School of Population Health

Transcranial direct current stimulation for Obsessive-Compulsive Disorder: An examination of treatment effectiveness and acceptability.

Peta Evelyn Green

ORCID: 0000-0003-0039-118X

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Declarations

To the best of my knowledge and belief, this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis does not contain any material that has been accepted for the award of any other degree or diploma in any University.

Thesis Format Statement

This dissertation has been prepared in the Curtin University 'hybrid thesis' format. Chapters One, Five and Seven provide context and reflection on the work. Chapters Two, Three, Four, and Six have been written and prepared as independent publications. As such, there is some unavoidable repetition and overlap in the literature cited. Each publication adheres to individual journal requirements, although the formatting of this thesis generally conforms to the Publication Manual of the American Psychological Association, 7th Edition. To assist with readability of this dissertation, tables and figures are placed in-text and references for all chapters are provided at the end of the thesis.

Human Ethics

The research presented and reported in this thesis was conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2007) – updated March 2014. The proposed research study received human research ethics approval from the Curtin University Human Research Ethics Committee (EC00262), Approval Number # HRE2020-0266.

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Impact of COVID-19 Statement

The following statement outlines how my research and submission for examination have been impacted by the COVID-19 pandemic and related restrictions. All impacts have been confirmed by my PhD supervisors.

In March 2020, in response to the COVID pandemic, Curtin temporarily closed its Bentley campus to all face-to-face activities. Concurrently, the Western Australian government introduced a series of regulations limiting the contact between people which impacted face-to-face clinical research and data collection. I no longer had access to study spaces or the Psychology Clinic where this research was to be conducted. I was unable to recruit participants, given the research involved face-to-face interventions. In March 2021, measures were put in place to allow candidates to have limited access to the campus for the purpose of continuing their research in exceptional circumstances. This allowed me to continue the trial with currently enrolled treatment resistant OCD cases, but not to recruit further participants for the planned RCT. There were several limited periods of face-to-face contact allowed, interspersed with further snap lockdowns across the state, in an attempt by the state government to contain the spread of COVID-19. Overall, the stop-start process of recruitment to the RCT, combined with limited participant uptake due to participant concerns about receiving the sham/placebo intervention, lead to a decision to cease recruitment for this trial, given it was no longer feasible within the timeframe for completion of the PhD course. A decision was made to instead focus efforts on understanding the acceptability and expectations concerning tDCS compared with a range of other treatment approaches, as this survey was able to be conducted online and was not impacted by COVID19 restrictions.

Abstract

Obsessive-compulsive disorder (OCD) is a debilitating disorder with an approximate lifetime prevalence of 1–3%. Despite advances in leading treatment modalities, including pharmacotherapy and psychotherapy, approximately 40 - 60% of people with OCD will not experience clinically significant improvement or will relapse. Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, has been explored mostly in relation to treatment-resistant depression, but there is a growing body of evidence to suggest that tDCS may improve OCD.

The aim of this thesis was to explore the therapeutic potential of tDCS for OCD symptoms. A systematic review of the literature involving randomised controlled trials (RCTs) of tDCS for OCD was conducted (study one). The quality of reporting was evaluated using the CONSORT (Consolidating Standards of Reporting Trials) statement, and the outcomes of tDCS as a therapeutic tool for OCD were examined. Study one revealed that despite numerous claims in the literature describing tDCS as a promising approach, only two trials demonstrated significant between group (active vs. Sham tDCS) differences. Among the RCTs included in the review, there were low levels of overall compliance with the CONSORT standards, highlighting the need for improvement in reporting. The outcomes of study one also highlighted the need for a standardised protocol for conducting research involving tDCS for OCD.

A treatment protocol was developed to clearly define the methodology for conducting a double-blind randomised sham-controlled study for tDCS for OCD. This included identifying the electrode type, size, electrolyte medium, stimulation sites and parameters, and how the electrodes were secured to the scalp. Patient

demographics, setting (inpatient/outpatient), and information concerning tDCS operators were also identified as essential to enable replication of the study and improve internal and external validity of the findings. The protocol also included an adequate follow-up period to assess whether treatment gains are maintained over time. A study was then proposed that included a double-blind randomised sham-controlled tDCS for OCD, with follow-up periods of 3-, and 6-months post intervention, to address the shortcomings of earlier research designs. This resulted in a published protocol for a double-blind randomised sham-controlled trial of tDCS for OCD to examine the therapeutic potential of tDCS for OCD symptoms (Chapter 3).

Study two (Chapter 4) sought to establish the acceptability and expectations of tDCS as a potential future treatment approach amongst OCD clients. A survey of 200 participants with moderate to severe OCD found that most participants would not be willing to try tDCS until there was more evidence that it was safe and effective. A relationship was observed between the acceptability of tDCS and symptom duration and severity that suggested those with treatment refractory OCD would be willing to try tDCS if it was available.

Study three was intended to be a double-blind randomised controlled trial involving tDCS for OCD. However, we were unable to recruit participants and after 18 months we decided to discontinue recruitment efforts for the trial. Recruitment was impacted by the COVID-19 pandemic with multiple stop-starts due to community lockdowns, but also the design itself was a barrier to recruitment. Whilst there was no promise that active tDCS would work, the risk of receiving no active tDCS (i.e., sham) came at a perceived high cost of attending the clinic for 15 one-hour sessions over a six-month period. The findings of the survey (i.e., that those with longer duration and severity of symptoms were willing to try tDCS) combined

with the challenges with recruitment for the RCT, led to the development of study three.

Study three (Chapter six) involved a case series to evaluate the effectiveness of a dual protocol approach to treatment resistant participants with OCD. The case series was designed to pilot a dual protocol approach of ERP combined concurrently with tDCS for treatment refractory OCD. The results were promising in the short-term with four participants achieving clinically significant change in OCD symptoms, meeting the criteria for remission, and three achieving a partial response. These treatment gains, however, were not upheld over time highlighting the need for better maintenance protocols and extended follow-up periods in all future trials.

Taken together, the results from the four studies support the continued investigation of tDCS combined with ERP for those with OCD who do not respond or are seeking an alternative treatment option to current leading treatment approaches. Our findings demonstrate that the quality of reporting for tDCS studies needs to be improved, and there is a need for the longer-term monitoring of OCD symptoms following any intervention involving tDCS in future trials. Whilst the results from the case series indicate that tDCS-ERP significantly reduces symptoms in treatment refractory OCD, the treatment gains were not maintained over time. This highlighted one of the shortfalls of previous studies that have reported positive results without an adequate follow-up. Further, despite numerous claims describing tDCS as a promising approach, there is insufficient evidence to support such claims. As such, tDCS should not be integrated into standard psychological care without further empirical support and remains a treatment for further investigation.

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Chapter 1. Understanding Current Obsessive-Compulsive Disorder Treatments

What is Obsessive-Compulsive Disorder?

Obsessive-compulsive disorder (OCD) is defined by the Diagnostic and Statistical Manual of Mental Disorders (5th ed., text rev.; DSM-5; American Psychological Association, 2022) and the World Health Organisation's International Statistical Classification of Diseases and Related Health Problems *(11th ed,; ICD-11; World Health Organisation, 2019)* as a debilitating psychiatric disorder that consists of obsessions and/or compulsions. Obsessions are recurrent, persistent, intrusive, and unwanted thoughts, images, or impulses/urges that are associated with anxiety. In an attempt to ignore, suppress, or neutralise these distressing obsessions, individuals perform compulsions. Compulsions are repetitive behaviours or mental acts typically performed to restore a sense of safety, or according to a rigid set of rules or to achieve a sense of "completeness" or a feeling of "just right" (World Health Organisation, 2019). For a diagnosis of OCD, there needs to be a presence of obsessions and/or compulsions that cause clinically significant distress and impact negatively on functioning (American Psychological Association, 2022).

Prevalence, Onset, Risk, and Course of OCD

It is estimated that approximately 114 million people experience OCD worldwide (Williams et al., 2017), with an approximate lifetime prevalence of 1.3% (Fawcett et al., 2020). The average age of onset is 19.5 years, with 25% of cases starting at 14 years of age. Males develop OCD at a younger age than females, but women are 1.6 times more likely to experience OCD than men, with a lifetime prevalence of 1.5% compared to 1.0% in men (Fawcett et al., 2020). The risk of OCD amongst first-degree relatives of adults with OCD is approximately two times higher than first-degree relatives of those without the disorder; however, the rate of

OCD amongst first-degree relatives increases 10-fold if the onset of OCD occurred in childhood or adolescence (American Psychological Association, 2022). Familial transmission is due in part to genetic factors and environmental factors such as adverse perinatal events, psychological trauma (e.g., physical and sexual abuse) and neurological trauma may modify the expression of risk genes and, hence, trigger the manifestation of obsessive–compulsive behaviours (Brander et al., 2016). The sudden onset of obsessive-compulsive symptoms in children has been associated with different environmental factors including various infectious agents and a postinfectious autoimmune syndrome (American Psychological Association, 2022).

OCD can follow an acute, episodic, or chronic course. An episodic course involves symptoms that are present only during an episode, whereas a chronic course involves symptoms that may wax and wane in severity but persist without remission (Sharma & Math, 2019). The typical course of chronic OCD spans several decades. For some people, the type of symptoms can change over time, but for others they remain the same or have the same symptom type. For example, an individual may continue checking behaviour, but the focus of the checking may shift (Mataix-Cols et al., 2002). The duration of OCD as an untreated illness is one of the highest for any severe mental disorder (Fineberg et al., 2019), and most adults with OCD have been suffering for at least 10 years before seeking treatment (García-Soriano et al., 2014). This latency to treatment is influenced by multiple socio-demographic and clinical characteristics including age, early onset of OCD symptoms, presence of contamination/cleaning symptoms, and employment status (da Conceição Costa et al., 2022). Addressing the barriers to diagnosis and treatment would give rise to improved engagement and outcomes.

Impacts on Functioning

When left untreated, OCD follows a chronic course and negatively impacts upon social, family, and occupational functioning and is associated with reduced quality of life (Abramowitz et al., 2009; Riesel, 2019). OCD symptoms can be so severe that they can negatively impact on multiple areas of a person's life, disrupting education, limiting employment and career development, and damaging relationships with loved ones and friends (American Psychological Association, 2022). The impact of OCD is partly driven by the time spent on obsessions and performing compulsions. For example, an individual compelled to perform checking behaviours will often not be able to leave the house on time to meet commitments and will avoid situations that may trigger obsessions or compulsions. Compared with other anxiety related disorders, OCD is associated with more marked social and work-related occupational impairment (American Psychological Association, 2022).

Specific obsessions may be associated with specific impacts on functioning. For example, obsessions about harm can result in relationships with family and friends being perceived as risky and lead to relationship avoidance (American Psychological Association, 2013, 2022). Obsessions about symmetry and the need for things to feel "just right" can make it difficult, if not impossible, to meet the deadlines associated with school or work projects and increases the risk of failure or job loss. Some compulsive behaviours can have serious health consequences (American Psychological Association, 2013). For example, obsessions about contamination can result in avoidance of help-seeking for fear of exposure to germs in a medical setting. When excessive washing is involved, dermatological problems (e.g., painful skin lesions) can develop, negatively impacting upon health-related quality of life. In some cases, the individual with contamination fears may impose

extreme hygiene measures on other family members, thereby impacting relationships and family functioning. Occasionally, fear of contamination can interfere with treatment for OCD when medications are not taken because they are considered to be contaminated (American Psychological Association, 2013).

When a person with OCD has poor insight about their disorder, they may not realise that their fears and worries are excessive or that they need help (De Avila et al., 2019). OCD also impacts on the lives of family and friends who unknowingly become caught up in compulsions (Boeding et al., 2013). Family and friends may offer reassurance, avoid things/situations that they think may trigger their loved one/friend's OCD, or may actively perform compulsions on behalf of the person (i.e., checking appliances are off, doors are locked, and in extreme cases - removing all clothes before entering the house; Boeding et al., 2013).

The occurrence of OCD in childhood or adolescence is associated with developmental difficulties (American Psychological Association, 2013). Childhood OCD has been associated with the avoidance of social engagement with peers, inability to leave home and live independently, limited social relationships, and a lack of autonomy (Veale et al., 2009). In some cases, the family dynamics may be impacted when OCD-related rules are imposed on family members by the OCD sufferer (for example, no visitors for fear of contamination; American Psychological Association, 2013). OCD presents a considerable burden to the individual, their family, health services, and society. It is therefore important to provide effective intervention.

Psychological Approaches for OCD

There are a range of psychological theories that have been put forward over the years for OCD, however, only the leading evidence-based theories and treatment approaches will be reviewed in the following sections.

Behavioural Theory of OCD.

Mowrer proposed a two-stage theory to explain how fear and avoidance behaviour of OCD is developed and maintained (Mowrer, 1960). Mowrer posited that fear acquisition can occur when a previously unconditioned stimulus is repeatedly combined with a situation that elicits distress. When confronted by this now conditioned stimulus, the individual engages in behaviours that initially reduce distress associated with the stimulus, thus negatively reinforcing the behaviour and leading to its repeated use. With OCD, these behaviours include repeated compulsions or rituals (e.g., avoidance, reassurance).

Behavioural Interventions for OCD

Mowrer's theory informed several behavioural interventions designed to reduce obsessional anxiety/distress with varying degrees of success.

Systematic Desensitisation. Wolpe (1969) developed 'systematic desensitisation' which involved applying relaxation techniques during exposure to the feared situations/thoughts/objects causing the distress. Compulsions were not directly addressed during this intervention, as it was thought that the pairing of the feared stimuli with relaxation would reduce distress and the person would not need to perform the compulsion (Wolpe, 1990). Systematic desensitisation for OCD had limited success and is not currently a first-line therapeutic option (Foa, 2010).

Aversion Therapy. Another behavioural treatment proposed for OCD was aversion therapy, which used punishment to change behaviour (Mastellone, 1974).

The underlying theory of aversion therapy suggested that pairing a compulsive behaviour with an unpleasant experience (e.g., snapping a rubber-band on the wrist) whenever an obsessive-thought occurred, would result in the behaviour being extinguished (see Mastellone, 1974 for more information). Whilst aversion therapy has been effective in some settings (e.g., using the drug disulfiram to induce nausea in alcohol dependence), it was not effective for OCD (Lam & Steketee, 2001). Another method of aversive therapy involved shouting "stop" as soon an intrusive thought occurred, but this technique also had limited success (Stern, 1978).

Exposure and Response Prevention. Exposure and response prevention (ERP) was initially developed by Meyer in the 1960s and was based on Wolpe's systematic desensitisation technique. Meyer introduced another component to the desensitisation technique by preventing the individual from leaving the feared situation or performing their usual rituals to relieve their distress. This behavioural treatment approach became known as ERP. ERP involves the development of a hierarchy of exposure exercises (from least to most distressing situation, stimuli, or image) to be confronted in treatment. During ERP, conditioned fear responses are extinguished by repeated and uninterrupted exposure to feared stimuli eliminating engagement in compulsive behaviours, resulting in habituation and eventual extinction over time. An intensive ERP approach was investigated by Meyer with two treatment resistant inpatients with contamination fears. Treatment involved repeatedly touching items that were perceived as dirty and elicited distress, whilst not being allowed to clean their hands. The bathroom taps were turned off and the patients were monitored by nursing staff to ensure strict control. The patients were offered encouragement and reassurance to refrain from engaging in rituals. Both patients achieved favourable outcome responses. Similar studies were conducted

later in the 70s, whereby patients were instructed to repeatedly touch contaminated objects that evoked distress and an urge to wash, also indicated similar results (Meyer & Levy, 1973; Meyer et al., 1974).

A review by Foa and Franklin (2000) indicated that whilst early studies demonstrated promising outcomes for ERP, there were limitations in the designs. They suggested that verbal reassurance, and monitoring which is another form of reassurance (i.e., that nothing bad is likely to happen in the presence of a professional, or a trusted individual) reduces distress levels and may have attenuated the results (Rachman & Shafran, 1998). With that in mind, later studies stipulated that no reassurance be offered during treatment and included homework to encourage the individual to practice exposure exercises at home (Foa et al., 1998). Also, rather than including the relaxation strategies that earlier approaches utilised, it was suggested that the individual must experience distress for emotional processing to occur (Foa & Kozak, 1986).

As indicated ERP is an effective treatment approach that results in clinically significant change for those with OCD, however, some are reluctant to participate for fear of having to confront their most feared thought, object or situation (Moritz et al., 2019) also, approximately 15% drop out of treatment (Ong et al., 2016). Attrition is in part due to the belief that the distress associated with not performing a compulsive ritual will be intolerable, as well as the belief that by not performing a ritual will cause something terrible to happen and they will be responsible for not preventing it (Meyer et al., 2014). These therapy-interfering beliefs may be a barrier for engagement which need to be addressed.

Cognitive Theory of OCD

The cognitive theory of OCD proposes that OCD is the result of dysfunctional thinking styles. Foa and Kozak (1986) suggested that people with OCD overestimate the level of danger associated with situations that are typically seen as safe. People with OCD exaggerate how bad things will be if they did occur and generally assume that intrusive thoughts, objects, or situations, are dangerous (Foa & Kozak, 1986). These assumptions cause distress and lead to reassurance-seeking or safety behaviours to relieve distress.

Salkovskis and Forrester (2002) suggest that whilst cognitive biases are an important component of the cognitive theory, it is the 'dysfunctional assumptions' associated with the thoughts that are problematic (Salkovskis & Forrester, 2002). These dysfunctional assumptions incorporate Rachman's explanations of thought-action-, thought-moral-, and thought-event-fusion (1993), and Wells' (1995) metacognitive model, with both authors proposing that those with OCD believe that intrusive thoughts have meaning and need to be controlled. These assumptions are centred on blame/responsibility for outcomes and Salkovskis and Forrester proposed that OCD is characterised by five 'dysfunctional assumptions', including (i) thinking about an action is the same as doing it; (ii) not preventing harm is the moral equivalent to causing harm; (iii) responsibility for harm is not reduced by extenuating circumstances; (iv) not performing a compulsion in response to a thought about harm is the same as an intention to harm; and (v) thoughts should be controlled (Salkovskis & Forrester, 2002).

Enhanced theories focussing on identifying OCD specific beliefs have been developed based on the work of Salkovskis et al., Rachman et al., and the Obsessive-Compulsive Cognitions Working Group, with the subsequent development of the

Obsessive-Compulsive Beliefs Questionnaire (OBQ) (Fergus & Carmin, 2014). The OBQ assesses several of the belief domains proposed as centrally important to OCD and measures six conceptually derived domains – responsibility (i.e., the belief that someone is able and obligated to prevent negative events); importance of thoughts (i.e., that the presence of a thought implies they are meaningful and dangerous); control of thoughts (i.e., that it is possible and necessary to control thoughts); overestimation of threat (i.e., exaggerated beliefs in the likelihood and severity of harm occurring); intolerance of uncertainty (i.e., that it is necessary to be certain, that ambiguity is intolerable); and perfectionism (i.e., that imperfection and mistakes cannot be tolerated) (Myers et al., 2008).

Cognitive Interventions for OCD.

Cognitive therapy for OCD has involved challenging dysfunctional thoughts and the beliefs associated with the need to perform compulsive rituals. The premise of cognitive therapy is that dysfunctional thinking styles and distorted cognitive appraisals are linked to affect and behaviour (Beck, 1970). Cognitive therapy typically involves challenging these cognitions to bring about change.

Thought Stopping. Thought stopping involved the use of a cue word to interrupt obsessive thought processes. For example, patients were instructed to use the word ‘stop’ when they experienced distress associated with rumination, and this was then followed by bringing to mind an image of a pleasant experience (James & Blackburn, 1995). However, James and Blackburn in their comparative evaluation of cognitive therapies (1995), suggested that the efficacy of thought stopping was questionable, and that it is an aversive method and, therefore, a behavioural technique rather than cognitive (James & Blackburn, 1995).

Challenging Automatic Thoughts. In contrast to the previous techniques, rather than targeting obsessive intrusive thoughts, this therapy focuses on negative automatic thoughts (NAT). NATs are regarded as recurrent, involuntary negative thoughts about oneself (e.g., I am worthless), that are rational and ego-syntonic (in line with personal beliefs) and are considered to be minimally intrusive. Obsessive intrusive thoughts on the other hand are irrational, unacceptable, ego-dystonic (in conflict with personal values), and highly intrusive (Julien et al., 2007). Salkovskis and Warwick (1985) explored mood, obsessive intrusive thoughts and NATs in a case study involving a patient with obsessional fears associated with developing cancer from contaminated beauty products. The patient underwent intensive ERP with repeated exposure to a feared face-cream over a three-day period, habituation was reported as successful and generalised to products at home. At follow-up, however, despite continuing with response prevention the patient's mood deteriorated and she became severely depressed. Her obsessional fears related to contamination and skin cancer returned more intensely and more frequently. The patient was readmitted to hospital with suicidal ideation and treated with pharmacotherapy but refused to engage in ERP. After 10-weeks of no improvement, the patient agreed to another attempt at an exposure exercise, but there was no reduction in distress, no evidence of habituation. The patient refused to participate in ERP again, and instead, cognitive therapy was used to target the NATs that had developed secondary to the obsessive intrusive thought. For example, the obsessive intrusive thought was that if they use face cream, it might be contaminated, and they will get skin cancer; the secondary NAT was that then their face would be scarred, and their partner and friends would leave and reject them. Salkovskis and Warwick suggested that the obsessive intrusive thoughts did not impact on mood unless

followed by NATs. They challenged the NATs using Beck's cognitive therapy techniques, which involves generating evidence for and against a negative belief to bring about change. After challenging the negative thoughts, the patient was asked to rate their belief in the thought and their mood using a visual analogue scale, and a negative linear correlation was reported, that is that mood improved as the belief in the NAT weakened (Salkovskis & Warwick, 1985). ERP was resumed after cognitive therapy and the patient's reported levels of distress were much lower as habituation occurred. Whilst it appears that changing cognitive beliefs prior to ERP may improve the outcomes of treatment, a limitation of this study is that the findings were based on a case study and therefore not generalisable.

Challenging Obsessional Thoughts. Challenging obsessional thoughts involves either rational emotive therapy, or self-instructional training. Rational emotive therapy (RET) focuses on challenging the validity and belief in the obsessional thoughts through rational disputations and cognitive restructuring (Ellis, 1962). Whereas, self-instructional training involves the patient imagining their feared situation, measuring how anxious they feel, observing and recording their obsessional thoughts, and replacing them with rehearsed more positive self-statements to reduce the level of distress (Meichenbaum, 1975).

