Bias Tool – Supporting evidence

Brunoni et al., 2017

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: 'patients were randomly assigned in a 2:3:3 ratio, with the use of a permuted-block design'
Allocation concealment (selection bias)	Low Risk	quote: using 'a computer-generated list, to receive one of three regimens'
Blinding of participants and personnel (performance bias)	Low Risk	Comment: double blind study: Quote: 'used fully automated devices that perform active or sham tDCS according to a randomized stimulation code'
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: 'Patients correctly guessed their trial-group assignment to escitalopram but not to active tDCS'.
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: 'Patients correctly guessed their trial-group assignment to escitalopram but not to active tDCS'.
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: 'missing data will be handled using an ITT approach
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	Low Risk	Quote: missing data will be handled using an ITT approach
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Loo et al., 2017

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: 'Participants were randomly assigned by a computer-generated random number sequence to active or sham tDCS with permuted-block randomization. Randomization was stratified according to . . .[diagnosis]'
Allocation concealment (selection bias)	Low Risk	Quote: 'Participants were randomly assigned by a computer-generated random number sequence to active or sham tDCS with permuted-block randomization. Randomization was stratified according to . . .[diagnosis]'
Blinding of participants and personnel (performance bias)	Low Risk	Quote: 'All participants, tDCS treaters… were blinded to the participants' tDCS group allocation in the RCT phase. The blinding was

		maintained until the entire study was completed'.
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: 'All participants … were blinded to the participants' tDCS group allocation in the RCT phase. The blinding was maintained until the entire study was completed'.
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: 'All … study raters were blinded to the participants' tDCS group allocation in the RCT phase'
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: 'using a mixed effects repeated measures (MERM) analysis. . . more appropriately handle missing data relative to more traditional repeated measures analytical methods'
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	Low Risk	Quote: 'using a mixed effects repeated measures (MERM) analysis. . . more appropriately handle missing data relative to more traditional repeated measures analytical methods'
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Brunoni et al., 2013

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: "A assistant not directly involved in other aspects of the trial performed a 1:1:1:1 permuted block randomization."
Allocation concealment (selection bias)	Low Risk	Quote: '"...the allocation was concealed using a central randomization method."
Blinding of participants and personnel (performance bias)	Low Risk	Quote: "...patients were blinded to the treatment"; "..., because the nurses were not blinded to the intervention, their interaction with the participants was minimal"
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: " The raters and patients were blinded to the treatment"
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: " The raters and patients were blinded to the treatment"
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: "Analyses were conducted in the intention-to-treat sample according to last observation carried forward through the time points. Missing data were considered to be at random" Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	N/A	work focused in the efficacy of tDCS during the acute phase of the major depressive episode

Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Palm et al., 2012

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: “patients were randomized in two groups.”
Allocation concealment (selection bias)	Low Risk	Quote: “...using a PC-generated random number list”. Concealment confirmed by the authors.
Blinding of participants and personnel (performance bias)	Low Risk	“double blind”; “Two indistinguishable CE-certified programmable constant current DCStimulator were used for active and placebo tDCS. ” Personnel blinding confirmed by authors
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: “double blind”.
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: “rating scales and cognitive tests were administered by experienced raters blind to treatment conditions..."
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: “Twenty patients completed the study, two dropped out because of personal reasons. The data of all 22 subjects were included in the analysis (last observation carried forward)."
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	N/A	Comment: work focused in the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Loo et al., 2012

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: “participants were stratified by gender and age and randomly assigned by a computergenerated random sequence”
Allocation concealment (selection bias)	Low Risk	Quote: “The treatment assignment was indicated by a code on study treatment sheets, which were concealed from raters.”
Blinding of participants and personnel (performance bias)	Low Risk	Quote: “ ...participants(...) masked to group allocation.”
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote: “"...participants (...) masked to group allocation."
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: “... raters masked to group allocation

Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote:" Intention-to-treat last observation carried-forward scores were used for the analyses". Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	N/A	Comment: work focused in the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Loo et al., 2010