Emmelkamp and colleagues explored the effectiveness of both cognitive approaches. Self-instructional training with in vivo ERP was compared with ERP alone (1980), and it was found that the combined approach was no more effective than exposure alone for OCD. In a later study, Emmelkamp and Beens (1991) explored the effectiveness of RET combined with in vivo ERP compared with ERP alone and reported that both significantly reduced OCD symptom severity, but there was no significant difference between the treatment approaches. Whilst the

cognitive approaches address some of the shortcomings of the behavioural approach such as the reassuring presence of the therapist or a trusted person on the patient's level of distress (Roper & Rachman, 1976), evidence suggests that it is no more effective.

Cognitive Behavioural Therapy for OCD

Cognitive Behavioural Therapy with Exposure and Response Prevention.

The cognitive behavioural theory of OCD comprises early behavioural theories within a cognitive framework to inform cognitive behaviour therapy (CBT). The CBT approach combines ERP with cognitive therapy to target the dysfunctional cognitions and maladaptive behaviours that maintain the disorder. ERP is the most efficacious psychological treatment for OCD (Olatunji et al., 2009; Öst et al., 2015). By graduated exposure to a feared stimulus whilst not engaging in compulsive behaviours, combined with hypothesis testing of the feared consequence, there is an eventual reduction in anxiety, and dysfunctional beliefs are corrected when the feared consequences do not occur. Self-efficacy is also improved as the individual is no longer reliant on avoidance or safety behaviours (Abramowitz, 2006).

Multiple systematic reviews of RCTs and meta-analyses support the efficacy of CBT for OCD (Olatunji et al., 2013; Öst et al., 2015; Rosa-Alcázar et al., 2008). When CBT with ERP was compared to a waitlist control, large effect sizes were observed in favour of CBT, and smaller, but still significant effect sizes were seen when compared to a serotonin reuptake inhibitory for OCD (Öst et al., 2015; Skapinakis et al., 2016) Ost et al., (2022) conducted a review and meta-analysis of CBT for OCD in adults treated in routine clinical care. Twenty-nine studies (8 randomized controlled trials) were included, comprised of 1669 participants. Very large within-group effect sizes (ES) were obtained for OCD-severity at post-

treatment (2.12), and follow-up (2.30), on average 15 months post-treatment. Remission rates were 59.2% post-treatment and 57.0% at follow-up. Attrition rate was 15.2%. Despite ERP being the treatment with the most robust psychotherapeutic outcomes, many patients (14-31%) are classed as non-responders to ERP (Foa et al., 2005; Norberg et al., 2008). Of those who do respond to ERP, approximately 50% experience at least partial relapse in OCD symptoms (Eisen et al., 2013; Simpson et al., 2005). It is therefore imperative to explore new approaches for managing OCD and improve the outcomes for those who do not fully benefit from current evidence-based treatments such as ERP.

One of the accounts for the limited outcomes of ERP is that during extinction, the obsessional fear is not 'unlearned' and fear-based associations do not resolve (Jacoby & Abramowitz, 2016). Instead, the obsession remains in memory and competes with newly learned non-threat (i.e., inhibitory) associations. This suggests that there is a deficit in the learning and inhibitory processes associated with successful ERP in non-responders. In accord with this, even after successful treatment, the conditioned response can spontaneously reoccur in other situations and at other points in time. People with anxiety disorders such as OCD, and those who are high risk for developing them, show abnormalities in the neural mechanisms that are thought to be central to fear conditioning, extinction, recall, and inhibitory learning (Craske et al., 2008; Lissek et al., 2005; Steuber & McGuire, 2022).

Inhibitory Learning Approach to Enhancing ERP. Given the supposition that even after successful ERP non-threat (i.e., inhibitory) association competes with and inhibits older threat associated fears (Craske et al., 2014) to maximise inhibitory learning and be effective, ERP needs to be delivered in such a way that the new non-threat association is strong enough to inhibit the original fear. According to the

model, this is done by i) learning that stimuli are safe and that it is safe to experience the emotions triggered by these stimuli, rather than waiting for habituation; ii) disconfirming expectations; iii) adding the element of surprise by stepping up the exposure exercise so that the person is pleasantly surprised by the non-occurrence of the feared outcome; iv) combining multiple fear cues during ERP; and v) adding a variety of contexts to exposures (Craske et al., 2014). More recently, the inhibitory learning model for exposure therapy has been extended to consider extinction learning with distal future feared outcomes, the role of avoidance, and alternative models/approaches to exposure therapy, including counterconditioning, novelty-enhanced extinction, latent cause models, and reconsolidation (Craske et al., 2022). Although there are no direct comparison trials of ERP for OCD with and without components to enhance inhibitory learning, evidence from experimental and open trials suggests this approach may benefit and be considered acceptable by recipients of exposure based approaches (see Farrell et al., 2022; Kühne et al., 2024; Sauer & Witthöft, 2022).

Despite ERP being a first-line treatment option for OCD, a significant number of people do not achieve clinically significant symptom relief. From a neurobiological perspective, one explanation for a lack of response to treatment in non-responders is that there are deficits in the mechanisms that are fundamental to extinction learning. These deficits may contribute to a poor response to exposure therapy and to the development of excess fear and anxiety. Cortical changes occur following effective treatment (psychotherapy and medication) indicating that in responders, treatment acts to normalise cortical activation in areas implicated in inhibition and extinction (Thorsen et al., 2015). It is therefore reasonable to suggest that targeting the neural mechanisms involved in extinction learning during ERP may

optimise inhibitory learning and potentially be the key to treatment efficacy. The neural circuitry involved in inhibitory learning are the cortico-striato-thalamo-cortical circuits (CSTC). Non-invasive brain stimulation is one neuromodulatory technique that is being used with some success in the treatment of other mental health disorders and may be a way of modifying the neural deficits associated with OCD. This has implications for the possibility of combined approaches involving non-invasive brain stimulation and exposure-based interventions.

Pharmacological Approaches for OCD.

Serotonin or 5-hydroxytryptamine, a monoamine neurotransmitter, has been implicated in the pathophysiology and treatment of OCD (Derksen et al., 2020.) An early hypothesis put forward by Spanish psychiatrists Fernández Córdoba and López-Ibor Aliño in 1967, was that OCD was the result of a dysfunctional serotonergic system (DeVeaugh-Geiss, 1994; Stein et al., 2001; Szechtman et al., 2020). This hypothesis was based on the chance observation that clomipramine, a tricyclic antidepressant, relieved obsessional symptoms in patients with depression (Szechtman et al., 2020). The theory gained impetus when antidepressants targeting serotonin reuptake were found to be more effective in the treatment of OCD than those antidepressants with minor effects on serotonin reuptake (Goodman et al., 1990; Hoehn-Saric et al., 2000; Leonard et al., 1989). This theory is supported by animal models which have demonstrated that administering serotonin 5-HT_{1b}, a receptor agonist, reverses compulsive-like behaviour in animals with decreased levels of serotonin in the prefrontal cortex (Arora et al., 2013). Further, a study exploring the role of 5-HT in mood and behaviour found utilising acute tryptophan depletion to temporarily reduce synaptic 5-HT caused a significant decrease in perceived control and increased intrusive thoughts following provocation in OCD

patients who had shown sustained clinical improvement to SSRI following provocation (Hood et al., 2017). It is suggested that serotonin reuptake inhibitor (SRI) pharmacotherapy reduces OCD-like behaviour by desensitising orbitofrontal 5-HT1BRs (Shanahan et al., 2011). However, inferring etiology from treatment response is problematic. The selective serotonin reuptake inhibitor (SSRIs) used to treat OCD are not specific to OCD and are used to treat a range of psychiatric disorders, and it may be that the amelioration of the original psychiatric disorder (i.e., depression) may underlie the reduction in OCD symptoms. Furthermore, there is a high percentage of patients with OCD who do not benefit from intervention with SRIs, suggesting that more than one neurochemical system may be involved in OCD symptomology (Szechtman et al., 2020).

Monotherapy with SRIs for OCD.

OCD typically responds to the antidepressant clomipramine, SRI, and the SSRIs sertraline, paroxetine, fluvoxamine, fluoxetine, and citalopram (Fineberg et al., 2015; Maziero et al., 2022). The side effects associated with Clomipramine make it less acceptable to patients than SSRIs and it is considered to be a second line pharmacotherapy for OCD (Katzman et al., 2014). However, pharmacotherapy is not always well tolerated or effective. Approximately 50% of patients are resistant to pharmacological management and are either unable to tolerate medication side-effects or only partially improve following treatment (Katzman et al., 2014). For those who do respond to medication, the average treatment gain is described as moderate, and the discontinuation of medications is associated with symptom relapse (Fineberg et al., 2015).

Augmented Approach of SSRIs with Antipsychotics for OCD

The lack of response to monotherapy in a significant proportion of treatment refractory patients, alongside the theory that more than one neurotransmitter is implicated in OCD, resulted in other compounds being trialled to improve the therapeutic effectiveness of SRIs. Neuroleptics were used to augment SSRIs for OCD in a placebo-controlled open-label trial involving treatment refractory patients (N = 17; (McDougle et al., 1989). All seventeen patients had participated in a placebo-controlled trial involving fluvoxamine with or without lithium and were deemed non-responsive. Neuroleptics (pimozide, thioridazine, or thiothixene) were then combined with either fluvoxamine alone (n = 8) or with fluvoxamine with lithium (n = 9) for 8-weeks. Nine participants met the criterion of responder on the clinical global impression scale (CGI-S), and a 62% reduction in symptom severity (Yale-Brown Obsessive Compulsive Scale [Y-BOCS] score) (McDougle et al., 1989). McDougle et al., suggested that the use of neuroleptic and fluvoxamine with or without lithium resulted in a greater therapeutic effect due to the interaction between dopamine and serotonin in the brain. A meta-analysis of 14 double-blind randomised controlled trials (RCTs) demonstrated that the addition of antipsychotics was significantly more effective than the addition of a placebo drug. Approximately 30% of participants who received antipsychotics showed significantly reduced Y-BOCS scores compared to 13% of those who received placebo (Dold et al., 2013). Whilst the authors concluded that augmented therapy is an evidence-based treatment strategy for treatment refractory patients with OCD, the results indicate that the combined approach only benefits one in three patients (Szechtman et al., 2020). Van Ameringen and colleagues reported similar findings after conducting an international cross-sectional study of real-life settings, involving 361 patients with OCD (2014).

Amongst the sample, 77.6% were prescribed SSRI with 50% of those on an augmented treatment (antipsychotics [30.3%, benzodiazepines [24.9%], and antidepressants [21.9%]). OCD symptom severity was measured using the Y-BOCS and the Clinical Global Impression-Severity Scale. They concluded that despite augmentation with antipsychotics being widely used, there was no significant difference between monotherapy and augmented therapies or between the different augmenters (Van Ameringen et al., 2014).

Augmented Approach of SRIs with CBT-ERP for OCD

Given the limited therapeutic benefit of augmenting SSRIs with antipsychotics, and evidence that the outcomes for the recommended first-line treatment options of CBT-ERP, and SSRIs for OCD were also limited, clinicians explored the effectiveness of augmenting SSRIs with ERP. Foa et al. (2005) conducted a double-blind randomised placebo-controlled trial comparing ERP alone, clomipramine alone, clomipramine with ERP, and a placebo medication. The trial involved intensive ERP for 4 weeks, followed by eight weekly maintenance sessions, and/or clomipramine (maximum dose 250mg) administered for 12-weeks. The Y-BOCS was the main outcome measure and response rates were determined by the CGI scale. All active treatments were superior to placebo (CGI improvement of 8%). The effect of ERP alone (CGI = 62%) was not significantly different to ERP plus clomipramine (CGI = 70%), but both were superior to clomipramine alone (CGI = 42%) (Foa et al., 2005). The lack of significant differences between ERP and ERP combined with clomipramine led the authors to suggest that there is no therapeutic cumulative effect on OCD, and that both clomipramine and ERP must involve similar underlying neural mechanisms.

Neuropsychological Approaches for OCD

Neuropsychological Models of OCD

There are several neuropsychological/biological models of OCD. The Feeling of Knowing model posits that the distress experienced in OCD is associated with not receiving a reward signal that a task is completed (Szechtman & Woody, 2004). This lack of reward signal is thought to be linked to overactivation of the limbic system, which is involved in controlling reward-related motivational behaviours and emotional responses, and drives the fight, flight, freeze response (Woody & Szechtman, 2013). Szechtman and Woody (2004) suggest there is a security motivation system (SMS) which is comprised of a hard-wired brain circuit to manage potential threats and acts in conjunction with the limbic system. They suggest that the SMS is sensitive to cues of partial or potential danger. When the SMS is activated in those with OCD, thoughts of potential risk/doubt are abnormally persistent and lead to a constant state of heightened anxiety and caution. It is reasonable to suggest that activation of the SMS motivates behaviours such as checking for potential danger. This is followed by repetitive compulsive behaviours which are done until an internal state of completion or "feeling of knowing" is achieved, which then terminates the feedback for the activation of the system (Szechtman & Woody, 2004). Those with OCD often report being unable to stop performing a task until they achieve a feeling of satisfaction/relief, which is consistent with the conceptualisation of the SMS as a monitoring system.

The prevailing neurobiological model of OCD is the frontal-striatal model and proposes dysfunction in the CSTC circuitry. Proponents of the frontal-striatal model suggest that OCD symptoms are associated with dysfunction (imbalance) in the feedback loop that leads to hyperactivity in the OFC pathways. The OFC plays a

key role in behavioural planning and expected reward evaluation, and it is suggested that it may be dysfunction of these processes that drive obsessive and repetitive compulsive behaviours (Bourne et al., 2012). There is some (albeit limited) neuroimaging evidence to suggest that OCD pathology may extend beyond the inclusion of the OFC to include the anterior cingulate cortex (ACC) and the amygdala (Milad & Rauch, 2012).The ACC is involved in identifying cognitive conflict and error detection/monitoring considered to be key to fear extinction. The ACC is also activated when a person needs to supress a response (inhibition), suggesting hyperactivity in those with OCD when they need to suppress a response to incongruent stimuli. One study involving lesions to the ACC demonstrated reduced symptoms in treatment refractory OCD (Sherif et al., 2023). Also, some evidence suggests a role for the amygdala in OCD. OCD-specific stimuli seem to be associated with amygdala hyperactivity (Simon et al., 2014). Whilst there is a potential role for the ACC and amygdala in OCD, their contributions remain unclear and there are mixed findings in the neuroimaging data. For the purposes of this study, and in consideration of the limitation of tDCS to accessible cortical areas, the CTSC is used as a basis.

Positron emission tomography (PET; imaging procedure that measures metabolic activity of the cells of body tissues) indicates that functional abnormalities in the OFC, ACC, and caudate can be ameliorated by pharmacotherapy (Chamberlain et al., 2005). A decrease in cerebral glucose metabolic rate in OFC and decrease in the basal ganglia, as well as an improvement in OCD symptoms, was observed after treatment with the tricyclic antidepressant clomipramine (Benkelfat et al., 1990).This effect was confirmed in another study involving OCD patients who reported a decrease in OCD symptoms Swedo et al. (1992). Similar results involving PET scans

following pharmacological treatment have been reported with the SSRIs paroxetine, and fluvoxamine (Rauch et al., 2002; Saxena et al., 1999).

Neurological studies indicate two key abnormal patterns of cortical activation associated with OCD. First, those with OCD demonstrate increased neuronal activity in the OFC, which is involved in decision-making, judgements, planning, and reward-guided learning. Second, OCD symptoms are associated with decreased activation in the pre-supplementary motor area (pre-SMA), involved in inhibitory control (Adler et al., 2000; de Wit et al., 2012; Harrison et al., 2009; Rauch et al., 2002; Ruffini et al., 2009; Saxena et al., 1999) which indicates that the pre-SMA is required to work harder to inhibit responses. Changes in patterns of activation (both hyperactivity and hypoactivity) in the frontal and motor cortices have been reported for a range of neuropsychiatric disorders, including attention deficit hyperactivity disorder and schizophrenia (Hasan et al., 2013). A similar imbalance in cortical activation between frontal areas and pre-SMA may underlie OCD (Brunelin et al., 2018; Hazari et al., 2016; Narayanaswamy et al., 2015). There is some evidence to suggest that OCD is in some part due to deficient pre-SMA response inhibition on striatal function (de Wit et al., 2012; Nachev et al., 2008), which supports the inhibitory learning theory. It has been suggested that reduced pre-SMA activation directly affects a person's ability to inhibit behaviours that may have developed as part of the fear learning process. Brain stimulation approaches have been developed to try to address this imbalance in neuronal activation and restore inhibitory control.

Neuropsychological Interventions for OCD

Brain stimulation has been used for various treatment refractory mental health disorders. These therapies work by applying a low electrical current to activate or inhibit targeted areas of the brain. The electrical current can be administered via

electrodes implanted in the brain (invasive, deep brain stimulation), indirectly by placing electrodes on the scalp (non-invasive, electroconvulsive therapy and transcranial direct current stimulation), or induced by applying magnetic fields to the head (non-invasive transcranial magnetic stimulation). The different types of neurostimulation for OCD will be presented in the following sections.

Electroconvulsive Therapy.

Electroconvulsive therapy (ECT) is a non-invasive brain stimulation procedure that involves inducing a seizure in a patient by passing short bursts of electricity (typically 0.9A) through the brain. Sedation is used during the administration of ECT, so the patient does not feel any discomfort. The electrical current is delivered via electrodes applied to the scalp at specific locations. The current is regulated by ECT devices to keep it constant, and as such varies up to 450 V maximum, depending on the patient, but is typically around half that. ECT usually involves 6 – 12 sessions, administered three times per week, on an in- or outpatient basis. The mechanism by which ECT exerts its effect is not fully understood.

ECT is one of the most widely used brain stimulation techniques and is effective for acute mania and/or MDD with severe suicidal ideation. Several systematic reviews have been conducted to examine the effectiveness of ECT for OCD. However, due to the absence of any RCTs, it cannot be stated that ECT effectively reduces symptoms of OCD (dos Santos-Ribeiro et al., 2018; Fontenelle et al., 2015). A study by Lins-Martins et al. (2015) involving OCD as comorbid to MDD in five patents, did not find any evidence to support its use for OCD. They reported that whilst ECT was helpful in the treatment of the comorbid mood disorders, it typically did not lead to any improvement in OCD symptoms (Lins-Martins et al., 2015). Common side effects of ECT include headaches, stomach

upset, muscle aches, disorientation, confusion, and temporary loss of memory (Datto, 2000).

Deep Brain Stimulation.

Deep Brain Stimulation (DBS) is an invasive neurosurgical brain stimulation technique. It is reserved for people with severe and incapacitating OCD who have not benefitted from conventional treatment (Greenberg et al., 2010). DBS involves the implantation of electrodes deep in the brain, and these electrodes are connected to an implantable electrical stimulator placed under the skin in the upper chest (Alonso et al., 2015). The electrical stimulation enables focal, adjustable, and reversible neuromodulation of electrical activity within the circuitry of the brain. Treatment for OCD involves neuro modulation of the CSTC circuits (Rapinesi et al., 2019). The optimal targets of the electrodes include the anterior limb in internal capsule, the ventral striatum, the anteromedial limbic subthalamic nucleus, and midbrain. Stimulation of these areas affect the OFC or anterior cingulate cortex via connections that pass through the internal capsule (Mar-Barrutia et al., 2021).

The mechanism underlying DBS for OCD is not fully understood. Althougth it was once thought to create lesions similar to ablative techniques, it is now suggested that DBS likely works by mediating the flow of information through the electrical circuits of the brain and facilitating the release of vital neurotransmitters to restore function (McIntyre & Hahn, 2010). This neuromodulation occurs via a combination of excitatory and inhibitory activation, and local and distal effects on the axonal fibres of the CSTC circuits (van Westen et al., 2015). DBS used in animal studies indicate that when the OFC striatal fibres were stimulated, compulsive behaviour (e.g., compulsive lever pressing) was improved. The same studies indicate that reduced fear conditioning and improved fear extinction were asociated with

more ventral stimulation (van Westen et al., 2015). It is suggested that DBS decreased anxiety levels through an increase in striatal dopamine and improvement of reward processing (van Westen et al., 2015).

A meta-analysis involving 31 studies and 116 patients conducted to examine the efficacy of DBS in OCD reported a response rate of 60% with an overall 45.3% reduction in Y-BOCS (Alonso et al., 2015). There was no significant difference in the efficacy of DBS (measured by reduction in Y-BOCS) between three targeted stimulation sites, which included striatal areas (n=85), the subthalamic nucleus (n=27), and the inferior thalamic peduncle (n=6). Drop out rate was low (n=5) and adverse effects were generally reported as mild, transient, and reversible (Alonso et al., 2015). Whilst it is evident that DBS is effective for some with OCD, it is important to examine what the restoration of functional integrity to the CSTC ciruitry means for treatment refractory patients in terms of changes to their life. Six patients and six carers were involved in a qualitative study that explored the phenomonological experience of patients who had undergone DBS for OCD (Acevedo et al., 2023). Reported changes included; reduction in OCD symptoms, feeling more alive, improved mood and mental focus, greater engagement with the world as they were no longer ruminating, their OCD was more manageable, and self-constructs re-emerged and were able to develop (Acevedo et al., 2023). Although DBS is effective for those with treatment refractory OCD, further research involving appropriately powered RCTs is required to identify optimal stimulation sites. DBS is an invasive technique involving surgery, anaesthesia, and high financial costs and is typicallt reserved for non-responsive patients with severe symptoms.

Repetitive Transcranial Magnetic Stimulation.

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive brain stimulation technique that modulates neural excitability through rapidly changing electromagnetic fields. This electromagnetic induction is generated by a coil placed over the scalp at the cortical area of interest (Rapinesi et al., 2019). Mixed low and high frequencies of the rTMS pulses result in decreased and increased neural excitability and brain activity, respectively (Rosa & Lisanby, 2012). It is thought that the inhibitory effect of low frequency rTMS on hyper-active medial prefrontal brain regions may reduce OCD symptoms (Perera et al., 2021). rTMS interacts with the CSTC circuits and may improve functional connectivity and balance (Lefaucheur et al., 2017). Another theory is that rTMS induces neuroplasticity, thereby facilitating new learning and reducing the need to perform compulsions. (Hallett, 2007). Administering rTMS during provocation of OCD symptoms provides an alternative approach to ERP and is a means of utilising neuromodulation to optimise inhibitory learning.

Based on fMRI studies that OCD symptoms are associated with increased activity in the OFC, Ruffini and colleagues, administered low frequency (LF) rTMS (80% motor threshold, 1 Hz seconds/minute for 10 minutes for 15 consecutive days) over the left OFC on 23 treatment refractory patients with OCD (Ruffini et al., 2009). A significant reduction in Y-BOCS scores was reported between the active and sham conditions, and this was evident up to 10 weeks post-rTMS. However, treatment gains were not maintained at 12-week follow-up (Ruffini et al., 2009).