Entry	Judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Quote: “Subjects were stratified by age and gender and then randomly assigned to active or sham treatment groups
Allocation concealment (selection bias)	Low Risk	Comment: allocation concealment confirmed by the authors
Blinding of participants and personnel (performance bias)	Low Risk	Quote: “with (...) subjects blind to treatment group assignment.”; Quote: “The switching on and off of the current was programmed into the stimulator and did not require intervention by the operator. The machine was placed behind the subjects’ heads so that they were unable to see the readout on the front panel of the stimulator..” Personnel blinding confirmed by the authors
Blinding of outcome assessment (detection bias; patient-reported outcomes)	Low Risk	Quote:" with (...) subjects blind to treatment group assignment."
Blinding of outcome assessment (detection bias; all-cause mortality)	Low Risk	Quote: "All ratings were conducted by a psychiatrist who was blinded to treatment condition..."
Incomplete outcome data addressed (attrition bias; short-term (2-6 weeks))	Low Risk	Quote: “Intention-to-treat last-observation carried-forward scores were used for the analyses" Comment: measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups
Incomplete outcome data addressed (attrition bias; long-term (> 6 weeks))	N/A	Comment: work focused on the efficacy of tDCS during the acute phase of the major depressive episode
Selective reporting (reporting bias)	Low Risk	All clinical rating scales and cognitive tasks listed in Methods were reported.

Appendix 8. *Ethics Approvals*

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Professor Cynthia H.Y. Fu
Professor of Affective Neuroscience
University of East London
University of East London
School of Psychology
Water Lane
E15 4LZ

Email: hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

30 August 2019

Dear Professor Fu

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Acceptability and feasibility of transcranial direct current stimulation therapy as a community-based treatment for major depression**
IRAS project ID:	[redacted]
REC reference:	
Sponsor	**University of East London**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Decision - Ethics ETH2021-0180: Prof Cynthia Fu (NHS)

ResearchUEL <haplo@uel.ac.uk>
Thu 6/10/2021 9:13 AM
To: Rachel Woodham <R.Woodham@uel.ac.uk>

ResearchUEL

Dear Cynthia

Application ID: ETH2021-0180

Original application ID: A1950

Project title: Acceptability and feasibility of transcranial direct current stimulation therapy as a community-based treatment for major depression

Lead researcher: Prof Cynthia Fu

Researcher: Miss Rachael Rimmer

Researcher: Miss Rachel Woodham

The Committee's response is based on the protocol described in the application form and supporting documentation.

Your project has received ethical approval for 4 years from the approval date.

If you have any questions regarding this application please contact your supervisor or the secretary for the University Research Ethics Sub-Committee.

Approval has been given for the submitted application only and the research must be conducted accordingly.

Should you wish to make any changes in connection with this research project you must complete 'An application for approval of an amendment to an existing application'.

Approval is given on the understanding that the UEL Code of Practice for Research and the Code of Practice for Research Ethics is adhered to.

Any adverse events or reactions that occur in connection with this research project should be reported using the University's form for Reporting an Adverse/Serious Adverse Event/Reaction.

The University will periodically audit a random sample of approved applications for ethical approval, to ensure that the research projects are conducted in compliance with the

consent given by the Research Ethics Committee and to the highest standards of rigour and integrity.

Please note, it is your responsibility to retain this letter for your records.

With the Committee's best wishes for the success of the project

Yours sincerely

Fernanda Silva

Administrative Officer for Research Governance

Ethics ETH2021-0180: Prof Cynthia Fu (NHS)

From: Catherine Hitchens <C.Hitchens@uel.ac.uk> on behalf of Research Ethics <researchethics@uel.ac.uk>
Sent: 11 March 2022 14:30
To: Rachael Michelle RIMMER <u1529350@uel.ac.uk>
Cc: Cynthia Fu <C.Fu@uel.ac.uk>; Richard Bottoms <R.Bottoms@uel.ac.uk>; Research Ethics <researchethics@uel.ac.uk>
Subject: RE: Change of Project Title on PhD Manager

Dear Rachael,

Thank you for your email.

I confirm that you have ethical approval for your PhD research project, as you are named as a researcher on ethics application form ETH2021-0180.

I understand that the research title on the ethics application form ETH2021-0180, cannot be amended to the new title of your thesis, for the reasons that you have given in your below email.

Please take this email as confirmation that on this occasion you are not required to submit an ethics application form to the University Ethics and Integrity Sub-Committee (EISC) to amend the title of your thesis.

Kind regards,

Catherine Hitchens
Ethics, Integrity and Compliance Manager
University of East London
KD2.10, Docklands Campus
4-6 University Way
London, E16 2RD
[redacted]
Monday – Friday 8.30am - 4.30pm
researchethics@uel.ac.uk

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