In addition to the CSTC circuits, neurophysiological studies using electroencephalograph (EEG) indicate that motor and pre-motor cortex hyperexcitability may be involved in OCD (Mantovani et al., 2006). Five treatment

refractory patients with OCD underwent rTMS (100% of motor threshold, 1 Hz for 10 minutes/day for 10 consecutive days) to the supplementary motor area (SMA). Three out of five patients experienced a clinically significant improvement in Y-BOCS scores (> 40%), which was maintained at 3-month follow-up (Mantovani et al., 2006). Further, the resting motor threshold of the right hemisphere increased following rTMS, restoring symmetry that was absent at baseline. Mantovani suggests that stimulation of the SMA impacts the motor cortex, which in turn affects the striatum (part of the CSTC circuits) (Mantovani et al., 2006).

A meta-analysis of RCTs involving rTMS as an augmented strategy for 484 participants, with some degree of treatment resistance, was conducted (Rehn et al., 2018). Two hundred and sixty-two participants received active rTMS and 222 participants received sham rTMS for an average of 14.63 ±6.0 sessions. Cortical target areas for stimulation included the dorsolateral prefrontal cortex (DLPFC), LDLPFC, RDLPFC, OFC, and SMA. The Y-BOCS was used to measure symptom change from pre-rTMS to the final follow-up session. The results indicated that low frequency rTMS over the SMA led to the most improvement in OCD symptoms (compared to other areas) and represented the greatest effect size ($g = 1.68$, 95% CI = .07 – 3.29, $p = .041$). Treatment gains were maintained at the 12-week follow-up for those who received active rTMS over SMA. This was followed by bilateral stimulation of DLPFC ($g = 1.18$, 95% CI = .45 – 1.91, $p = .002$), and then the R-DLPFC ($g = 0.58$, 95% CI = 0.20 – 0.97, $p = .003$). There was no significant difference between active and sham rTMS when the L-DLPFC was stimulated (Rehn et al., 2018). rTMS in this study reduced OCD symptoms for all cortical sites stimulated (except L-DLPFC). This suggests that the improvements are due to the effect rTMS had on the CSTC circuitry, rather than individual cortical targets.

A recent meta-analysis of randomised sham-controlled trials by Perera et al. (2021) involved 26 studies that used rTMS. They reported that active rTMS was superior to sham in reducing OCD-related symptoms, and overall, rTMS had a modest effect on reducing Y-BOCS scores. Targeting the bilateral DPFC showed the largest effect size, and both low- and high-frequency rTMS were significantly superior to sham (Perera et al., 2021). The authors stated several limitations and noted that most studies included in their meta-analysis were clinical trials with small sample sizes, and there was no consensus on treatment parameters. Further, three out of four studies involving bilateral DPFC were from the same research group (Perera et al., 2021). Although rTMS is promising, it is limited by the relatively high cost of equipment and the mixed findings for its effect on OCD symptoms.

Transcranial Direct Current Stimulation for OCD.

Transcranial direct current stimulation (tDCS) is a non-invasive stimulation technique used to modulate cortical activity and, consequently, change behaviour (Nardone et al., 2012). tDCS delivers low intensity electrical currents to modulate neuronal activity (Nitsche et al., 2008). tDCS works by delivering a positive (anodal) or negative (cathodal) electrical current via electrodes (placed on the skull) to a targeted brain area. The low current modifies cortical excitability by facilitating the depolarisation or hyperpolarisation of neurons, respectively. Research in healthy individuals has found that anodal (excitatory) tDCS over frontal areas improves executive function including attention, learning, memory, and inhibitory control (Coffman et al., 2014; Hansen, 2012; Loftus et al., 2015). Lawrence et al. (2018) reported that anodal tDCS over frontal areas led to improved cognitions in those with Parkinson’s disease.

Although there is limited research in brain stimulation interventions for OCD, preliminary studies involving tDCS for patients defined as resistant to both CBT and pharmacotherapy have been encouraging. Hazari et al. (2016) conducted an open-label study using anodal tDCS over pre-SMA to increase pre-SMA activation, and cathodal tDCS over OFC to decrease OFC activation. The selection of this tDCS montage is based on the hyperactivation of OFC and hypoactivation of the pre-SMA observed in neuroimaging studies of OCD. The patient, who was taking Escitalopram and Clonazepam, received 2mA of current for 20 min, twice a day for 10 days (20 sessions). This tDCS montage was based on the theory that OCD is due to deficient pre-SMA response inhibition on heightened fronto-striatal activation (de Wit et al., 2012; Nachev et al., 2008). The patient demonstrated an 80% reduction in OCD symptom severity, which was maintained for 7-months post-intervention with minor fluctuations. The patient did relapse at the 7-month time point, but their symptoms improved following a further 8 sessions of tDCS. On both occasions that tDCS was applied, the patient's OCD symptoms had remitted within 5 - 10 days. Narayanaswamy et al. (2015) used the same tDCS protocol combined with therapeutic SSRIs in two patients, who received 2mA of current for 20 min, twice a day for 5 days (10 sessions). Both patients demonstrated significantly reduced OCD symptom severity (52% and 46.7% reduction) that was maintained at 1 and 2-month follow-up assessments. However, despite a few studies reporting positive effects of tDCS on OCD, the efficacy of non-invasive brain stimulation remains ambiguous (Benninger et al., 2010; Hindle et al., 2013) and there is a lack of consensus regarding stimulation protocols. Further, there are several limitations associated with the published studies.

Most of the tDCS and OCD studies are single-patient case studies and are therefore not generalisable. Many studies do not provide any theoretical framework for electrode placement, thereby limiting the interpretation of potential neural mechanisms by which behavioural change occurs. Very few studies include an OCD symptom measure as the primary outcome, and other aspects of functioning (such as quality of life) are not explored. Brunelin et al. (2018) conducted a systematic review of studies examining brain stimulation for those with OCD and concluded that although a number of studies demonstrated improvements in OCD, there was a lack of methodological rigor that reduced the quality of the findings. To date, no study has involved an integrated approach of tDCS plus ERP for OCD.

Significance, Rationale, and Aims

The overall aim of this PhD was to explore the therapeutic potential of tDCS for OCD symptoms. To achieve this aim, a systematic review of the literature involving RCTs of tDCS for OCD was conducted (study one). The quality of reporting was evaluated using the CONSORT (Consolidating Standards of Reporting Trials) statement, and the outcomes of tDCS as a therapeutic tool for OCD was examined. The outcomes of study one highlighted the need for a standardised protocol for conducting research involving tDCS for OCD. The aim of study two was to conduct a survey to establish the acceptability and expectations of tDCS as a potential future treatment approach amongst OCD clients. A double-blind randomised controlled trial involving tDCS for OCD was planned for study three, but recruitment challenges during the COVID-19 pandemic resulted in recruitment being discontinued. The difficulty with recruiting and the outcomes of study two (survey) led to the development of Study three, a case series to evaluate a dual protocol approach of ERP combined concurrently with tDCS for treatment refractory OCD.

Chapter 2. Study One - Transcranial Direct Current Stimulation for Obsessive Compulsive Disorder: A systematic review and CONSORT evaluation

Introduction to Study One

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Authorship

All signed authors acknowledge that this statement is an accurate representation of their contribution to the above research output.

Author	Contribution	Acknowledgement
Peta E Green	Development of the research question and the design, manuscript preparation, writing and editing manuscript drafts.	[redacted]
Andrea M Loftus	Assisted with the development of the research question and the design, contributed to writing revisions to the manuscript, and editing manuscript drafts.	[redacted]
Rebecca A Anderson	Assisted with the development of the research question and the design, contributed to writing revisions to the manuscript, and editing manuscript drafts.	[redacted]

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Abstract

Transcranial direct current stimulation (tDCS) has shown some promise as a novel treatment approach for a range of mental health disorders, including OCD. This

study provides a systematic review of the literature involving randomised controlled trials of tDCS for OCD, evaluates the quality of reporting, and examines the outcomes of tDCS as a therapeutic tool for OCD. This systematic review was prospectively registered with PROSPERO (CRD42023426005) and the data collected in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. The quality of reporting of included studies was evaluated in accordance with the Consolidating Standards of Reporting Trials (CONSORT) statement. Eleven RCTs were identified. Evaluation of the reviewed studies revealed low levels of overall compliance with the CONSORT statement highlighting the need for improved reporting. Key areas included insufficient information about - the intervention (for replicability), participant flow, recruitment, and treatment effect sizes. Study discussions did not fully consider limitations and generalisability, and the discussion/interpretation of the findings were often incongruent with the results and therefore misleading. Only two studies reported a significant difference between sham and active tDCS for OCD outcomes, with small effect sizes noted.

The variability in protocols, lack of consistency in procedures, combined with limited significant findings, makes it difficult to draw any meaningful conclusions about the effectiveness of tDCS for OCD. Future studies need to be appropriately powered, empirically driven, randomised sham-controlled clinical trials.

Keywords Transcranial direct current stimulation; obsessive-compulsive disorder; randomised controlled trial; systematic review; CONSORT evaluation.

Introduction

Obsessive-compulsive disorder (OCD) is a debilitating psychiatric disorder with an approximate lifetime prevalence of 1-2% (Diagnostic and Statistical Manual

of Mental Disorders 5th ed., text rev.; DSM-5-TR; American Psychological Association, 2022). Left untreated, OCD can cause significant impairments in social, family, and occupational functioning (Abramowitz et al., 2009). Current evidence-based treatment options for OCD are pharmacotherapy and/or cognitive behaviour therapy that includes exposure and response prevention (CBT-ERP). Whilst OCD typically responds to serotonin reuptake inhibitors (SRIs) and selective serotonin reuptake inhibitors (SSRIs), pharmacotherapy is not always effective and approximately 40 - 60% of people with OCD are either unable to tolerate side-effects or only partially respond to these approaches (Gershkovich et al., 2017). Discontinuation of medications is also associated with symptom relapse (Fineberg et al., 2015). Similarly, of those who respond to CBT-ERP, approximately 60% demonstrate at least partial relapse (Eisen et al., 2013; Simpson et al., 2005) and a significant percentage of those treated for OCD (14-31%) are classed as non-responders (Foa et al., 2005; Norberg et al., 2008).

Given the percentage of non-responders and rate of relapse for those with OCD, non-invasive brain stimulation is being investigated as a therapeutic approach. Transcranial direct current stimulation (tDCS) is a low-cost, safe, and well tolerated non-invasive brain stimulation technique (Kuo et al., 2017) that involves delivering a low intensity electrical current (1-2mA) via two electrodes on the scalp, an anode (excitatory) and a cathode (inhibitory). Depending on the location of the electrodes, tDCS has been demonstrated to modulate local and network-level brain activity and alter maladaptive behaviour (Nardone et al., 2012).

It is feasible that tDCS may be effective in addressing deficits in the neural feedback loop thought to underly extinction and inhibitory learning, which are implicated in the onset and maintenance of anxiety and OCD (see Craske et al.,

2008; Lissek et al., 2005). The clinical efficacy of tDCS has been researched most commonly in relation to treatment-resistant depression (George et al., 2009). However, there is a growing body of evidence that suggests tDCS can improve OCD symptoms (Brunelin et al., 2018; Nuñez et al., 2019; Pinto et al., 2022).

Until 2018, published studies involving tDCS for OCD included case reports (n=8), open-label trials (Bation et al., 2016; Dinn et al., 2016; Najafi et al., 2017), and one randomised controlled partial crossover trial (D'Urso et al., 2016). It is difficult to establish the efficacy of tDCS for OCD from these trials due to methodological variations, lack of protocol reporting, and highly mixed results. For example, two of the case reports involved 20 sessions of anodal tDCS to increase cortical activation of the pre supplementary motor area (pre-SMA) and cathodal tDCS to reduce activation of the OFC (Hazari et al., 2016; Narayanaswamy et al., 2015). Both patients in Narayanaswamy et al.'s case report demonstrated reduced pre-post Yale Brown Obsessive Compulsive Scale (YBOCS) scores (40% and 46.7%) and this was maintained for 1 to 2 months. The participant in the Hazari et al. case report demonstrated a YBOCS reduction of 80% that was maintained for 7-months post-intervention with minor fluctuations (Hazari et al., 2016). D'Urso et al. (2016a) also applied anodal tDCS stimulation to pre-SMA across 10 sessions. They found that the participant's Y-BOCS score initially increased (i.e., OCD symptoms worsened). In response, they changed the electrodes so that the cathode (inhibitory) was positioned over pre-SMA and reported an improvement in OCD symptoms (D'Urso et al., 2016). D'Urso et al. extended their findings by conducting a follow-up crossover design study (N=10) and found that cathodal (but not anodal) tDCS of pre-SMA led to significant improvements in Y-BOCS (D'Urso et al., 2016). da Silva et al. (2016) also applied cathodal tDCS over SMA in their case studies (n=2). They

reported a small, delayed improvement in Y-BOCS (18% at 6-months post intervention) in one person, while the other demonstrated a 45% improvement of symptoms at 6-months post-intervention. Despite a number of studies reporting such improvements in OCD symptoms in response to tDCS, the small sample sizes, heterogeneity of tDCS protocols, and lack of methodological rigor reduces the quality of the findings (Brunelin et al., 2018). The optimal montage and efficacy of tDCS remains ambiguous.

A more recent systematic review and meta-analysis evaluated the efficacy of tDCS for OCD and the optimal tDCS montage using electric field monitoring (Pinto et al., 2022). The review included eight studies (4 open-label and 4 randomised controlled trials [RCTs]) up until 2021 and excluded several studies due to bias related to methodological issues. Pinto et al. concluded that tDCS is a promising intervention to reduce OCD symptoms, despite reporting no significant effect of active tDCS compared to a sham condition. Pinto et al. attributed the lack of a positive effect to there only being four RCTs included in their meta-analysis, which were limited by their small sample sizes and highly variable tDCS placement and dose (Pinto et al., 2022). Since this review, there have been several further RCTs concerning tDCS for OCD published, adding to the available data for a new overarching review. To date, however, no systematic reviews or meta-analyses on this topic have used the Consolidating Standards of Reporting Trials (CONSORT) statement, the ‘gold standard’ for assessing the reporting quality of clinical trials (Altman et al., 2001) to consider the quality of the RCTs being included in their reviews.

The aim of the present study was to conduct a systematic review of the literature to date involving RCTs of tDCS for OCD (including parallel, and crossover

design), and evaluate the reviewed studies using the CONSORT statement as a framework for understanding the quality of methodological and outcome reporting.

Materials and Methods

This systematic review was prospectively registered with PROSPERO (CRD42023426005).

Search Strategy and Selection of Studies

The Prospero Registered proposal aimed to include RCTs, open trials, case-reports/studies, and case-series. However, a preliminary search yielded multiple RCTs, which allowed for a more focussed review of RCTs only.

Data for this systematic review was collected in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). A systematic database search was conducted on 28th June, 2023 of Ovid® MEDLINE, Emcare, Global Health, Embase, PsycInfo, PsycArticles, PubMed, Cochrane, and Google Scholar. The reference lists of earlier relevant reviews were searched by hand. ClinicalTrials.gov was also searched for unpublished results to reduce the risk of bias. The final search was updated on October 7th, 2023.

The initial ‘advanced search’ was conducted using the keywords (Transcranial direct current stimulation) AND (obsessive compulsive disorder), limits/filters included human*, English language, additional limits were adults 18+ OR all adults (19 plus years), adulthood 18+, and randomised controlled trial OR control* OR sham. A total of 120 articles were identified, which were reduced to 68 records after screening and removal of duplicates. The remaining records were then assessed for eligibility.

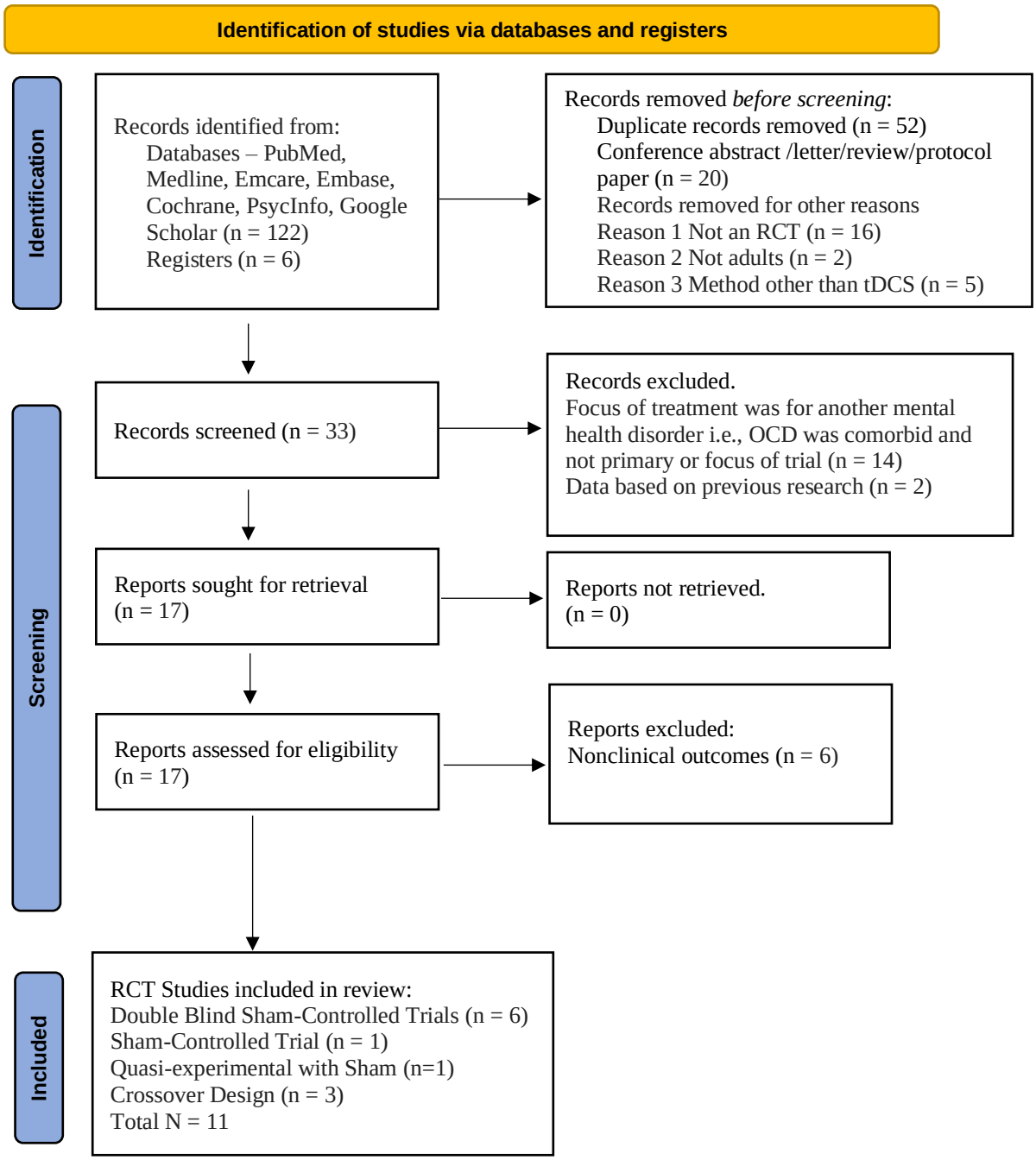
Selection Criteria

We included RCTs involving tDCS for OCD conducted in adults who met the diagnostic criteria for OCD in accordance with the Diagnostic and Statistical Manual of Mental Disorders versions IV-TR and 5-TR or the World Health Organization's International Statistical Classification of Diseases and Related Health Problems (ICD) 10th and 11th ed. (World Health Organisation, 1992, 2021) criteria.

Exclusion criteria included a) case reports and case studies; b) studies without a standardised OCD outcome measure; c) studies where investigators were targeting their treatment for another condition (i.e., OCD was a comorbid condition); d) non-invasive brain stimulation techniques other than tDCS. See Figure 1 for identification, screening, and inclusion criteria.

Figure 1

PRISMA flow diagram



Quality Assessment

The quality of the included studies was evaluated in accordance with the CONSORT statement (Moher et al., 2012). The CONSORT statement is a 25-item checklist which was developed to improve the quality of reporting of RCTs. First published in 1996, it has been updated as the CONSORT 2010 Statement (Moher et

al., 2012) with extensions to include randomised controlled nonpharmacologic treatment trials and other trial designs. The guidelines facilitate critical appraisal and interpretation of trial reports. Data was extracted and tabulated by the first author (PG), and results were cross-checked by a postgraduate psychology research student. Any disparities in quality assessment were settled by one of the co-authors/supervisors (R.A.A, A.M. L). As the replication and translation of tDCS, as undertaken in these studies, is only possible when detailed information about methods is provided, this study also collated data on the degree to which the tDCS protocol was reported on a range of relevant factors (e.g., electrode size, contact medium, dose stability).

Outcomes

At its inception, this study sought to examine the clinical effectiveness of tDCS for OCD via a meta-analysis. We elected not to undertake this due to the heterogeneity in protocols and the conflicting, and often lack of empirical bases for the choice of stimulation sites. There was limited overlap in procedures in terms of electrode montages, dose (i.e., duration and frequency) and, in particular, stimulation sites. The lack of consistency in protocols represents a significant limitation that would cast doubt over any meta-analysis results and render interpretations less meaningful (Kriston, 2013). A descriptive summary has been provided of the study outcomes and conclusions as an alternative.

Results

Systematic Review

Eleven RCTs with 363 participants were included in this review. See Table 1 for a summary of the key characteristics of the eleven RCTs.

Table 1

Main Characteristics and Findings of Randomised Controlled Trials Involving Transcranial Direct Current Stimulation (tDCS) for obsessive-compulsive disorder (OCD).

Author	Study Design	Sample Characteristics						Stimulation Parameters						Results
		N	Age Range M(SD) years	Gender n = female	Y-BOCS M(SD) Duration years	Treatment Resistant	Concomitant Treatment	Stimulation Site: Anode	Stimulation Site: Cathode	Electrode Size (cm^2)	Current mA	Number Frequency of Sessions	Duration	Significant between group (active v. sham) pre- to post-test difference in Y-BOCS
Yekta et al. (2015)	Sham-controlled	20	20 – 45 M - NR	NR	19.1 Duration NR	Yes	SSRI	R - DLPFC	L – DLPFC	35cm^2	2mA	15 (daily)	20min Sham 30sec ramp up/down	NR
Deepak (2017)	Double blind, sham-controlled	30	18 – 65 33.7 (10.8)	15	26.0 (6.4) Duration 7.4 (7.2)	No	NR inferred same as previous treatments	L- DLPFC	SMA	NR	2mA Sham 1mA	10 (Mon-Fri for 2 weeks).	20 min Sham 30 sec ramp up/down	No
Bation et al. (2019)	Double-blind sham-controlled	21	18 – 70 43 (15.9)	12	29.25 (8.15) Duration 21.2 (13.65)	Yes	SRI stable dose at least 6 weeks before trial and maintained throughout.	R Cerebellum	L – OFC	35cm^2	2mA	10 (twice daily with 3 hours between sessions)	20 min Sham 40 ms ramp up/down + brief pulses of 1.1 μA over 15ms every 550 ms.	No
Gowda et al. (2019)	Double-blind sham-controlled	25	18 – 45 28.4 (5.5)	4	26.57 (5.1) Duration 9.1 (5.1)	Yes	Medications stable dose at least 3 months before trial and maintained throughout.	Pre-SMA	R Supra-orbital Area	35cm^2	2mA	10 (twice daily 3 hrs between sessions) non-responders offered OLE phase - active tDCS 2/day for another 5 days.	20 min Sham 40 ms ramp up/down + brief pulses of 1.1 μA over 15ms every 550 ms.	Yes $F = 4.95$, $p = 0.04$, $\eta^2 = 0.18$
Yoosefee et al. (2020)	Double-blind sham-controlled	60	18 – 60 37.3 (24.1)	49	29.9 (6.2) Duration NR	No	20 mg of fluoxetine twice daily.	L – DLPFC	R - OFC	35cm^2	2mA	24 (three per week for 8 weeks)	20 min Sham 30 sec ramp up/down	No

da Silva et al. (2021)	Double-blind sham-controlled	44	18 – 65 37.67 (11.6)	26	29.94 (6.06) Duration NR	Yes	Stable dose of medications > 6 weeks before trial and maintained throughout (SSRIs, clomipramine, antipsychotics, and BDZs (max 20mg/day).	L deltoid	SMA	25cm^2	2mA	20 (Mon-Fri for 4 weeks)	30 min Sham 30 sec	No[1]
Harika-Germaneau et al., (2024)	Multisite double-blind sham-controlled	80	18 – 70 41.1 (11.5)	37	27.9 (4.1) Duration 14.4 (10.7)	Yes	Current medication regimen maintained throughout treatment and follow-up period	R - OFC	Bilateral SMA	35cm^2	2mA	10 (Mon-Fri for 2 weeks)	30 min Sham 30secs	No[2]
Akbari et al. (2022)	Quasi-experimental with pre-, post-test	40	18-45 years M=27	NR	Y-BOCS NR Duration NR	Yes	NR	Group 1 R Cerebellum	Pre-SMA Group 2 R Cerebellum L – OFC Group 3 R Cerebellum L Cerebellum Sham R Cerebellum L – OFC	35cm^2	2mA	10 (twice daily)	15 min	Yes $F = 3.56$, $p < 0.05$, $\eta^2 = 0.24$.
Fineberg et al. (2023)	Crossover multicentre design (3 arms). All participants at each centre	19	> 18 45 (16.6)	9	24.1 (5.2) Duration 31.1 (19.7)	No	Stable dose > 6 weeks before randomisation and maintained throughout. Eligible meds SSRI, TCA,	Arm 1 R Deltoid	SMA Arm 2 R Deltoid L – OFC Arm 3 NR NR	NR	2mA	4 (twice daily over 2 consecutive days) 28 - days between arms	20 min Sham brief ramp up/down period.	No

[1] Between group difference observed at 12-weeks post intervention $F_{(1, 84.06)} = 84.06$, $p < 0.03$, $d = 0.62$

[2] Between group difference observed at 12-weeks post intervention $F_{(1, 75)} = 4.60$, $p < 0.035$, $\eta^2 = 0.058$

	receive all arms						antipsychotic, BDZs						
D'Urso et al. (2016)	Partial Crossover with 2 arms (Participants receive both arms but only if Y-BOCS increases).	12	18 – 65 39.0 (13.1)	7	28.5 Duration NR	Yes	Stable dose > one month before trial and maintained throughout. Eligible medications include - SSRI, TCA, SGA, Mood stabilizers, BDZs.	Arm 1 Pre - SMA R Shoulder Arm 2 R Shoulder Pre - SMA	25cm^2	2mA	10 per arm. If Y-BOCs decreases or is unchanged after 10, participant remains in same arm for another 10	20 min	N/A
(Todder et al., 2018)	Crossover Design with 3 arms (all participants receive both arms)	12	38.5 (12)	5	28.5. Duration 10.8 (6.9)	Yes	Medication stable for min 2 months prior to trial. CBT – ERP to induce anxiety.	Arm 1 OFC R Shoulder Arm 2 R Shoulder OFC Sham R Shoulder OFC	35cm^2	2mA	3 (48hrs between sessions) 1 week between arms.	20 min Sham 30 sec ramp up/down	N/A

Note. tDCS: transcranial direct current stimulation, L: left, R: right, RCT: randomised controlled trial, DLPFC: dorsolateral prefrontal cortex; NR: Not Reported; OFC: orbitofrontal cortex; (pre) SMA: (pre) supplementary motor area; mA: milliampere, μA: microampere, hrs: hours, min: minutes, ms: millisecond, Y-BOCS: Yale-Brown Obsessive Compulsive Scale, OLE: open-label extension, (SD) standard deviation, TCA: tricyclic antidepressant, SGA: second generation antipsychotics, BDZs: benzodiazepines, SSRI: selective serotonin reuptake inhibitor, CBT-ERP: cognitive behavioural therapy with exposure and response prevention, N/A: Not applicable, no true sham condition

CONSORT Evaluation

Table 2 presents a summary of the CONSORT evaluation of the 10 studies.

Trial Design. Six of the eleven studies were randomised double-blind sham-controlled trials. One was a multicentre randomised, double-blind sham-controlled design, and one was a randomised, double-blind, sham-controlled, cross-over, multicentre trial. Two were randomised controlled cross-over trials. One was a quasi-experimental trial with pre-post testing.

Recruitment and Sample Size. All but one study reported where participants were recruited from (e.g., universities/research institutes [n=4], clinics [n=3], and hospitals [n=3]), with the exception of Harika-Germaneau, Heit, et al. (2024) it was unclear where tDCS took place and whether the sample were inpatients or outpatients at the time. A common shortcoming was the lack of dates defining the recruitment period, which was only reported by five studies (Akbari et al., 2022; da Silva et al., 2021; Gowda et al., 2019; Yoosefee et al., 2020).

Participants. A total of *363* participants were enrolled across the *eleven* trials. The number of participants in each trial varied from 12 to *80*. Age ranged from 18 – 70 years (Mean = 37years). The gender of participants was reported by nine trials which comprised of 136 male participants (45%) and 164 female (55%) overall. Baseline OCD symptom severity (as measured by the Y-BOCS) was reported by ten studies and ranged from 19 (moderate) to 30 (severe) with a mean Y-BOCS of 27 (severe). The duration of OCD was reported by six studies and ranged from 7.4 to 31.1 years.

Eligibility

All trials recruited adults only. The age range of participants varied across trials and included 18 years or older, 20-45 years, 18-45 years (n = 2), 18–65-years (n = 3), 18-60 years, 18-70 years (n = 2). One study did not report an age range. All

trials required that OCD meet the diagnostic criteria of the DSM-IV, DSM-5 (later studies), or ICD-10 or -11, with eight stipulating a minimum Y-BOCS symptom severity of 16. Two trials recruited participants with a slightly higher minimum Y-BOCS of ≥ 20, and one trial did not specify symptom severity in their eligibility criteria.

Eight out of the eleven trials recruited treatment resistant participants, but the definition of treatment-resistance was inconsistent across studies. Most trials described treatment resistance as a lack of response to SSRIs. However, the number of SSRIs trialled without response varied from one to at least two SSRIs, with one study specifying either no response to two SSRIs or one SSRI and clomipramine. Three studies included a lack of response to CBT by a trained psychologist in addition to a lack of response to SSRIs. Three out of the eight trials also stipulated that an SSRI be trialled for at least 3-months at a maximum tolerated dose, with no response. By contrast, one trial's criteria were a lack of response to an SSRI trialled for 2-weeks prior the intervention. Three of the trials included participants prescribed psychotropic medications with a proviso that the medication dose had been stable prior to the inclusion in the study. Studies varied in their definition of medication stability from 4 to 12 weeks.

The exclusion criteria varied across studies ranging from only one exclusion criteria (psychotropic medications) to a more extensive list of eight different exclusion criteria. The most common exclusion criteria were history of psychotic disorder, head/brain injury, metal or implanted device in brain, substance abuse, and pregnancy.

Interventions

The CONSORT Intervention item consists of 4 parts including a description of different components, and whether/how - interventions were standardised; adherence to protocol was assessed or enhanced; and adherence of participants was assessed or enhanced. Table 3 provides an overview of the level of information in each of the trials required to replicate a tDCS protocol in real-world conditions and understand the generalisability of findings. All studies included a *description of the different components* of the intervention to varying degrees, but not all studies included enough detail for replication. For example, two studies did not report the size of electrodes used, and half of the studies did not indicate how the electrodes were secured to the head. Five studies did not provide an adequate description of previous treatment, whether pharmacotherapy was concomitant and, if it was, if the dose remained stable throughout the trial and was maintained during the follow-up period.

Four out of eleven studies reported the use of *standardised* diagnostic procedures and assessment-tools and described the psychometric properties of the outcome measures. However, none of the studies included how the interventions were standardised. *Adherence to the protocol* was assessed and enhanced by only one of the trials. Yoosefee et al. (2020) reported that tDCS was delivered by a doctor and nurse trained in the technique, and procedures were monitored to ensure blinding of participants to the intervention was maintained. da Silva et al. (2021) was the only trial of the eleven trials to address the *participant's adherence to the interventions* by arranging for medications to be prescribed and provided daily at the outpatient clinic where brain stimulation took place to ensure the dose remained stable during the trial.

Outcomes Measures and Follow-Up

Overall, the pre-specified primary and secondary outcomes were well reported. A reduction in symptom severity, as measured by the Y-BOCS, was the primary outcome for ten trials. The other trial by Yekta et al. (2015) indicated that decision making, and a reduction of obsession symptoms, assessed using the Y-BOCS, were their primary outcomes. CONSORT standards also require trials to identify whether there were any changes to trial outcomes after the trial commenced. This was an area that was poorly done and only explicitly addressed by Yoosefee et al. (2020). In terms of adverse outcomes of tDCS, all except two trials (Akbari et al., 2022; Yekta et al., 2015) described assessing adverse events and reported that tDCS was generally well-tolerated. The most common adverse effects reported were mild headache, local redness, and itching or tingling of the skull at the electrode site. Three moderate severity events were reported by da Silva et al. (2021), including drowsiness, change in appetite, and muscle tic, but the authors noted that none of the events required any specific intervention. Follow-up periods were included in the design of six trials and varied from 4-weeks to 3-months.

Randomisation and Blinding

A common limitation across all studies was the reporting on randomisation. Despite all trials involving randomisation, the details of the random allocation sequence were often missing or unclear. Five out of eleven studies described the type of randomisation used, and the method used to generate the random allocation sequence. Only two provided details of any restrictions (such as blocking and block size). Likewise, the implementation of random allocation was poorly addressed. Half of the studies reported who generated the random allocation sequence, and who was responsible for enrolling and assigning participants to interventions. However,

only four studies described the methods used to conceal the random allocation sequence. Blinding on the other hand was well reported with ten of the trials providing a description of who (e.g., participants, those administering interventions, and/or those assessing the outcomes) was blinded after assignment to interventions.

Statistical Methods

Generally, most trials (ten) described what statistical methods were used to compare groups for primary and secondary outcomes, and where applicable, reported methods utilised for additional analyses. Seven trials provided sufficient information to be included in a meta-analysis (mean, standard deviation) pre- to post-intervention. Six trials reported an estimated effect size for between group differences for primary and secondary outcomes, and only four studies also reported the precision of the effect size (i.e., 95% confidence intervals [CI]).

Sampling Issues and Participant Flow

Sample size was only addressed by four trials Harika-Germaneau, Heit, et al. (2024); da Silva et al. (2021); Gowda et al. (2019) and (Yoosefee et al., 2020) who reported utilising a power analysis to determine the sample size necessary to observe a significant treatment effect. Four trials did describe their small sample size as a limitation in the discussion section of their trials, whereas three trials did not address sample size, or the issues associated with an underpowered trial.

A participant flow diagram was used by seven out of eleven trials to illustrate the number of participants who were randomly assigned, losses and exclusions after randomisation together with reasons, and the numbers who received the intended treatment and were analysed for the primary outcome. None of the trials reported the delay between randomisation and the initiation of the intervention. Also, no trial

explicitly reported why the trial ended or was stopped, leaving the reader to assume that they stopped due to achievement of sample size and/or follow up was completed.

Discussion Section Items

The limitations, generalisability, and interpretation of the results in most trials were not adequately addressed in the discussion section of articles. All but one study identified at least one limitation associated with their trial. Four trials identified potential sources of bias, recognised imprecision as a limitation (associated with locating stimulation sites without assistance of a neuro-navigation tool), and possible issues associated with blinding (i.e., who was and who was not blinded).

The generalisability of the results in terms of intervention, comparators, patients, care providers and centres involved in the trial was also limited. Most studies (eight out of eleven) discussed generalisability in their papers by acknowledging their patient characteristics in relation to established norms. They did not, however, discuss generalisability in terms of the characteristics of the care providers and unique features of the treatment settings involved with their trials.

The interpretation of findings in the discussion sections was not always consistent with results. Indeed, half of the studies made concluding statements that were incongruent with their results. Despite the majority of trials reporting no significant between group differences in the post-intervention active versus sham outcome measures, tDCS was still described as a promising approach for OCD in the following ways: *"...finding that active tDCS was superior to sham is clinically meaningful..." (p. 1033) (da Silva et al., 2021), "...tDCS has a strong potential to yield positive results and have therapeutic promise..." (p. 59) (Deepak, 2017),* and *"...tDCS could be a clinically helpful resource..."(p.1138) (D'Urso et al., 2016).* Furthermore, some studies only discussed selective results for example, one study

reported an improvement in a decision-making task, one of their primary outcomes, but in the discussion stated that obsessive-compulsive symptoms were also significantly reduced without reporting the post intervention Y-BOCS scores or including the statistical analyses to support the statement. The premise of their interpretation was that impaired decision making is associated with OCD.

Other Information Section

The other information section is comprised of trial registration, access to full protocol, and funding. Half of the studies reported whether their trial was registered, and provided the registration number, and name of the registry. Only half of the studies reported where the full trial protocol could be accessed. Seven of the studies addressed funding, reporting where applicable, the sources, role of funders, and if there was any additional support in kind (such as supply of drugs).

Outcomes Summary of tDCS for OCD

There was a high variability in electrode montages. Whilst the intensity of stimulation was consistent across studies, the stimulation sites, electrode sizes, electrolyte medium, method of securing the electrodes to the scalp, tDCS devices, and the duration and frequency of stimulation were variable (see Table 3). We note that while one randomised sham-controlled study met criteria for inclusion in this review (Fineberg et al., 2023), the authors had explicitly stated that it was a feasibility trial to inform the design of future studies, and to gauge safety, acceptability, and the size of any treatment effect. This trial demonstrated no statistically significant difference between active and sham conditions. Eight further studies involved a sham-controlled design. Of these, Gowda et al. (2019) reported a greater reduction in YBOCS scores and a significantly higher response rate in the active condition, with four out of twelve in the active tDCS group improving,

compared to no responders in the sham group. Akbari et al. (2022) reported a significant difference between the post-test mean scores of OCD symptoms, favouring the active condition ($F = 3.56$, $P < 0.05$, $\eta^2 = 0.24$). Two trials reported no between group difference at immediate post, or at 6-week post-intervention, however, there was a significantly larger reduction in Y-BOCS in tDCS group compared to the sham at 12 weeks $F_{(1, 84.06)} = 84.06$, $p < 0.03$, $d = 0.62$ moderate effect size (da Silva et al., 2021), and $F_{(1, 75)} = 4.60$, $p < 0.035$, $\eta^2 = 0.058$ medium effect (Harika-Germaneau, Gosez, et al., 2024). This suggests that perhaps there is a delayed effect of tDCS and highlights the importance of longer follow-up periods. No significant between group (active v. sham) pre- to post-test differences in Y-BOCS was found in the other four trials. The remaining two studies did not have a true sham-control condition to determine between group differences.

Table 2

CONSORT Evaluation of Treatment Studies in Chronological Order of Publication Date.

	CONSORT ITEMS																								
AUTHOR	Title/abstract	Background/objectives	Trial design	Participants	Interventions*	Outcomes	Sample size	Randomization	Allocation	Implementation	Blinding	Statistical Methods	Participant flow	Recruitment	Baseline data	Numbers Analysed	Outcomes and Estimation	Ancillary Analyses	Harms	Limitations	Generalizability	Interpretation	Registration	Protocol	Funding
Yekta et al., 2015	⦿	⦿	⦿	⦿	⦿	⦿	○	○	○	○	⦿	⦿	⦿	○	⦿	⦿	○	○	○	⦿	⦿	⦿	○	○	○
D'Urso et al., 2016	⦿	●	●	●	⦿	⦿	⦿	○	○	○	●	●	⦿	⦿	●	●	○	○	●	⦿	⦿	●	○	○	○
Deepak, D. K. 2017	⦿	●	⦿	●	⦿	○	⦿	⦿	○	○	●	●	⦿	○	●	●	⦿	○	●	⦿	○	○	○	○	○
Todder et al., 2018	⦿	●	⦿	⦿	⦿	⦿	○	○	○	○	●	●	⦿	○	○	●	○	○	●	⦿	⦿	⦿	○	○	○
Bation, R., et al., 2019	⦿	●	⦿	⦿	⦿	⦿	⦿	●	○	●	●	●	⦿	⦿	●	●	⦿	○	●	⦿	⦿	⦿	●	●	●
Gowda et al., 2019	⦿	●	⦿	●	⦿	⦿	●	●	●	●	●	●	⦿	⦿	●	●	⦿	○	●	⦿	⦿	⦿	●	●	●
Yoosefee et al., 2020	●	⦿	●	●	⦿	●	●	●	●	●	●	●	⦿	●	●	●	●	○	●	⦿	⦿	⦿	●	●	●
da Silva et al., 2021	●	●	●	●	⦿	⦿	●	●	●	●	●	⦿	⦿	⦿	●	●	●	⦿	●	⦿	⦿	●	●	●	●
Akbari et al., 2022	⦿	⦿	⦿	●	⦿	⦿	○	○	○	○	●	⦿	⦿	⦿	○	●	⦿	○	○	○	○	⦿	○	○	●
Fineberg et al., 2023	⦿	●	●	●	⦿	⦿	⦿	⦿	⦿	●	●	●	⦿	⦿	●	●	●	○	●	⦿	⦿	●	●	●	●
Harika-Germaneau et al., 2024	●	●	●	●	⦿	●	●	●	●	●	●	●	●	●	●	●	●	○	●	●	⦿	●	●	●	●

Note. Not Reported ○, Present with limitations⦿, Reported ●, *See table 3 for tDCS replication.

Table 3

Inclusion of Information Needed to Interpret Findings and Replicate tDCS in Real World Conditions

		Electrodes				Electrode Montage		Stimulation Parameters						Setting		Treatments				
								Active			Sham					Previous	Concomitant			
AUTHORS	**tDCS Device (Type/model)**	Type	Size	Contact medium	How secured	Anode	Cathode	Intensity mA	Duration	Frequency	Intensity mA	Duration	Frequency	Type/Location	In-/out-patient	Type & Duration	Dose stability	Type & Duration	Dose stability*	**Adverse Events Assessed**
Yekta et al., 2015	●	●	●	●	○	●	●	●	●	●	●	●	●	●	○	○	○	●	●	●
D'Urso et al., 2016	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Deepak et al., 2017	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	○	○	○	○	●
Todder et al., 2018	●	●	●	○	●	●	●	●	●	●	●	●	●	●	●	●	●	◉	●	●
Bation, R., et al., 2019	●	●	●	●	○	●	●	●	●	●	●	●	●	○	○	●	●	◉	◉	●
Gowda et al., 2019	●	●	○	●	●	●	●	●	●	●	●	●	●	●	○	◉	●	◉	◉	●
Yoosefee et al., 2020	●	●	●	●	●	●	●	●	●	●	●	●	●	●	○	◉	●	●	●	●
da Silva et al., 2021	●	●	●	●	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Akbari et al., 2022	●	●	●	●	○	●	●	●	●	●	○	○	○	●	○	○	○	○	○	○
Fineberg et al., 2023	○	○	○	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Harika-Germaneau et al., 2024	●	●	●	●	●	●	●	●	●	●	●	●	●	◉	●	◉	●	◉	●	●

Note. Not Reported ○, Present with limitations◉, Reported ●; Contact medium (saline solution, electrode gel); *If dose stability was maintained throughout treatment and follow-up periods.

Discussion

This aim of this study was to conduct a systematic review to identify the current research base of RCTs involving tDCS for OCD; to evaluate the quality of the reporting using the CONSORT criteria for the reporting of RCTs of nonpharmacologic treatment, and, to examine the outcomes of tDCS for OCD in RCTs. Eleven RCTs were included in the evaluation. The results indicated low levels of overall compliance with the CONSORT standards highlighting the need for improvement in reporting. It is important to note that research in this field is relatively new, and while none of the studies to date met all of the criteria of the CONSORT, the level of reporting appears to have improved with time. Examination of the outcomes of tDCS for OCD revealed that only two trials found a significant between group (active v. sham) differences, however, one was limited in terms of the quality of reporting. The trial that showed a significant pre- to post-treatment differences in Y-BOCS and demonstrated a more robust reporting of the trial design, involved anodal stimulation of the pre-SMA (Gowda et al., 2019).

Despite the paucity of supporting outcomes in well controlled trials, and the narrow specificity of stimulation sites that have found between group differences favouring active over sham conditions using statistical and clinically significant change methods, favourable reporting of the "promise" of tDCS is common.

The ability to draw any meaningful conclusions about tDCS for OCD, including via a meta-analysis, appears premature, given the variability of stimulation protocols and target sites. These conclusions are further complicated by the methodological limitation of many of the studies. Further issues included small sample sizes (especially in the context of the heterogeneity of OCD), lack of protocol standardisation and assessment to ensure adherence to the protocol, and the absence

of neuro-navigation for consistent location of targeted stimulation sites between sessions, participants, and trials. We acknowledge that, although ideal, the latter would add significant cost to any trial though, and thus may not be feasible. Most trials recruited treatment resistant patients who continued prescribed medication throughout the trial. However, the criteria for what was deemed 'dose stability' (i.e., the minimum period of time required between commencing pharmacotherapy and commencing a trial) varied from 2 to 12weeks. As the efficacy of most antidepressants indicated for OCD have been observed to increase by about 1.5 times across weeks 4-12 (Cheng et al., 2019), this would need be taken into account when evaluating outcomes. Another limitation was the lack of maintenance and follow-up. tDCS studies in other mental health conditions, such as depression, indicate that maintenance sessions may improve clinical outcomes and duration of effects (Martin et al., 2013).

In terms of study reporting, areas that were identified as generally well reported included trial designs, recruitment settings, inclusion/exclusion criteria, and blinding. More than half of the trials included a participant flow diagram (as recommended by CONSORT), making it easier for the reader to see whether losses/exclusions occurred after randomisation, and the number of participants included in the outcomes analyses. However, the period of time between recruitment and the intervention was not reported. The inclusion of the participant flow is important to identify any potential risk of bias. For example, a loss of numbers after randomisation could be due to the participant's inability to continue due to an exacerbation of symptoms or harm from the treatment. Likewise, if the period of time between recruitment (i.e., inclusion/exclusion measures) and the intervention is

not reported, it casts doubt over the validity of the baseline data (i.e., collected no more than 2 weeks prior to commencement of intervention) and the overall result.

The CONSORT criteria of *Intervention* were reasonably met, with most protocols described at a level that allowed the reader to gain a broad understanding of how a trial took place. However, more detail is required for researchers and clinicians to not only determine the quality and clinical significance of a trial, but also for replication of a trial. For example, electrode type, size, electrolyte medium, and how they are secured to the head all need to be reported. Electrodes deliver the current from the tDCS device to the scalp and can be metal or conductive rubber and can vary in size between highly focal to more dispersed charge. An electrolyte medium (i.e., saline solution, gel, or cream) is used as a buffer between the scalp and the electrodes to prevent skin injury and optimise delivery of current. The electrolyte medium can be placed directly on the electrode or, where electrodes are placed in a sponge case, saline solution is used. The volume of saline solution should be measured and described to ensure consistency and reproducibility of stimulation both within-, and between-participants, and to protect the integrity of the results (i.e., if sponges are over-saturated, saline spreads to an area greater than the sponge and targeted brain site). The method used to affix the electrodes to the scalp should also be reported. Elastic straps are often used, but if these are not tight enough, the electrodes can move during a session and change the distribution of current delivery. If the elastic straps are too tight, there is an increased likelihood of saline solution spread and dissipation of the current across the scalp. To ensure consistency throughout a trial, operators should be trained in standardised tDCS techniques, and adherence to established tDCS protocols should be monitored for internal validity

and replicability of results. Only one of the trials addressed adherence to intervention protocol and this is therefore an area that needs improvement in future trials.

Whilst recruitment settings were generally well reported, it was unclear in the majority of trials where *treatment* took place, and whether the sample were inpatients or outpatients at the time. Inpatients receive around the clock care, medication compliance is often monitored, the likelihood of exposure to OCD triggers, and everyday life-stressors (i.e., work, managing a household, raising a family etc.) may be minimised, as are factors like travel, finding parking, and attending appointments on time. With the conditions/environment of inpatients being more strictly controlled, the results are less generalisable. Likewise, inadequate reporting of participant demographics (education level, employment status, socio economic status), access to- and affordability of treatment for OCD, and the level of treatment acceptability impacts on the capacity to generalise.

Future Directions

To draw any meaningful conclusions about the effectiveness of tDCS for OCD, there is a need for appropriately powered, randomised clinical trials that include a sham condition to explore possible placebo effects. To address limitations properly requires investment to facilitate multicentre collaboration to enhance recruitment. Future studies should also include participants with a larger range/grouping of OCD symptom severity to identify the characteristics of potential responders as possible predictors of response, include maintenance and follow-up periods, and would ideally incorporate neuro-navigation techniques to improve precision of locating stimulation sites.

Conclusion

This systematic review and evaluation of the reporting standards of the literature involving tDCS for OCD revealed low levels of overall compliance with the CONSORT standards highlighting a need for improvement in reporting. Aside from the limitations and lack of generalisability of the results in many of the trials, interpretations were often incongruent with the results, and conclusions contained misleading statements suggesting tDCS is a “promising approach" for OCD. Given the limited robust evidence to suggest that any change in Y-BOCS scores may be anything other than a placebo effect, which is in itself interesting, it is timely to consider the value in continuing to conduct underpowered tDCS trials for OCD. Future researchers must conduct appropriately powered, randomised sham-controlled clinical trials with longer follow-up periods, and reported in accordance with the CONSORT statement, to determine whether tDCS is an efficacious intervention for OCD.

Chapter 3. Protocol for Transcranial Direct Current Stimulation for Obsessive-Compulsive Disorder

This study consists of the published protocol for the proposed randomised controlled trial (RCT) that did not proceed due to the inability to recruit, see Chapter 5. This protocol informed the procedures that were used in Study 3 (Chapter 6). The purpose of publishing a protocol was to allow for replicability by other researchers, and to aid in promoting transparency in the research process. Minor edits have been made to the present chapter (e.g., Australian spelling, and referencing style) to ensure consistency within the present thesis.

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Authorship

All signed authors acknowledge that this statement is an accurate representation of their contribution to the above research output.

Author	Contribution	Acknowledgement
Peta E Green	Development of the research question and the design, manuscript preparation, writing and editing manuscript drafts.	[redacted]
Andrea M Loftus	Assisted with the development of the research question and the design, contributed to writing revisions to the manuscript, and editing manuscript drafts.	[redacted]
Rebecca A Anderson	Assisted with the development of the research question and the design, contributed to writing revisions to the manuscript, and editing manuscript drafts.	[redacted]

Abstract

Obsessive-compulsive disorder (OCD) is a debilitating disorder with an approximate lifetime prevalence of 1–3%. Despite advances in leading treatment modalities, including pharmacotherapy and psychotherapy, some cases remain treatment resistant. Non-invasive brain stimulation has been explored in this treatment-resistant population with some promising findings; however, a lack of methodological rigor has reduced the quality of the findings. The current paper presents the protocol for conducting research into the efficacy of transcranial direct current stimulation (tDCS) in the treatment of OCD. A double-blind randomised controlled trial (RCT) will be conducted involving active tDCS vs. sham tDCS on 40 general OCD patients. The intervention consists of 2 mA anodal stimulation over the pre-supplementary motor area (pre-SMA) with the cathode positioned over the orbitofrontal cortex (OFC). Participants will receive 10 sessions of 20 min of either sham- or active-tDCS over 4 weeks. Outcomes will be categorical and dimensional measures of OCD, as well as related secondary clinical measures (depression, anxiety, quality of life), and neurocognitive functions (inhibitory control, cognitive flexibility).

Keywords

OCD, transcranial direct current stimulation, non-invasive brain stimulation, neuromodulation, obsessive-compulsive, protocol, randomised controlled trial.

Introduction

The frontostriatal model suggests that the symptoms of obsessive-compulsive disorder (OCD) are associated with dysfunction in the feedback loop, which leads to hyperactivity in the orbitofrontal cortical (OFC) pathways. As a result, individuals pay more attention to threatening stimuli. Neurological studies indicate that OCD symptoms are associated with increased neuronal activity in the OFC (Adler et al.,

2000; Harrison et al., 2009; Ruffini et al., 2009) and decreased activation in the pre-supplementary motor area (pre-SMA) (de Wit et al., 2012) responsible for inhibitory control. Changes in patterns of activation (both hyperactivity and hypoactivity) in the frontal and motor cortices have been reported in a range of neuropsychiatric disorders, including Attention Deficit Hyperactive Disorder (ADHD) and Schizophrenia (Hasan et al., 2013). It has been suggested that an imbalance in cortical activation may underlie OCD (Brunelin et al., 2018; Hazari et al., 2016; Narayanaswamy et al., 2015). With this in mind, several studies have attempted to address this imbalance in neuronal activation using non-invasive brain stimulation.

Transcranial direct current stimulation (tDCS) is a non-invasive stimulation technique used to modulate cortical activity and, as a consequence, change behaviour (Nardone et al., 2012). tDCS delivers low intensity electrical currents to modulate neuronal activity (Nitsche et al., 2008). tDCS works by applying a positive (anodal) or negative (cathodal) current via electrodes to a targeted brain area. The current modifies cortical excitability by facilitating the depolarisation or hyperpolarisation of neurons respectively. Research in healthy individuals has found that anodal (excitatory) tDCS over frontal areas improves cognitive functioning (Coffman et al., 2014; Hansen, 2012). Lawrence (Lawrence et al., 2018) reported that anodal tDCS over frontal areas led to improved cognition in those with Parkinson's Disease.

Although there is limited research in brain stimulation interventions for OCD, preliminary studies involving tDCS for patients defined as resistant to both CBT and pharmacotherapy have been encouraging. Hazari (Hazari et al., 2016) conducted an open-label study using anodal tDCS over pre-SMA to increase pre-SMA activation, and with the cathode over OFC to decrease OFC activation. The patient, who was on Escitalopram and Clonazepam, received 2mA of current for 20 min, twice a day for

10 days (20 sessions). This tDCS montage was based on the theory that OCD is due to deficient pre-SMA response inhibition on frontostriatal function (de Wit et al., 2012; Nachev et al., 2008). The patient demonstrated an 80% reduction in OCD symptom severity, which was maintained for 7-months post-intervention with minor fluctuations. Whilst the patient did relapse at the 7-month time point, their symptoms improved following a further 8 sessions of tDCS. On both occasions that tDCS was applied, the patient's OCD symptoms had remitted within 5 - 10 days. Narayanaswamy (Narayanaswamy et al., 2015) used the same tDCS protocol combined with therapeutic SSRIs in two patients, who received 2mA of current for 20 min, twice a day for 5 days (10 sessions). Both patients demonstrated significantly reduced OCD symptom severity (52% and 46.7% reduction) that was maintained at 1 and 2-month follow-up assessments. However, despite a few studies reporting positive effects of tDCS on OCD, the efficacy of non-invasive brain stimulation remains ambiguous (Brunelin et al., 2018) and there is a lack of consensus regarding stimulation protocols in regards to frequency, dose, intensity, and electrode montage/positioning. Further, there are several limitations associated with the published studies.

Many of the tDCS and OCD studies published are single-patient case studies, only two have included more than 10 participants (D'Urso et al., 2016; Najafi et al., 2017) and thus the results are not generalisable. No study to date has included a sham-control group. Few studies used an OCD symptom measure as the primary outcome, and those that did, did not indicate whether a change in the OCD symptom measure was clinically significant. Other aspects of functioning such as quality of life, inhibitory control, and cognitive flexibility, have not been explored. Brunelin (Brunelin et al., 2018) conducted a systematic review of studies examining tDCS for

those with OCD and concluded that although a number of studies demonstrated improvements in OCD, there was a lack of methodological rigor that reduced the quality of the findings.

Materials and Methods

The proposed clinical trial (ACTRN12620000990921) will be a double-blind randomised sham-controlled trial of tDCS for OCD to examine the therapeutic potential of tDCS for OCD symptoms. To the best of our knowledge, there has not been a double-blind sham-control RCT of tDCS for OCD, limiting conclusions about the effectiveness of this treatment approach.

Hypotheses

We hypothesise that active tDCS over the pre-SMA and OFC, will be associated with a clinically and statistically significant decrease in OCD symptoms and beliefs, a significant decrease in comorbid depression and anxiety symptoms (if present), and a significant increase in quality of life. We also propose there will be improved inhibitory control, and cognitive flexibility.

Participants

Sampling. Recruitment of participants will occur through several channels. Primary recruitment will occur via the Curtin University Psychology Clinic, which houses a specialist OCD service, whereby promotional material will be distributed to suitable clients. A media release will be made through Curtin University, and private clinics specialising in OCD will be contacted/informed about the project and sent copies of advertising materials. Individuals who wish to take part in the study will follow instructions on the promotional material to contact the researcher. Interested participants will then be sent an information pack and consent form. Potential participants will be telephone screened for tDCS suitability and risk assessment to

address the exclusion criteria prior to commencing the study. Participants who meet the inclusion criteria will then be contacted by the researcher to confirm their willingness to participate, informed of start dates, given the opportunity to ask questions, and to arrange the pre-treatment (baseline) assessment of outcomes. Following the post-intervention assessments (session 10), a time will be scheduled for the three-month and six-month follow-up outcome assessments.

Inclusion Criteria

1. Participants aged over 18-years with obsessive and/or compulsive behaviours who meet the criteria of a clinical diagnosis of OCD 300.3 (F42.2) in accordance with the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychological Association, 2013), using the MINI International Neuropsychiatric Interview - Version 7.0.0 (M.I.N.I) (Sheehan et al., 1998).
2. A minimum Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score of 16, representing a minimum of moderate symptom severity.
3. Participants taking medications (SRI/SSRIs) to manage OCD symptoms will be included as long as the dose has been stable for at least twelve-weeks prior to participation, (Andrews et al., 2018) and they do not plan to change dose during the study.

Exclusion Criteria

1. Participants with a recent history of brain surgery, neurological condition associated with brain abnormalities (e.g., traumatic brain injury; recent stroke, tumour), implanted cranial devices, hearing aids (unless they can be removed), active skin lesions on the scalp.

2. History of migraine, epilepsy, seizures, unstable medical and/or psychiatric conditions; history of psychosis or bipolar disorder; high suicide/self-harm risk.
3. Current or past (within the last 1-month) use of benzodiazepines, anticonvulsants, Lithium Carbonate, psychostimulants, dextromethorphan and pseudoephedrine; recreational drug use.
4. Currently undergoing ERP therapy for OCD; any neuromodulation therapy (e.g., ECT, transcranial magnetic stimulation, tDCS) within the last 3-months.

Randomisation

Participants will be randomly allocated to one of two treatment groups through block randomisation (Schulz & Grimes, 2002), (1) active tDCS, or (2) sham tDCS. A computer-generated randomisation list will be used to allocate participants to groups at a ratio of 1:1 in blocks of four.

Blinding

The investigators (researcher, and supervisors) and the participants will be blinded to group allocation. Each of the 40 participants will be allocated a personal identification (ID) number and be randomly assigned to either the active or sham condition. The administrator (a third party) will create forty protocols, each with the participant's ID number, and load them onto the device. The procedure will be password protected, and the researcher (operator) will not have access to the password. Once the double-blind mode is activated on the device, all non-essential information is hidden on the monitor, keeping the operator unaware of which protocol refers to active stimulation and which protocol is sham. When a participant arrives for their session, the operator will select the protocol number that corresponds

to the participant's ID number on the tDCS device and will not know which condition they have been allocated to.

Study Design

Stimulation will occur in the Curtin Psychology Clinic where tDCS will be administered by the researcher. All participants will complete ten 20-minute sessions of either active or sham tDCS stimulation, over 4 weeks (all outcome-measures to be conducted pre-, and post-intervention, and at three- and six-month follow-ups). See figure 1.

Figure 1.

Transcranial Direct Current Stimulation Protocol and Outcome-Measures Administration

	Week 1				**Week 2**			**Week 3**			**Week 4**	**Follow-up**	
Outcome Measures	**Pre-intervention Assessment**	**10 sessions of tDCS (Active or Sham)**									**Post-intervention Assessment**	**3-mth**	**6-mth**
		S1	**S2**	**S3**	**S4**	**S5**	**S6**	**S7**	**S8**	**S9**	**S 10**			
	T1		**T2**			**T3**			**T4**			**T5**	**T6**	**T7**
MINI	x											x	x	x
Y-BOCS	x		*x*			*x*			*x*			x	x	x
DASS 21	x		*x*			*x*			*x*			x	x	x
OBQ-44	x		*x*			*x*			*x*			x	x	x
Q-LES-Q-SF	x											x	x	x
Stop-Sig	x											x	x	x
Set-Shifting	x											x	x	x

Session (S); Timepoint (T); Outcome-measure (x); Month (mth).

Note. tDCS stimulation protocol for the active and sham groups involves 10 sessions, conducted over four weeks. Participants attend the clinic three times per week with all outcome measures administered at 4-timepoints. Pre-intervention/baseline on day one, post-intervention two days after the final tDCS session (S10), and follow-up measures at three-, and six-months. The Y-BOCS, DASS-21, and OBQ-44 will also be administered at the end of week-1(T2), week-2(T3), and week-3(T4) of the intervention period to monitor changes in symptom severity and/or the sub-domains.

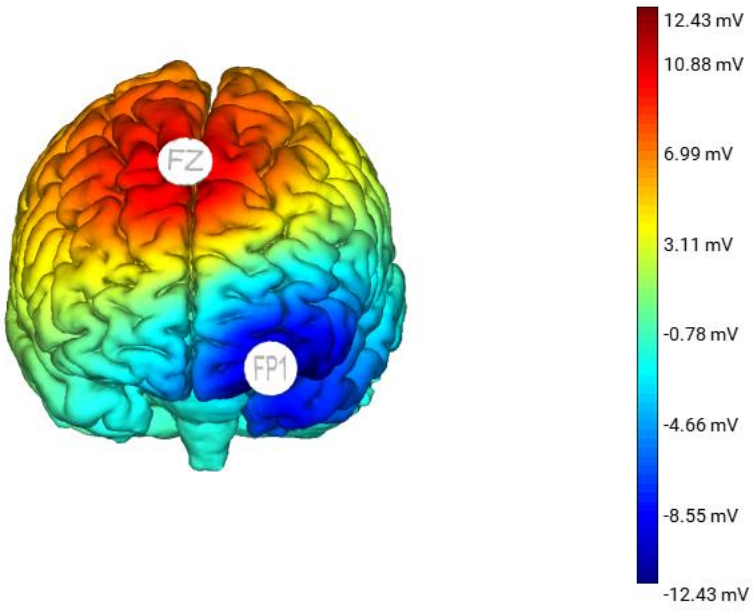
Participants will be seated in a comfortable armchair whilst receiving tDCS which will be delivered for 20-minutes using a battery-driven (Necbox) multi-channel direct current stimulator, the Starstim 20^{TM} (Neuroelectrics, Barcelona, Spain). Stimulation will be administered over the scalp via two 25cm^2 Sponstim (Neuroelectrics, Barcelona, Spain) electrodes. The electrodes consist of a sponge cover, a carbon rubber core, and a nickel-plated brass metallic pin. The external surface of the sponges will be soaked in 5ml of 0.9% saline solution, to minimise the risk of skin irritation, and inserted into Fz (pre-SMA) and Fp1 (OFC) of an adult-sized neoprene cap (S, M, or L) which is pre-labelled according to the 10-20 EEG system of electrode positioning. The participant's head will be measured to locate Cz (mid-line central part of the head), and then the cap will be placed on the participant's head. Once the cap is in the correct position (with Cz lined up), it will be secured in place with a chin strap, and the medical sockets connected to the electrodes. An impedance check will be conducted to ensure optimal conductivity. If the impedance level is high, more saline solution will be added onto the surface of the sponges by inserting a curved syringe through a hole in the cap near the electrode.

Each session will involve 20 minutes of either active or sham stimulation. The tDCS montage (stimulation site, intensity, duration, and frequency) was informed by Kekic's 2016 systematic review (Kekic et al., 2016). The participants in the active group will receive a constant current 2 mA stimulation via the anode placed over the pre-SMA and cathode placed over the left OFC. The anode will increase neural activation of the pre-SMA, and the cathode will decrease neural activation of the left OFC (see Figure 2). For the sham stimulation, the electrode montage will be identical to the active tDCS group, however, the participants will

only receive tDCS for 30 seconds at the start, ramp up (0 – 2 mA) and end, ramp down (2 – 0 mA), of the session. This allows the participants to experience some sensation of tDCS. All participants (active and sham) will be informed that they may or may not perceive any sensation during the treatment, a procedure that has been demonstrated to effectively blind participants and the researcher to the stimulation condition they are in (Gandiga et al., 2006).

Figure 2.

A 3D standardised model of the estimated electric field generated from anodal stimulation over Fz with the cathode placed over Fp1.



Note. This model was produced using the Neuroelectric Stim 20TM Preview function.

Outcome Measures

Diagnostic screening, neuropsychological, and cognitive assessment measures for this study will be administered at baseline, post-intervention, three-month-, and six-month follow-up. The Y-BOCS, Dass-21, and OBQ-44 will also be administered at the end of the 1st-, 2nd- and 3rd-week of the intervention period to

identify if, and when, changes may occur.

Diagnostic Screening. The MINI-7.0.0 [20] for clinical diagnosis of OCD.

OCD Symptom Severity. The Y-BOCS (Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989) measures symptom type and severity over the last seven-day period and consists of two 10-item subscales, obsessions, and compulsions.

The Depression Anxiety Stress Scales. The Depression Anxiety Stress Scales (DASS-21) (Lovibond & Lovibond, 1995), is a self-report measure, to identify and measure any negative affect (if present).

Quality-of-Life. The Quality-of-Life Enjoyment and Satisfaction Questionnaire - short form (Q-LES-Q-SF) (Stevanovic, 2011), also a self-report measure, has 16 items evaluating overall enjoyment and satisfaction with physical health, mood, work, household and leisure activities, social and family relationships, daily functioning, sexual life, economic status, overall well-being, and medications.

OCD Beliefs. The Obsessive Beliefs Questionnaire (OBQ-44) measures OCD beliefs. The OBQ-44 includes (1) perfectionism and intolerance of uncertainty, (2) importance and control of thoughts, (3) responsibility, and (4) overestimation of threat, which are positively associated with obsessive-compulsive symptoms and worry (Myers et al., 2008).

Inhibitory Function. The Stop Signal Task is a choice go/no-go reaction time task to measure inhibitory control. In this computerised task participants are required to discriminate between left and right arrows by pressing the appropriate response key as fast as possible (go) but inhibit their motor response if a beep is played after the presentation of the arrow (no-go) (Verbruggen et al., 2019). The task is designed so that the frequency of the ‘go’ cues are greater than the ‘no-go’

cues resulting in the ‘go’ response becoming prepotent thus, requiring control to inhibit/withhold the response (Chamberlain et al., 2005).

Cognitive Flexibility. Set-shifting task will be used to measure cognitive flexibility. Set-shifting measures the ability to shift attention and respond to a particular aspect of a stimulus depending on a reinforced contingency. The rules or contingencies of the task, change and alternate rapidly requiring the participant to pay attention and respond with the pertinent rule in mind, switching from the old to the new. Individuals with OCD demonstrate repetitive and perseverate behaviour and impairments in set-shifting ability have been reported to be a key neurocognitive feature of OCD (Chamberlain et al., 2005; Veale, 2014).

Potential Side Effects

The procedure is considered very low risk, and no significant adverse events have been reported with low-current procedures such as the ones proposed in this study. Potential side effects of low-current tDCS include localised scalp itching or tingling sensation at the site where the electrode was placed, and seldom-occurring headache or fatigue (Poreisz et al., 2007). If any of these side effects occur the participant will be monitored and if they do not dissipate within an hour (the typical duration of symptoms/s) the participant will be referred for assessment by a medical practitioner. Any adverse side effects will be reported to the appropriate ethics committee. Discontinuation and/or withdrawal from the study will be recorded in the study database.

Data – Sample Size, Management, Analysis

This study will provide evidence for the efficacy of the treatment approach, which may in turn lead to effectiveness trials for clients with more complex or particular OCD profiles. There are no suitable tDCS trials to guide a power analysis

for this study, however, a G*Power calculation indicated that 30 participants (15 per group) are required to detect a moderate effect ($\alpha = .05$; power = .80). We will aim to recruit 40 participants (20 per group) to allow for attrition.

A series of generalised linear mixed models (GLMMs), one for each of the seven outcome measures, will be used to determine whether active and sham tDCS differ at pre- versus post-intervention on the outcome measures. The GLMMs will be completed using the GENLINMIXED procedure in SPSS (Version 26). GLMMs are used to control for outcome variables when the data is not normally distributed and includes random and fixed effects (McCulloch & Neuhaus, 2005). This study has one nominal random effect (participant) and one nominal fixed effect (group: tDCS **vs.** Sham), one ordinal fixed effect (time: pre, post, three- & six-month follow-up), and the Group x Time interaction. GLMMs are robust against unequal groups (Krueger & Tian, 2004) and unlike ANOVAs, GLMMs do not rely on participants providing data at each assessment point reducing the effect of participant attrition on statistical power.

This study will conform to the guidelines under section 2 of the Australian Code for Responsible Conduct of Research. All hard data (diagnostic screening, consent forms, psychometric measures) will be stored in a clinic file as part of the current clinic procedure. Data will be extracted and stored in a de-identified manner separate from the Clinic file. Deidentified data will be shared if required by a Journal. All electronic data will be password protected, stored on the Curtin research drive, and backed up on an external hard drive, which will be kept in a locked drawer. Data will be kept for a minimum of 25 years as per the Western Australian University Sector Disposal Authority (WAUSDA) guidelines for clinical trials, and only the researcher and supervisors will have access to data.

Ethics and Dissemination

This study will be conducted in accordance with the National Health and Medical Research Council (NHMRC, 2007) and the Code of Ethics (APS, 2007). Ethics has been approved by the Curtin University Human Research Ethics Committee HRE2020-0266. All participants will provide written informed consent following a verbal and written explanation of the study protocol and the opportunity to ask any questions. Participants will be informed that participation is voluntary and that they have the right to withdraw at any time without question (APS, 2007; NHMRC, 2007). Results will be presented at conferences and reported in international peer-reviewed journals.

Discussion

This paper presents the protocol of a study designed to explore the efficacy and advance the knowledge of tDCS as a potential therapy for OCD. Current evidence-based treatments for OCD are pharmacotherapy and/or psychotherapy, however, considerable issues associated with tolerance and/or resistance to these treatments and subsequent relapse, have led to a call for an alternative approach. Non-invasive brain stimulation has been explored in treatment resistant cases demonstrating some promising findings. However, the efficacy of tDCS as a treatment option remains ambiguous due to a lack of methodological rigour and clarity. We believe this is the first double-blind randomised controlled trial to assess the efficacy of tDCS as a novel treatment intervention for OCD. This study will inform whether there is sufficient evidence of a treatment effect to progress to effectiveness trials and/or a larger, multicentre RCT, which has higher costs and greater potential participant burden due to half of all participants receiving a sham treatment that is likely ineffective.

Acknowledgments: The authors would like to thank Emily Corti for her assistance and technical support, and Dr. Robert Kane for his statistical advice.

Chapter 4. Study Two - Examining the acceptability of transcranial direct current stimulation as a treatment approach for obsessive-compulsive disorder.

The following chapter has been submitted for publication in The Journal of Obsessive Compulsive and Related Disorders and is currently under review. Only minor edits have been made to the present chapter (e.g., Australian spelling, and referencing style) to ensure consistency within the present thesis.

Authorship

All signed authors acknowledge that this statement is an accurate representation of their contribution to the above research output.

Author	Contribution	Acknowledgement
Peta E Green	Development of the research question and the design of the survey instrument, manuscript preparation, writing and editing manuscript drafts.	[redacted]
Andrea M Loftus	Assisted with the development of the research question and the design of the survey instrument, contributed to writing revisions to the manuscript, and editing manuscript drafts.	[redacted]
Blake J Lawrence	Provided statistical consultation and support.	[redacted]
Rebecca A Anderson	Assisted with the development of the research question and the design of the survey instrument, contributed to writing revisions to the manuscript, and editing manuscript drafts.	[redacted]

Abstract

There are a growing number of studies exploring transcranial direct current stimulation (tDCS) for obsessive-compulsive disorder (OCD). However, there are no published consumer-based studies on its acceptability and the likelihood of uptake. This study examined the acceptability of several treatment approaches for OCD, including tDCS, and explored the impact of any prior treatment for OCD, symptom severity, and different levels of information on acceptability and treatment preference. Two hundred participants with moderate to severe OCD rated the acceptability of evidence-based treatments for OCD [cognitive behavioural therapy with exposure and response prevention (CBT-ERP), pharmacotherapy], and novel treatments [tDCS, and deep brain stimulation (DBS)] following a lay explanation and ranked them in order of preference. Participants then re-rated/-ranked each of the treatments following a scientific explanation. CBT-ERP (46.5%) was the preferred treatment over pharmacotherapy (40%), tDCS (9.5%), and DBS (4%). Levels of information (lay versus scientific), prior treatment experience, and symptom severity had a significant effect on acceptability (p <.05) but not on treatment preferences. Responses to open ended questions indicated that individuals with OCD require more information regarding the safety, efficacy, and effectiveness of tDCS before they could consider its acceptability. Greater symptom severity and any prior treatment experience for OCD increased the overall acceptability of tDCS. Whilst tDCS was not a preferred treatment option, providing additional scientific information may be the key to improving acceptability.

Keywords

Obsessive-compulsive disorder, treatment acceptability, non-invasive brain stimulation, transcranial direct current stimulation, cognitive behavioural therapy with exposure and response prevention, pharmacotherapy treatment preferences.

Introduction

Obsessive-compulsive disorder (OCD) is a debilitating psychiatric disorder with an approximate lifetime prevalence of 1-2% (American Psychological Association, 2013). Current evidence-based treatment options for OCD are pharmacotherapy and/or cognitive behaviour therapy that includes exposure and response prevention (CBT-ERP). While some with OCD do respond to serotonin reuptake inhibitors (SRIs) and selective serotonin reuptake inhibitors (SSRIs), pharmacotherapy is not always effective and approximately 60% of those with OCD do not respond to these approaches (Gershkovich et al., 2017). Further, discontinuation of medications is associated with symptom relapse (Fineberg et al., 2015). Whilst CBT-ERP is an acceptable and the most effective psychological treatment (Olatunji et al., 2009; Öst et al., 2015; Villena-Jimena et al., 2018), a significant percentage of OCD sufferers (14-31%) are classed as non-responders (Foa et al., 2005; Norberg et al., 2008). Of those who do respond to treatment, approximately 60% demonstrate at least partial relapse (Eisen et al., 2013; Simpson et al., 2005).

People with anxiety disorders and those at high risk for developing them demonstrate deficits in the neural mechanisms underlying extinction and inhibitory learning (Craske et al., 2008; Lissek et al., 2005; Steuber & McGuire, 2022). Optimising inhibitory learning therefore offers the potential to compensate for the

neural deficits that present in individuals with OCD and enhance treatment efficacy by inhibiting the return of fear (see Craske et al., 2012).

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that delivers low intensity electrical currents to modulate cortical activity. Depending on the location of delivery, tDCS has been demonstrated to alter maladaptive behaviour (Nardone et al., 2012). A recent systematic review and secondary meta-analysis recommended the use of tDCS in nine neurological and psychiatric conditions, including OCD (Fregni et al., 2021). However, the review only included 8 studies on OCD, and all were based on a limited number of treatment resistant cases of OCD.

Given the percentage of non-responders and rate of relapse for those with OCD, it is important to explore new therapeutic approaches. Consumer preferences and clinical recommendations for treatment of OCD have been explored and found to be in concordance (Villena-Jimena et al., 2018). Whilst research into the efficacy of tDCS for OCD is in its early stages, there is no research examining the acceptability of tDCS as a treatment option. Treatment preferences and the acceptability of first line and novel treatment approaches for OCD were explored by Patel et al. (2016); Patel and Simpson (2010). They reported that CBT-ERP was the preferred first line treatment approach over serotonin reuptake inhibitor (SRI) medications. However, tDCS was not amongst the novel treatments options they explored. Despite the growing number of studies involving tDCS, there are no published consumer-based studies on its acceptability, and we have no information about what the likelihood of uptake would be.

The present study examined the acceptability and preferences for four treatment approaches (CBT-ERP, pharmacotherapy, tDCS, and DBS) for OCD.

Acceptability was defined as the degree that participants with moderate-severe OCD were comfortable with a given treatment and would be willing to use it. This study expands on the research of Patel and colleagues by including tDCS as an emerging treatment approach. Accordingly, study aims were to 1) examine the acceptability and preferences for the four treatments, 2) determine whether acceptability and preferences changed based on the nature of the information provided about the four treatments (lay versus scientific summary), and 3) explore the impact of symptom severity and any prior treatment experience on the acceptability and preferences for the four treatment approaches. The study also included open ended questions to examine other factors that influenced responses.

Method

An anonymous online survey examined treatment acceptability and preferences amongst adults who self-identified as having OCD symptoms. Recruitment was via social media, university media alerts/press releases, professional contacts of the supervisors, and snowball recruitment. Advertisements directed interested participants to a QualtricsXM® survey site where further information regarding the study, inclusion and exclusion criteria was provided, and informed consent was obtained. Demographic information was collected including age, gender, marital-status, whether they were employed, and diagnostic-status of OCD, by whom that diagnosis was made (i.e., psychiatrist, psychologist, GP), and treatment history. Participants then completed the survey.

Materials

OCD symptom severity was assessed using the Obsessive-Compulsive Inventory-Revised (short version, (OCI-R) Foa et al., 2002), an 18-item self-report measure. The possible range of scores is 0-72, and the mean score for persons with

OCD is 28.0 (*SD* = 13.53) (Foa et al., 2002). The OCI-R demonstrates good reliability and convergent validity and is often used to differentiate individuals with OCD from those without OCD (Foa et al., 2002).

Two sets of treatment descriptions were developed for the study. The first set provided lay summaries of each of the four treatments in the study. For example,

> *Transcranial Direct Current Stimulation (tDCS) is a painless, non-invasive brain stimulation technique. It involves placing two electrodes on your head that deliver a constant, low-intensity current to the brain. This current stimulates the parts of the brain which are thought to be implicated in OCD. You are awake during treatment, and no anaesthesia or surgery is involved. Usually, treatment lasts for 20 minutes, 3 times per week for 4 weeks. Doses and intensities can vary.*

The second set provided information about the level of evidence supporting each of the four treatments in the study. For example,

> *tDCS is a painless non-invasive brain stimulation technique that has been found to be helpful for depression and schizophrenia. Research suggests that tDCS may improve OCD symptoms, and further research is underway.*

All information in the lay and scientific summaries were sourced from the Royal Australian New Zealand College of Psychiatrists (2018) and the International OCD Foundation (2020). The four treatment descriptions within the lay and scientific sets were matched as closely as possible for sentence structure, wording, and reading ease using a readability formula (Ley & Florio, 1996).

Participants were asked to rate the acceptability of each treatment using a 5-point Likert Scale that ranged from 1(unacceptable) to 5 (acceptable). When 3 (uncertain) was selected, a free text box was presented, and participants were asked

"Is there anything more you would like to know to help you make a decision? Please specify". All participants were then asked to rank their preference (1, most preferred to 4, least preferred) for each of the four treatment options.

Following treatment acceptability and preference rankings based on the lay summaries, participants were then informed that the four treatment approaches have different levels of scientific support, and the brief additional scientific summaries were provided. Having read the scientific summary statements for each treatment option, participants were then asked to re-rate/-rank treatment acceptability and preferences again.

Data Analysis.

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 26. Descriptive statistics and a series of ANOVAs; Mann Whitney U tests and Kruskal Wallis one-way ANOVAs for non-parametric ordinal (ranked) data were used to examine associations between demographic, symptom, and treatment variables and preferences. The data from the open-ended questions concerning 'uncertainty' about tDCS were reviewed by all authors manually to identify concerns and potential barriers to engagement with tDCS.

Results

Participants

The survey was accessed by 416 respondents from 16 different countries who self-identified as having OCD symptoms. Two hundred and eighteen participants completed the survey, however, only participants who demonstrated a score ≥16 on the OCI-R were included in the data analysis (N =200). This threshold was set based on meeting a minimum of moderate OCD symptoms in a prior study (Abramovitch et al., 2020). The mean age was 33-years, participants were predominantly female, and

tertiary educated. The mean OCI-R was 36.27 with a standard deviation (SD) of 11.86, approximately two thirds had been formally diagnosed with OCD with the greatest portion being diagnosed by a psychiatrist and over half of the respondents had received treatment. See Table 1 for a description of participant demographics.

Table 1

Participant demographics

	Total (N=200)	
Characteristic	***N***	**%**
Age ($\overline{x}$ ± SD)	33 ± 11years	
Female	132	66.0%
Education – Highest Level Attained?		
High School	45	22.5%
TAFE/Technical Collegee	48	24.0%
Bachelor Degree	70	35.0%
Master's Degree	34	17.0%
PhD	3	1.5%
Employment Status?		
Employed	104	52.0%
Unemployed looking for work	26	13.0%
Homemaker	9	4.5%
Retired	5	2.5%
Student	38	19.0%
Unemployed unable to work	13	6.5%
Other	5	2.5%
Marital Status?		
Single (never married)	98	49.0%
Married/Living with partner	78	39.0%
Separated/Divorced	22	11.0%
Widowed	2	1.0%
Country/Region		
Africa	1	0.5%
Australia	122	61.0%
Europe	13	7.0%
Other Asia-Pacific	9	4.0%
North America	53	26.5%
South America	2	1.0%
Been diagnosed with OCD?		
Yes	138	69.0%
No	62	31.0%

Diagnosed by Whom?	***N*=138**	
General Practioner	24	17.4%
Psychiatrist	65	47.1%
Psychologist	46	33.3%
Other	3	2.2%
Ever been prescribed medication for OCD?	***N*=113**	
Yes	100	88.5%
No	13	11.5%
Ever received CBT-ERP?		
Yes	66	58.0%
No	47	42.0%
Other treatments for OCD?		
Yes	87	77.0%
No	26	23.0%
OCI-R Total Syptom Severity	***N* = 200**	
$\overline{x}$=36; Range 16 - 69		
Moderate 16-27	58	29.0%
Severe >28	142	71.0%

Lay Summary

Acceptability.

The mean acceptability ratings following the lay summary are presented in Table 4. Pharmacotherapy was rated as more acceptable than CBT-ERP, followed by tDCS, and then DBS. Paired samples t-tests revealed a significant difference between the means of each of the treatments ($p < .001$), except between how participants rated CBT-ERP and pharmacotherapy $p = .865$.

Impact of any prior treatment for OCD on acceptability. Mann Whitney U tests revealed that any prior treatment experience was associated ($p < .05$) with how participants rated the four treatments. Participants who had previously received treatment for OCD rated the four treatments higher than those who had no prior experience with treatment (see Table 2). Given the majority of participants had received multiple prior treatments (Pharmacotherapy = 88%, CBT-ERP = 58%, and

77% had tried other treatments for OCD), it was not feasible to identify the impact of individual forms of prior treatments on acceptability.

Impact of symptom severity. A series of Mann Whitney U tests revealed that symptom severity was associated with the acceptability of tDCS, pharmacotherapy, and DBS, but not CBT-ERP following a lay summary (see Table 2).

Table 2.

Impact of any prior treatment (left), and Symptom Severity (right) on treatment acceptability following a lay summary statement.

	Yes	No	Yes	No	Yes	No	Yes	No
Acceptability	**tDCS**		**Pharma**		**CBT-ERP**		**DBS**	
Mean Rank	107.72	91.13	109.59	88.69	110.11	88.02	110.03	88.13
U	4100.00		3888.00		3829.50		3839.00	
Z	-2.12		-2.77		-2.84		-2.73	
Sig (2-tailed)	0.03*		0.01*		0.01*		0.01*	
r	0.15		0.20		0.20		0.19	

	Mod	Severe	Mod	Severe	Mod	Severe	Mod	Severe
Acceptability	**tDCS**		**Pharma**		**CBT-ERP**		**DBS**	
Mean Rank	85.13	106.78	84.07	107.21	97.81	101.60	85.00	106.83
U	3226.50		3165.00		3962.00		3219.00	
Z	-2.54		-2.81		-0.47		-2.49	
Sig (2-tailed)	0.01*		0.01*		0.66		0.01*	
r	0.18		0.20		0.03		0.18	

N = 200. Any prior treatment for OCD - Yes n = 113, No n = 87; OCI-R = Obsessive Compulsive Inventory – revised; OCD Symptom Severity on OCI-R - Moderate n = 58, Severe n = 142

Note: U = Mann-Whitney U; tDCS = Transcranial Direct Current Stimulation; Pharma = Pharmacotherapy; DBS = Deep Brain Stimulation; CBT-ERP = Cognitive Behaviour Therapy with Exposure and Response Prevention; * = significance probability value <.05, r = effect size; Cohen (1988) reports the following intervals for r: .1 to .3: small effect; .3 to .5: intermediate effect; .5 and higher: strong effect.

Preferences

When participants were provided with a lay summary, they ranked CBT-ERP as their most preferred treatment, followed by pharmacotherapy, tDCS, and then DBS (see table 6).

Impact of any prior treatment for OCD on preferences. Participants who had previously received OCD treatment were more likely to endorse DBS as a preferred option compared those who had not received any prior treatment. However, given the small number of individuals choosing DBS as their preferred option, this finding should be interpreted with caution. Prior experience with treatment did not significantly impact how tDCS, pharmacotherapy, or CBT-ERP were ranked (see Table 3). Prior treatment experience was not associated with treatment preferences following a scientific summary.

Impact of symptom severity. There was no association between symptom severity and treatment preferences when a lay summary was presented (all p values > .05, see Table 3). Following the scientific summary paired samples t-tests revealed that participants with severe OCD symptoms (Mean Rank = 110.74, n = 58) ranked DBS significantly higher than those who had moderate symptoms, (Mean Rank = 96.32, n = 142) with respect to other treatments, U = 3524.00, z = 1.99, p = .05, two-tailed test. The effect size was small (r = .14). There was no association between symptom severity on treatment preferences for tDCS, pharmacotherapy, and CBT-ERP, all p values > .05.

Table 3.

Impact of any prior treatment (left) and Symptom Severity (right) on treatment preferences following a lay summary.

	Yes	No	Yes	No	Yes	No	Yes	No
Preference	**tDCS**		**Pharma**		**CBT-ERP**		**DBS**	
Mean Rank	97.96	103.80	101.21	99.58	98.19	103.51	107.71	91.13
U	4628.00		4835.50		4654.00		4100.50	
Z	-0.76		-0.21		-0.69		-2.42	
Sig (2-tailed)	0.45		0.83		0.49		0.02*	
r	0.05		0.01		0.05		0.17	

	Mod	Severe	Mod	Severe	Mod	Severe	Mod	Severe
Preference	**tDCS**		**Pharma**		**CBT-ERP**		**DBS**	
Mean Rank	105.44	98.48	97.53	101.71	96.36	102.19	107.22	97.76
U	3831.5		3946		3878		3728.5	
Z	-0.83		-0.49		-0.7		-1.26	
Sig (2-tailed)	0.41		0.62		0.49		0.21	
r	0.06		0.03		0.05		0.09	

N = 200. Any prior treatment for OCD - Yes n = 113, No n = 87; OCI-R = Obsessive Compulsive Inventory – revised; OCD Symptom Severity on OCI-R - Moderate n = 58, Severe n = 142

Note: U = Mann-Whitney U; tDCS = Transcranial Direct Current Stimulation; Pharma = Pharmacotherapy; DBS = Deep Brain Stimulation; CBT-ERP = Cognitive Behaviour Therapy with Exposure and Response Prevention; * = significance probability value <.05, r = effect size; Cohen (1988) reports the following intervals for r: .1 to .3: small effect; .3 to .5: intermediate effect; .5 and higher: strong effect.

Scientific Summary

Acceptability.

Two-tailed, paired samples t-tests compared the rating of treatment options following a lay versus scientific summary statement. A scientific summary was associated with significantly increased ratings for tDCS, DBS, and CBT-ERP, but did not impact pharmacotherapy (see Table 4).

Table 4.

Treatment acceptability, lay versus scientific statements.

	Summary Statement				
	Lay	**Scientific**			
Treatment	***M (SD)***	***M (SD)***	***t***	***p***	***g***
Pharmacotherapy	3.88 (.92)	3.94 (.85)	1.30	.20	.09
CBT-ERP	3.86 (1.05)	4.01 (0.87)	2.34	.02*	.16 small
tDCS	3.32 (1.01)	3.71 (0.89)	6.94	.00*	.49 med
DBS	2.60 (1.14)	2.96 (1.13)	6.30	.00*	.44 med

Note. tDCS = Transcranial Direct Current Stimulation; DBS = Deep Brain Stimulation; CBT-ERP = Cognitive Behaviour Therapy with Exposure and Response Prevention; t = paired sample t-tests; *= significance probability value <.05, g = Hedges g effect size (.2 small, .5 medium, .8 large).

Impact of any prior treatment for OCD on acceptability. Mann Whitney U tests revealed that following a scientific summary, prior treatment continued to be associated with treatment acceptability except for tDCS (see Table 5).

Impact of symptom severity on acceptability. A series of Mann Whitney U tests revealed that symptom severity was associated with the acceptability of DBS following a scientific summary, p = .01. Participants with severe symptoms rated

DBS as more acceptable than those with moderate symptoms. Symptom severity was not associated with the acceptability of tDCS, CBT-ERP, and pharmacotherapy following a scientific summary (see Table 5).

Table 5.

Impact of any prior treatment (left) for OCD, and symptom severity (right) on acceptability of treatments following a scientific summary.

Any Prior Treatment for OCD									**OCD Symptom Severity - OCI-R**								
	Yes	No	Yes	No	Yes	No	Yes	No		Mod	Severe	Mod	Severe	Mod	Severe	Mod	Severe
Acceptability	**tDCS**		**Pharma**		**CBT-ERP**		**DBS**		**Acceptability**	**tDCS**		**Pharma**		**CBT-ERP**		**DBS**	
Mean Rank	105.8	93.61	109.25	89.14	107	92.06	110.84	87.07	**Mean Rank**	94.16	103.09	94.10	103.11	104.84	98.73	85.35	106.69
U	4316.5		3927		4181.5		3747.5		**U**	3750.50		3747.00		3866.50		3239.50	
Z	-1.7		-2.81		-1.99		-2.98		**Z**	-1.14		-1.15		-0.743		-2.45	
Sig (2-tailed)	0.09		0.01*		<0.05*		<.01*		**Sig (2-tailed)**	0.25		0.249		0.46		0.01*	
r	0.12		0.2		0.14		0.21		**r**	0.08		0.08		0.05		0.17	

N = 200. Any prior treatment for OCD - Yes n = 113, No n = 87; OCI-R = Obsessive Compulsive Inventory – revised; OCD Symptom Severity on OCI-R - Moderate n = 58, Severe n = 142

Note: U = Mann-Whitney U; tDCS = Transcranial Direct Current Stimulation; Pharma = Pharmacotherapy; DBS = Deep Brain Stimulation; CBT-ERP = Cognitive Behaviour Therapy with Exposure and Response Prevention; * = significance probability value <.05, r = effect size; Cohen (1988) reports the following intervals for r: .1 to .3: small effect; .3 to .5: intermediate effect; .5 and higher: strong effect

Preferences

Two-tailed, paired samples t-tests compared the ranking of treatments in order of preference from their most preferred to least preferred treatment following a lay versus scientific summary statement. CBT-ERP was ranked as their most preferred treatment; followed by pharmacotherapy, tDCS, and then DBS. Provision of a scientific summary resulted in no significant change to both the order and the percentages of individuals endorsing a treatment as their first preference (all p values > 0.5). See table 6 for ranking of treatment preferences following a lay versus scientific explanation.

Table 6

Ranking treatments preferences lay vs scientific explanation

	Summary Statement				
	Lay		**Scientific**		
Treatment	**n**	**%**	**n**	**%**	**p**
CBT-ERP	93	46.5	90	45	0.67
Pharmacotherapy	80	40	87	43.5	0.51
tDCS	19	9.5	19	9.5	0.46
DBS	8	4	4	2	0.34

Note. N = 200; p – significance probability value < .05; tDCS = Transcranial Direct Current Stimulation; DBS = Deep Brain Stimulation; CBT-ERP = Cognitive Behaviour Therapy with Exposure and Response Prevention

Summary of Open-Ended Questions

When participants rated the acceptability of treatments, those who were uncertain were asked to comment about what more they would like to know to decide. Of the 57 participants who said they were uncertain about tDCS, 31 provided comments. The comments reflected that 23.1% wanted more information for example, *"Information about clinical trials, if doctors recommend it"*. 23.1% wanted

to know if the treatment is safe, and if there are any side effects *"Are there possible side effects, and if so, what are they?"* 17.1% wanted to know what scientific evidence there was to support its use, for example, *"Need more scientific evidence"*; and 17.1% asked "*what the long-term effects were*?". Other miscellaneous comments (17.1%) included "*what does tDCS feel like?*", "*what's the cost?*", and "*what patient satisfaction is like?*".

Following the scientific summaries, only 29 participants remained uncertain about tDCS and 13 of those provided comments. The comments thus reflected that the majority (46.1 %) required more scientific evidence to make a decision; 23.1% wanted to know what the long-term effects were; and the remaining 30% were miscellaneous comments including potential side effects and whether the treatment would be painful.

Discussion

To the best of our knowledge, this study is the first to explore consumer perspectives on the acceptability of tDCS as an emerging treatment approach for OCD. Treatment preferences and the acceptability of tDCS, and other treatment approaches, for OCD were examined. This study also explored the factors that influence acceptability and preference ratings of treatment options for OCD, including symptom severity and prior treatment. Further, this study sought to examine whether participants required other information in making decisions about treatment options, and what the nature of that information may be.

Acceptability and Treatment Preference

The findings of this study indicate that participants preferred CBT-ERP followed by Pharmacotherapy, over those with a more limited evidence base as an OCD treatment option (tDCS and then DBS). This is consistent with previous

research by Patel and Simpson (2010) who found treatment preferences for OCD favoured CBT-ERP and pharmacotherapy to other novel treatment approaches with (DBS, Transcranial Magnetic Stimulation) and without an evidence base (Investigational-Medication, Investigational-Psychotherapy, Meditation, Yoga, or Herbal Remedies). Similar results were reported by McHugh et al. (2013) following a meta-analytic review examining patient preferences for psychiatric treatment. They found a three-fold preference for psychological treatment relative to medication for a range of psychiatric disorders (McHugh et al., 2013). Given that OCD is an anxiety disorder associated with hypervigilance for threat, and involves a need for certainty and control (Haciomeroglu, 2020), it makes sense that people may be wary of novel treatments and more comfortable with the more familiar, established approaches. Based on the 'mere exposure-effect', a phenomenon whereby people develop (Schoeller, 2023)preferences for things merely because they are familiar with them (Zajonc, 1968), it may be necessary to raise awareness of tDCS (i.e. via social-, print-media) and provide consumers with more information. Otherwise, it may be difficult to engage participants in treatment trials to test these novel approaches.

Level of Information

The nature of information provided (lay versus scientific summary) did have an impact on the acceptability of treatments. The provision of additional information about the level of evidence supporting each of the four treatments increased the acceptability of all but pharmacotherapy. Given that 88% of participants indicated they had prior experience with prescription medication for OCD, this finding may be attributed to a ceiling effect. That is, participants had already accepted medication as a viable option for OCD, and therefore their acceptability scores could not significantly increase when further information was provided. The provision of a

scientific summary increased the acceptability of the other treatment options, including tDCS. Key features of OCD include pathological doubt (Schoeller, 2023) and an intolerance of uncertainty (Tolin et al., 2003). It seems reasonable to suggest that the provision of scientific information helped to reduce some of the doubt and uncertainty surrounding the other treatment options, which in turn increased their acceptability.

Although the level of information (lay versus scientific summary) impacted significantly upon treatment acceptability, it had no impact upon preference ratings. CBT-ERP remained the most preferred treatment option over pharmacotherapy, tDCS, and DBS. One account for this may be found in participant responses to the open-ended questions included in the study. Participants indicated that they needed more information about the given treatment option, including whether the treatment is safe, what it feels like (sensation), if there are any side-effects, and whether there is any evidence to suggest it actively reduces OCD symptoms. Unless the scientific summary provided this specific information about a treatment option, participants may not have been inclined to change their preference rating. This highlights the importance of identifying what information is important to the consumer and providing that specific information, supported by evidence-based research, to increase the likelihood of engagement with emerging treatments options like tDCS.

Symptom Severity

Those with greater self-reported OCD symptom severity rated all treatment approaches, except CBT-ERP, as more acceptable compared to those with moderate symptoms. This suggests that those with more severe symptoms are more accepting of other treatments, even when there is limited evidence of their efficacy for OCD. This indicates that those with more severe symptom severity are less inclined towards

CBT-ERP, possibly because CBT-ERP can be quite confronting and distressing. Those with more severe OCD symptoms are more likely to experience taboo obsessions (for example, paedophilic intrusive thoughts) that are more distressing to talk about and confront in exposure exercises than typical obsessions such as contamination or symmetry (Abramowitz et al., 2003).

Despite our findings and the literature suggesting that individuals prefer psychotherapy over pharmacotherapy (McHugh et al., 2013; Patel et al., 2016; Patel & Simpson, 2010), the impact of symptom severity on treatment preferences was not explored in these studies. Whilst treatment guidelines for OCD (National Institute of Clinical Excellence - NICE) state that the combined approach is best-practice for those with more severe symptoms, individuals are more likely to be prescribed pharmacotherapy as a first-line treatment option to reduce the level of distress (Konstantinidou & Evans, 2015). The primary benefit of medications is that some people may see a quicker, short-term improvement in their symptoms, especially if their case is severe. Medication may therefore be perceived as a 'magic bullet'. Another possible explanation for CBT-ERP not being as acceptable by those with severe symptoms may be that they have tried this approach without improvement. Some practitioners struggle to deliver CBT-ERP effectively (Gillihan et al., 2012), and it could be that those who have tried it without success may now only be open to a medicalised approach.

Limitations

Recruitment for the current study was predominantly via social media and OCD support groups. A degree of sampling bias may therefore exist, as these participants are more likely to be looking for information about different treatment approaches for OCD, have good insight into their OCD symptoms, and may not have

responded well to previous treatments. Our sample were also predominantly female, well educated, employed, and from western countries, with severe symptom severity. Although OCD is more common in adult females (APA, 2013) the sample may not be generalisable to those with mild to moderate symptoms or from different backgrounds.

The present study relied upon self-report of an OCD diagnosis and the OCI-R to confirm the presence and severity of obsessive-compulsive symptoms. An independent diagnosis would have strengthened the generalisations of the study findings to the wider OCD community. The presence of comorbidities such as major depression and other anxiety disorders and their severity, were not measured and may have impacted upon treatment acceptability and preferences. For example, if a respondent had a negative experience with medication prescribed for another anxiety disorder, they would be less likely to rate pharmacotherapy as acceptable for OCD. A study of depression in an outpatient population found that participant's acceptance of a change to treatment was associated with the results of previous experience with treatment (Wisniewski et al., 2007).

The current study did not assess participant's level of understanding of different treatments prior to their involvement in the study. If a participant was already familiar with one or more treatments included in the study, this may have biased their responses. Future studies should consider the role not only of prior experience with a treatment, but prior knowledge of a treatment. Further, the current study was limited by its sample size as it was not possible to examine some of the finer details such as the impact of prior experience with particular treatments or treatment combinations on treatment acceptability and preferences for OCD.

Conclusion

Evidence-based treatments for OCD (CBT-ERP, and pharmacotherapy) were the most preferred treatment options over tDCS, and DBS. Being offered more information (lay versus scientific summary) about the individual treatments increased the acceptability ratings of most but had no impact on treatment preferences. tDCS was more acceptable to those who had previous experience with any treatment for OCD and those who reported greater symptom severity, indicating that this may be a viable treatment option for those who are treatment resistant. In order for tDCS to be adopted into any healthcare approach, consumers need to be informed about what it is, what it feels like, that this approach is safe and demonstrates comparative efficacy to established evidence-based treatments for OCD.

Chapter 5. Recruitment challenges for RCT

Introduction

A double-blind randomised controlled trial (RCT) to examine the impact of tDCS on OCD had been planned for this PhD. The RCT design was in accord with the CONSORT requirements for nonpharmacological interventions (Boutron et al., 2017) and had been prospectively registered on the Australian New Zealand clinical trials register (ANZCTR). The details relating to the design, hypotheses, materials and methodology for the RCT was informed by the protocol developed for tDCS for OCD (Green et al., 2020), and can be found in chapter three. Despite an 18-month recruitment period for this trial, we were unable to recruit any participants. Whilst difficulty in recruiting for clinical research studies is a well-recognised problem (Mirza et al., 2022), the COVID-19 pandemic presented an additional barrier for this RCT.

COVID-19

Following the announcement of COVID-19 as a pandemic in early March 2020 (World Health Organization, 2020), Australia, like many countries around the world went into a lockdown to prevent its spread. Preventive practices put into place by the federal and state governments (Storen & Corrigan, 2020) related to the COVID-19 pandemic included state borders being closed, quarantine if affected or in close-contact with an infected person, staying at home where possible, social distancing, restricting the number of people that could gather in indoor and outdoor venues, and other protective regulatory restrictions. These mandates had a direct impact on non-COVID research with some organisations choosing to postpone all face-to-face research activities. Curtin University's COVID-19 response saw non-essential research restricted to predominantly online formats, with a limited number of approvals granted for continued face-to-face projects based on the risks associated

with discontinuation. These precautions were necessary for participant safety and community spread of COVID-19. They did, however, also result in delays in study trial recruitment timelines and decreased enrolment numbers (Röhr et al., 2021; Sathian et al., 2020). With the easing of some COVID-19 restrictions, recruitment of participants for the RCT commenced in October 2020. However, Western Australian outbreaks of COVID-19 were associated with snap lock downs, which created uncertainty about the capacity to engage clients if recruited. This resulted in further delays with advertising.

Recruitment

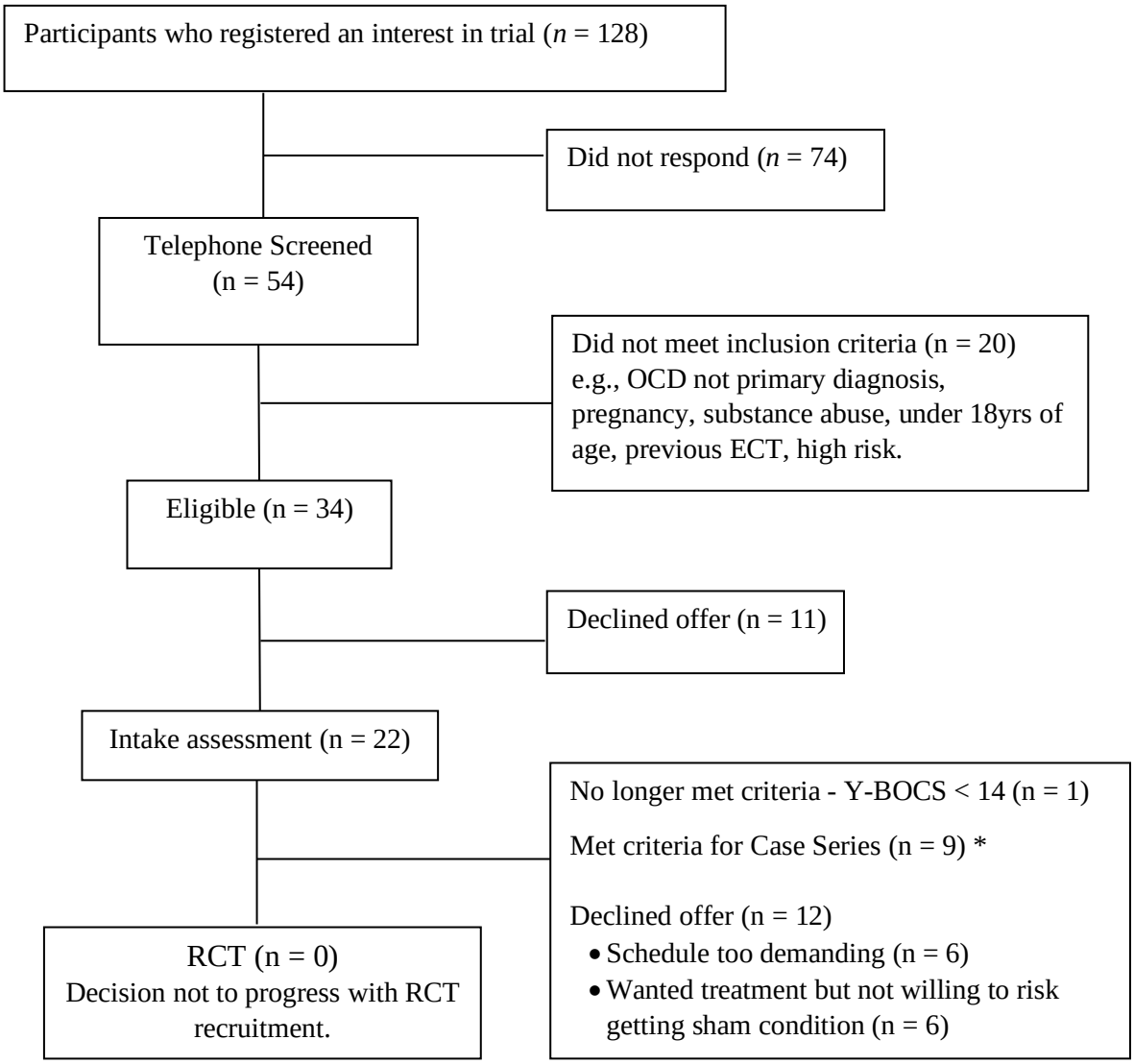
Recruitment occurred across October 2020 and continued until July 2022. Primary recruitment was via the Curtin University Psychology Clinic, where promotional material was distributed to suitable clients with OCD. A media release was made through Curtin University, and via social media (Facebook, Instagram, Twitter). Individuals who were interested in taking part in the study followed instructions on the promotional material and contacted the researcher. Participants of study two, the survey, were also invited to indicate at the end of the survey if they were interested in taking part in the RCT and were subsequently contacted.

One hundred and twenty-eight people expressed an interest in the trial and were contacted via the telephone. Seventy-four did not respond. The remaining participants were sent further information relating to the trial along with a consent form to participate in telephone screening to address the trial's inclusion/exclusion criteria for tDCS suitability. The telephone screening and intake assessments were conducted by the researcher and reviewed by the researcher's clinical supervisor (Dr Rebecca Anderson) in the Curtin psychology clinic. Of the 54 participants that were screened, 20 did not meet the inclusion criteria, 11 declined an offer to participate in

further assessment. Twenty-two participants attended intake interviews conducted via video link and were deemed by the research team as eligible for inclusion in the RCT. One participant's Y-BOCS was < 14 and no longer met criteria for inclusion, six declined an offer to participate due to concerns that the intervention schedule was too rigorous, and another six were not willing to risk not receiving the active treatment when randomised to their treatment condition. Nine participants were identified as treatment refractory and were offered and accepted a place in a planned case series (Chapter 6) involving a combined treatment approach of exposure and response prevention conducted concurrently with tDCS. At this stage, a decision was made by the researcher and supervisory team to no longer progress with the RCT due to the difficulty experienced with recruiting, and because of the time constraints of the PhD timeline (see Figure 1 for a participant flow diagram).

Figure 1

Participant Flow diagram



Note. * Nine participants identified as treatment refractory were offered and accepted a place in a planned case series involving a combined treatment approach of exposure and response prevention conducted concurrently with tDCS and seven accepted.

Discussion

Challenges in recruitment to clinical research studies are a well-recognised problem and certainly precede the COVID-19 pandemic. (Mirza et al., 2022). For example, a report from 2015 showed that 19% of registered RCTs were closed or

terminated due to insufficient participants (Carlisle et al., 2015). However, the likes of the COVID-19 pandemic, an unforeseen natural disaster, was likely to derail even the most carefully planned trial. A recent systematic review examining the global impact of the COVID-19 pandemic on clinical trials and research, reported difficulties in recruiting participants as the primary concern followed by financial concerns related to either study cancellation or from delayed endpoints (Sathian et al., 2020). One of the trials in the review reported that the primary impact of COVID-19 was the participants' decreased willingness to come to the study site for fear of contamination (Daniel et al., 2022). Amongst the traits of OCD is a profound sense of perfectionism, over-responsibility, fear of perceived threat of harm to self- and/or others, and an intolerance of uncertainty, all of which can make it difficult to leave the house and be a barrier to participation. Public health guidelines set by health organisations to prevent the spread of the virus did not consider people with OCD and/or perfectionism. The prospect of those with OCD having to protect themselves from COVID-19 “perfectly” likely placed a significant burden on them, and potentially increased the fear and uncertainty relating to a risk of contamination and/or infecting others. Of those that did meet criteria for the trial, none were willing to participate if there was a risk that they would be allocated to the sham condition. This was compounded by the cost of travel and time that was required to attend the clinic three times per week for four weeks at the risk of no benefit if they were allocated to the sham condition.

Another contributing factor to unsuccessful recruitment has been the lack of empirical evidence to support its use. One of the outcomes of the survey that examined the acceptability of tDCS for OCD was that respondents were concerned

about the safety of tDCS and wanted more evidence to support its use before they would find it an acceptable treatment option (see previous chapter).

Future Directions

Whilst global pandemics cannot be planned for, to mitigate the risk/benefit dilemma, future studies should consider a multiple arm RCT design involving a dual protocol approach. This would involve all participants receiving exposure and response prevention conducted in conjunction with either sham or active tDCS. This approach would ensure all participants received some form of therapy for OCD symptoms.

Chapter 6. Study Three - Dual protocol exposure and response prevention and transcranial direct current stimulation for treatment refractory obsessive-compulsive disorder: A case series

The following chapter has been submitted for publication in the Journal of Psychiatric Research and is currently under review. Manuscript Number: JPSYCHIATRRES-D-24-00933

Minor edits have been made to the present chapter (e.g., Australian spelling, and referencing style) to ensure consistency within the present thesis.

Authorship

All signed authors acknowledge that this statement is an accurate representation of their contribution to the above research output.

Author	Contribution	Acknowledgement
Peta E Green	Development of the research question and the design, manuscript preparation, writing and editing manuscript drafts.	[redacted]
Andrea M Loftus	Assisted with the development of the research question and the design, contributed to writing revisions to the manuscript, and editing manuscript drafts.	[redacted]
Rebecca A Anderson	Assisted with the development of the research question and the design, contributed to writing revisions to the manuscript, and editing manuscript drafts.	[redacted]

Abstract

Transcranial direct current stimulation (tDCS) is a promising treatment approach for a range of mental health disorders, including obsessive-compulsive disorder (OCD). tDCS has been explored as an adjunct treatment to pharmacotherapy for treatment-refractory OCD but has not been evaluated as a concurrent adjunct to exposure and response prevention (ERP). This case series was prospectively registered with the

Australian New Zealand Clinical Trials Registry (ANZCTR): 12621000035820. Seven participants with treatment-refractory OCD completed 10 sessions of 2mA tDCS applied with the cathode over the orbitofrontal cortex and the anode over the pre-supplementary motor area combined with exposure and response prevention. OCD symptom severity was measured at baseline, during the intervention, and at 3-, and 6-month follow-ups. Across the active treatment phase, four participants achieved clinically significant change in OCD symptoms (>10-point reduction in Yale-Brown Obsessive-Compulsive Scale) and met the criteria for remission, and three achieved a partial response. Of these, three remained in remission at 3 months. Only one participant remained in remission at 6 months, with all others who had demonstrated change relapsing. One participant demonstrated no change in symptoms during the study.

This study indicates a need for further examination of tDCS in conjunction with ERP for treatment refractory OCD, with six of the seven participants achieving remission or partial response across the active treatment. However, there is a clear need for improved maintenance protocols so that gains are not lost longer term. This study highlights the importance of longer-term follow-up in all future tDCS trial design.

Keywords

Transcranial direct current stimulation; obsessive-compulsive disorder; treatment refractory; treatment resistant; non-responders; exposure and response prevention; dual protocol.

Introduction

Current evidence-based treatment options for obsessive compulsive disorder (OCD) are pharmacotherapy and/or cognitive behaviour therapy that includes exposure and response prevention (ERP). Most will experience some reduction in

OCD symptoms with these interventions either alone or in combination (Skapinakis et al., 2016). However, 40-60% of participants do not have a satisfactory outcome and a significant percentage of those (14-31%) do not meet the criteria for clinically significant response, prompting the exploration of novel augmentation approaches (Foa et al., 2005; Norberg et al., 2008; Pallanti & Quercioli, 2006).

An emerging treatment approach for OCD is transcranial direct current stimulation (tDCS) - a low-cost, safe, and well-tolerated non-invasive brain stimulation technique (Kuo et al., 2017). tDCS involves delivering a low intensity electrical current (1-2mA) via two electrodes on the scalp - an anode (excitatory) and a cathode (inhibitory). Depending on the location of the electrodes and the strength of stimulation, tDCS can modulate local and network level brain activity and alter behaviour (Nardone et al., 2012). A systematic review and meta-analysis of the use of tDCS in neurological and psychiatric disorders reported that active tDCS is "definitely effective" (level A), for depression, and "probably effective" (level B), for neuropathic pain, fibromyalgia, migraine, post-operative patient-controlled analgesia and pain, Parkinson's disease (motor and cognition), stroke (motor), epilepsy, schizophrenia, and alcohol addiction (Fregni, 2021).

Brain imaging studies suggest that OCD is related to striatal pathology. The fronto-striatal model suggests that OCD symptoms are associated with hyperactivity in the orbitofrontal cortical (OFC) pathways. Those with OCD demonstrate increased (compared to non-OCD) neuronal activity in the OFC and decreased activation in the pre-supplementary motor area (pre-SMA) responsible for inhibitory control (Adler et al., 2000; de Wit et al., 2012; Harrison et al., 2009; Ruffini et al., 2009). It has been suggested that an imbalance in cortical activation between frontal areas and pre-SMA may underlie OCD (Brunelin et al., 2018; Hazari et al., 2016; Narayanaswamy et al.,

2015). From an inhibitory learning perspective, hypoactivity in pre-SMA would be associated with reduced capability to inhibit OFC hyperactivity (de Wit et al., 2012; Nachev et al., 2008). tDCS is emerging as a way to rebalance disrupted cortical activity such as that reported in OCD.

Preliminary studies involving tDCS for treatment refractory OCD patients defined as non-responsive to both CBT and pharmacotherapy have been encouraging. Hazari et al. (2016) conducted an open-label study using anodal tDCS to increase activation of pre-SMA, and cathodal tDCS to decrease activation of OFC. This tDCS montage was based on the theory that OCD is associated with deficient pre-SMA response inhibition on fronto-striatal function (de Wit et al., 2012; Nachev et al., 2008). The patient, who was on Escitalopram and Clonazepam, received 2mA of current for 20 minutes, twice a day for 10 days (20 sessions). They reported an 80% reduction in OCD symptom severity, which was maintained for 7-months post-intervention with minor fluctuations. Whilst the patient did relapse at the 7-month point, their symptoms improved following a further eight sessions of tDCS. During the initial trial and at the 7-month time point, the patient's OCD symptoms had remitted within 5 - 10 days of receiving tDCS. Narayanaswamy et al. (2015) used the same tDCS protocol combined with therapeutic selective serotonin reuptake inhibitors (SSRI) in two patients, who received 2mA of current for 20 minutes, twice a day for 5 days (10 sessions). Both patients demonstrated significantly reduced OCD symptom severity (52% and 46.7% reductions) that was maintained at 1 and 2-month follow-up assessments. Recently, two randomised sham-controlled trials involving tDCS for treatment-refractory OCD reported significant between group differences (active versus sham) in symptom severity from pre- to post-treatment, providing further support for targeting OFC and pre-SMA/SMA in treatment

resistant OCD (Akbari et al., 2022; Gowda et al., 2019). A recent systematic review reveals that these results were not achieved when other cortical sites were targeted (e.g., dorsolateral pre-frontal cortex or the cerebellum; Green et al., 2024).

tDCS has been explored as an adjunct treatment to pharmacotherapy for OCD but has only been combined with psychotherapy for OCD in one published study. Adams et al. (2022) administered fronto-polar tDCS followed by ERP in a study involving two patients and reported symptom improvements in both patients at one-month follow-up. To the best of our knowledge, tDCS has not been administered concurrently with ERP for OCD, although concurrent application may lead to more promising treatment effects (Dedoncker et al., 2020). ERP involves learning to confront avoided stimuli that trigger obsessions and compulsions (i.e., exposure) whilst not performing compulsions (i.e., response prevention). The major theoretical underpinnings of ERP are emotional processing via habituation and inhibitory learning. For example, a patient with a fear of contamination could be instructed to confront their feared situations (e.g., touching the door handle of a public toilet) and/or imagine their feared consequence (e.g., hands contaminated with faecal matter), and refrain from washing their hands. Tolerance to subjective distress increases over time (i.e., habituation), and by violating expectations of a feared event when a compulsion is not performed (e.g., not getting sick or infecting others) a new safe association inhibits the previous fear-based learning (i.e., inhibitory learning; see Foa et al., 2006; Jacoby & Abramowitz, 2016). Emotional processing and inhibitory learning are associated with activation of the cortico-striatal-thalamo-cortical circuit (Gonçalves et al., 2016; Peters et al., 2016), including the OFC and pre-SMA. Applying tDCS to these brain areas activated during ERP may enhance inhibitory learning, induce neuroplasticity, and potentially improve the efficacy of ERP.

The present study is a case-series of a dual protocol approach combining ERP with tDCS for treatment refractory OCD. We propose that cathodal stimulation to decrease activation of left OFC and anodal stimulation to increase activation of pre-SMA during ERP will lead to clinically significant reduction in OCD symptom severity as measured by the Yale Brown Obsessive Compulsive Scale (Y-BOCS; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989). We also propose that there will be a reduction in secondary outcome measures on the Depression Anxiety Stress Scales (DASS-21; Lovibond & Lovibond, 1995), Obsessive Beliefs Questionnaire (OBQ-44; Myers et al., 2008), and the Quality-of-Life Enjoyment and Satisfaction Questionnaire - short form (Q-LES-Q-SF; Stevanovic, 2011). To the best of our knowledge, this is the first study to administer tDCS concurrently with ERP in an OCD population.

Methods

This study was approved by Curtin University's Human Research Ethics Committee (HRE2020-0266), prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR: 12621000035820) and undertaken in accordance with the ethical standards as per the 1964 Declaration of Helsinki and its later amendments.

Sample

Seven treatment refractory participants who met the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM–5; American Psychological Association, 2013) diagnostic criteria for OCD were enrolled in the study. Treatment refractory was defined as a Y-BOCS score ≥16, and a lack of response to at least two SSRI trials of adequate dose and duration, and lack of response to ERP by a trained practitioner (Pallanti & Quercioli, 2006). As the term treatment refractory is often

used interchangeably with treatment resistance and/or non-responder, participant treatment history was reviewed against Pallanti and Quercioli's categorisations of non-response to OCD treatment (2006). Our inclusion criteria were consistent with a minimum level 3 of 'non-response' for all participants (see footnotes, Table 1). Medicated participants were required to be on a stable dose of SSRI for at least 12 weeks prior to the study, and doses remained stable during the intervention and follow-up period. A description of the seven participants who completed treatment, including their level of 'non-response' to prior treatments (Pallanti & Quercioli, 2006), is presented in Table 1. All participants provided written informed consent.

Table 1

Participant demographics and level of prior non-response

ID	Age*	Gender	Pre-intervention Y-BOCS	OCD Duration	Comorbidities	Prior psychotherapy	Prior pharmacotherapy	Current pharmacotherapy	Level of prior non-response #
A	22	M	20	2	MDD, GAD, ADHD	ERP, MBCT, MCT, ACT	Fluvoxamine, Fluoxetine, Sertraline, Vyvanse	Fluoxetine, Vyvanse	4
B	18	F	23	5	Social Anxiety, GAD	ERP	Fluvoxamine, Fluoxetine	Fluoxetine	3
C	24	F	27	4	MDD, GAD	ERP, MBCT, MCT,	Escitalopram, Paroxetine	Paroxetine,	7
D	24	F	26	3	MDD, BPAD,	ERP, MBCT, DBT	Lamotrigine, Escitalopram, Olanzapine	Escitalopram Lamotrigine	7
E	25	F	20	3	GAD	ERP	Fluoxetine, Sertraline	Fluoxetine	3
F	62	M	24	26	Agoraphobia, GAD	ERP	Paroxetine, Sertraline	Sertraline	3
G	22	F	31	12	MDD, GAD	ERP, MBCT, MCT,	Sertraline, Pristiq, Lexapro, Fluoxetine, Clomipramine	Clomipramine	6

Note: *Age and OCD duration are in years. Y-BOCS = Yale Brown Obsessive Compulsive Disorder; MDD = Major Depressive Disorder; GAD = Generalised Anxiety Disorder; ADHD = Attention Deficit Hyperactive Disorder; BPAD = Bipolar and Affective Disorder; ACT = Acceptance and Commitment Therapy; MCT = Metacognitive Therapy; MBCT = Mindfulness Based Cognitive Therapy; DBT = Dialectical Behavioural Treatment. # Levels of prior non-response descriptors: Level 1 = non-response to an SSRI (Selective Serotonin Reuptake Inhibitor) or ERP (Exposure and Response Prevention); level 2 = an SSRI plus ERP; level 3 = 2 SSRIs tried plus ERP; level 4 = at least 3 SSRIs tried plus ERP; level 5 = at least 3 SRIs including CMI (Clomipramine) plus ERP; level 6 = at least 3 SRIs, CMI augmentation plus ERP; level 7 = at least 3 SRIs including CMI + ERP + psychoeducation and other classes of medication (benzodiazepine, mood stabilizer, neuroleptic, psychostimulant); level 8 = at least 3 SRIs including intravenous CMI + ERP + psychoeducation; level 9 = at least 3 SRIs including CMI + ERP + psychoeducation and other classes of antidepressant agents (norepinephrine reuptake inhibitors, monoamine oxidase inhibitors); level 10 = all above treatments, neurosurgery.

Primary Measures

Diagnosis. The Mini International Neuropsychiatric Inventory-7.0.0 (Mini—7.0.0), was used to establish a diagnosis of OCD. The Mini is a short diagnostic structured interview for the DSM-5, with well-established reliability and validity (Sheehan et al., 1998).

OCD Symptom Severity. OCD symptom severity was assessed using the Y-BOCS, a self-report measure of symptom type and severity over the last seven-day period. The Y-BOCS consists of two 10-item subscales (obsessions and compulsions) and has excellent interrater-reliability (.98) and convergent and discriminant validity (.81; Goodman, Price, Rasmussen, Mazure, Delgado, et al., 1989; Goodman, Price, Rasmussen, Mazure, Fleischmann, et al., 1989; Kim et al., 1990).

Secondary Measures

Anxiety and Depression Symptoms. The Depression Anxiety Stress Scale – Short form (DASS-21; Lovibond & Lovibond, 1995) was used to measure the severity of anxiety and depression symptoms. The DASS-21 is a self-report measure, which identifies and measures any negative affect (if present) and has internal consistency and concurrent validity in the acceptable to excellent ranges (Antony et al., 1998).

Obsessive Beliefs. The OBQ-44 (Myers et al., 2008) was used to measure the type of beliefs associated with OCD. The OBQ-44 is comprised of three subscales, including (1) perfectionism and intolerance of uncertainty, (2) importance and control of thoughts, and (3) inflated responsibility and perceived threat of harm, which are all positively associated with obsessive–compulsive symptoms and worry.

The OBQ-44 has good internal consistency and criterion-related validity in clinical and non-clinical samples (Steketee et al., 2003).

Quality of Life. Quality of life was measured utilising the Quality-of-Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF; Stevanovic, 2011), which contains 16 items evaluating overall enjoyment and satisfaction with various aspects of life. The Q-LES-Q-SF is also a self-report measure with good internal consistency (0.90) and test-rest reliability (0.93; Stevanovic, 2011).

All OCD measures were administered at pre-intervention, immediate post-intervention, three-month-, and six-month follow-up. The Y-BOCS, DASS-21, and OBQ-44 were also administered at the end of the 1st, 2nd, and 3rd week of the intervention period to identify if/when changes occurred. A timeline of the intervention and measure administration is presented in Figure 1. Participants were monitored for side-effects and adverse events during and after each active treatment session.

Figure 1

Intervention and assessment timeline

Outcome Measures				**Week 1**			**Week 2**			**Week 3**			**Week 4**			**Follow-up**	
	Baseline Symptom Monitoring			**Pre-intervention Assessment**	**Active Treatment Phase 10 sessions of tDCS with ERP**										**Post-intervention Assessment**	**3-mth**	**6-mth**
	B1	**B2**	**B3**	**T1**	**S1**	**S2 T2**	**S3**	**S4**	**S5 T3**	**S6**	**S7**	**S8 T4**	**S9**	**S 10**	**T5**	**T6**	**T7**
Y-BOCS	x	x	x	x		x			x			x			x	x	x
DASS 21	x	x	x	x		x			x			x			x	x	x
OBQ-44				x		x			x			x			x	x	x
Q-LES-Q-SF				x											x	x	x

Note. B = baseline; S = session; T = time point; x = outcome-measure; mth = month. Baseline (B1, B2, and B3) assessments were conducted on three different occasions to monitor and ensure symptom stability. TDCS with ERP involved 10 sessions, conducted over four weeks. Participants attended the clinic three times per week with all outcome measures administered at 4-timepoints. Pre-intervention/baseline on day one, post-intervention 2-days after the final tDCS session (S10), and follow-up measures at three-, and six-months. The Y-BOCS, DASS-21, and OBQ-44 were also administered at the end of week-1(T2), week-2(T3), and week-3(T4) of the intervention period to monitor changes in symptom severity and/or the sub-domains.

Procedure

Baseline monitoring of a participant's symptoms was conducted across three time points, (B1, B2, B3) prior to the intervention, as part of the inclusion criteria to establish symptom stability (see Figure 1). Symptom stability was defined as no changes in the Y-BOCS and DASS-2 scores greater than 10 points across a minimum of three data points. During the pre-intervention monitoring period, a semi-structured interview was used to assess obsessive thoughts, stimuli that trigger the obsessions; compulsive rituals and avoidance behaviours; and the cognitions that link obsessions and compulsions (i.e., the anticipated feared consequence of confronting feared situations without performing rituals; see Rees, 2009). Psychoeducation was also delivered, which comprised an explanation about OCD and a description of how ERP targets the symptoms of OCD. Information gathered during the assessment and monitoring period was used to plan collaboratively with each participant a specific set of ERP exercises. The intervention was conducted in the Curtin Psychology Clinic by the first author [PG] - a postgraduate clinical psychology doctoral student, trained in the protocol and under the supervision of a Senior Clinical Psychologist with expertise in OCD [RA] and a senior academic specialising in neuropsychology and brain stimulation [AL].

Exposure and Response Prevention (ERP). Consistent with published treatment protocols for ERP (Rees, 2009), in each 50-minute session, a pre-planned and agreed upon set of ERP exercises, commencing with an exposure of moderate severity, was performed without engaging in compulsions (response prevention).

tDCS. The tDCS protocol was informed by Green et al. (2020). Participants completed 10 sessions of tDCS stimulation combined with ERP over 4 weeks (see Figure 1). Each session involved 20 minutes of constant current 2 mA tDCS

delivered at the same time as ERP. To decrease neural activation of the left OFC, the cathode electrode was placed over Fp1 in accord with the 10–20 international system for EEG electrode placement. To increase neural activation of the pre-SMA, the anode electrode was placed over Fz. Participant experience of tDCS was monitored at beginning and end of each session, including any noted side-effects. Follow-up measures were conducted at post intervention, three-month, and six-months. During the follow-up period, participants were requested to continue with pharmacotherapy as usual, but not to engage in any additional psychotherapy.

Data Analysis

Scores on outcome measures were visually inspected for potential outliers and assumption testing for T-tests conducted. T-tests were used to determine whether there was any statistically significant difference between pre- and post-intervention, pre- and 3-month-, and pre- and 6-month-post- intervention follow-up scores.

Stages of response (SoR), see Pallanti and Quercioli (2006) was used to indicate the level of treatment response, which provides a description of the magnitude of change as well as what it means for the participant. The SoR has seven stages determined by the percentage of change in the Y-BOCS. Recovery is described as follows: Not at all ill with < 8 on the Y-BOCS; remission is < 16 on Y-BOCS; full response > 35% reduction of Y-BOCS; partial response is > 25% but < 35% Y-BOCS reduction; relapse is a return of symptoms and 25% increase in Y-BOCS from remission score; and refractory is no change or worsening of symptoms with all available therapies.

Results

Side Effects and Adverse Events

No adverse events were reported. Minor events were reported by four participants across the 10 sessions, including fatigue (3 reports), itching at the site of the electrode placement (2 reports), sleepiness (1 report), headache (1 report), difficulty concentrating (2 reports), and minor itching/burning at the site of the electrode placement (2 reports). Seven of these reports were from one participant. The discomfort level of the itching/burning was reported as 1 or 2 out of 10 (1 being low-level of discomfort). One participant reported experiencing a 'slight burning sensation' after stimulation was complete. Another participant, who was bald-headed, indicated feeling 'a bit of burning' at the start of stimulation and redness after the electrodes were removed that lasted an hour.

Primary Outcome Measure

Y-BOCS. Visual inspection of the box plots and assumption testing indicated that Participant (G) was an influential outlier (see supplementary material). Participant G demonstrated a consistent pattern of responding across the outcome measures that was distinctly different from all other participants (see Figure 2). Following extensive discussion, the researchers decided to remove G from the statistical analyses, but that their scores would still be considered in all clinical significance reporting.

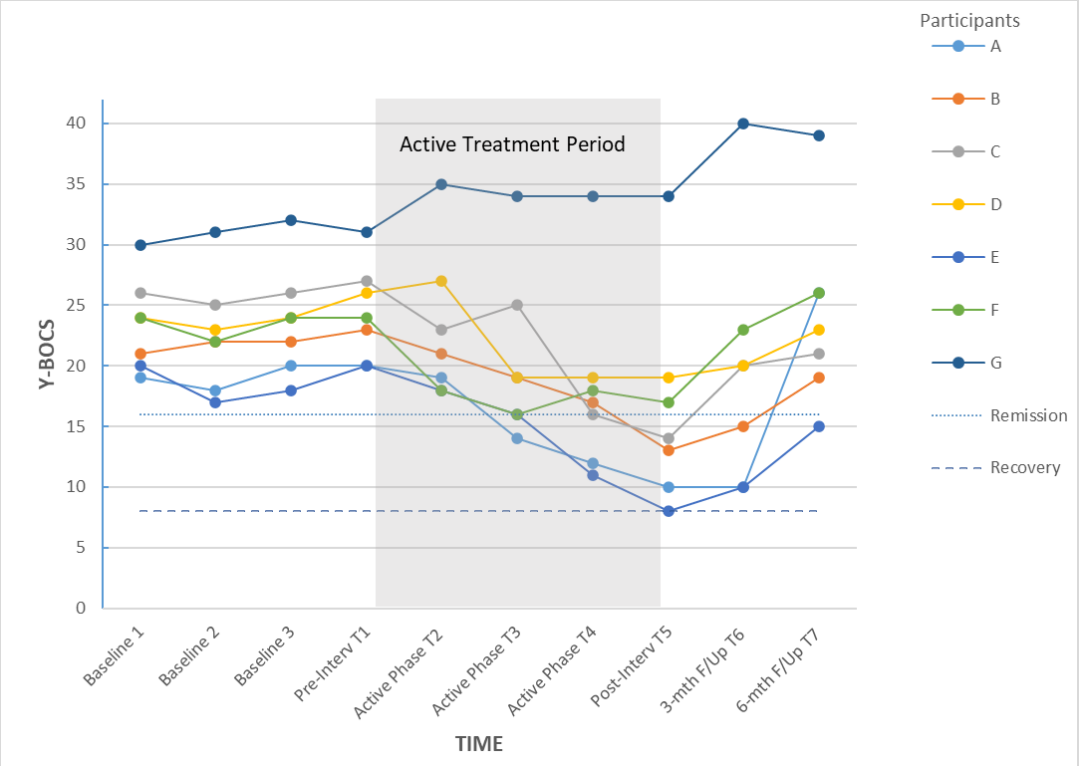
Visual observations indicated a trend of decreased Y-BOCS symptoms during the active treatment phase, with a gradual return to baseline levels by the 6-month follow-up (see Figure 2). This was supported by the finding that post-intervention Y-BOC scores (M = 13.50, SE = 1.69) were lower than pre-intervention Y-BOC scores

(*M* = 23.33, *SE* = 1.20). This difference, 9.83, 95% CI [7.23, .44], was significant $t(5) = 9.70$, $p < .001$, and represented a large effect, $d = 2.48$.

Individual level clinical changes are reported in Table 2. After 4-weeks of treatment, four participants (A, B, C, and E) achieved clinically significant change in OCD symptoms (>10-point reduction in Yale-Brown Obsessive Compulsive Scale) and met the criteria for remission (Y-BOCS < 16). Two participants (D and F) were partial responders (> 25% but < 35% reduction in Y-BOCS). Participant G had demonstrated no change in symptoms across the active treatment. At three-month follow-up, three participants (A, B, and E) remained in remission. Three participants (C, D, and F) demonstrated at least a 25% increase in their Y-BOCS score from their remission score and met the criteria for relapse. Participant G's condition worsened. At 6-months follow-up, only one participant maintained their remission status. All other participants relapsed.

Figure 2

Effects of an integrated approach of tDCS with ERP on Y-BOCS over time



Note: Y-BOCS = Yale Brown Obsessive Compulsive Scale; T = Time; Inter = intervention; mth = month; F/Up = follow-up; Remission = Y-BOCS ≤ 16; Recovery = Y-BOCS < 8.

This figure demonstrates symptom stability prior to the active treatment period, then a trend of decreased Y-BOCS scores during the active treatment period, followed by a gradual return to baseline levels by the final follow-up period.

Table 2

Individual level Clinical OCD outcomes using stages of response categories.

	Pre-Intervention		Immediate Post-Intervention		3-month Follow-up		6-month Follow-up	
Participant	Y-BOCS	Severity Rating	Y-BOCS	SoR	Y-BOCS	SoR	Y-BOCS	SoR
A	20	Moderate	10	Remission	10	Remission	26	Relapse
B	23	Moderate	13	Remission	15	Remission	19	Relapse
C	27	Severe	14	Remission	20	Relapse	21	Relapse
D	26	Severe	19	Partial Response	20	Relapse	23	Relapse
E	20	Moderate	8	Remission	10	Remission	15	Remission
F	24	Severe	17	Partial Response	23	Relapse	26	Relapse
G	31	Severe	34	Refractory	40	Refractory	39	Refractory

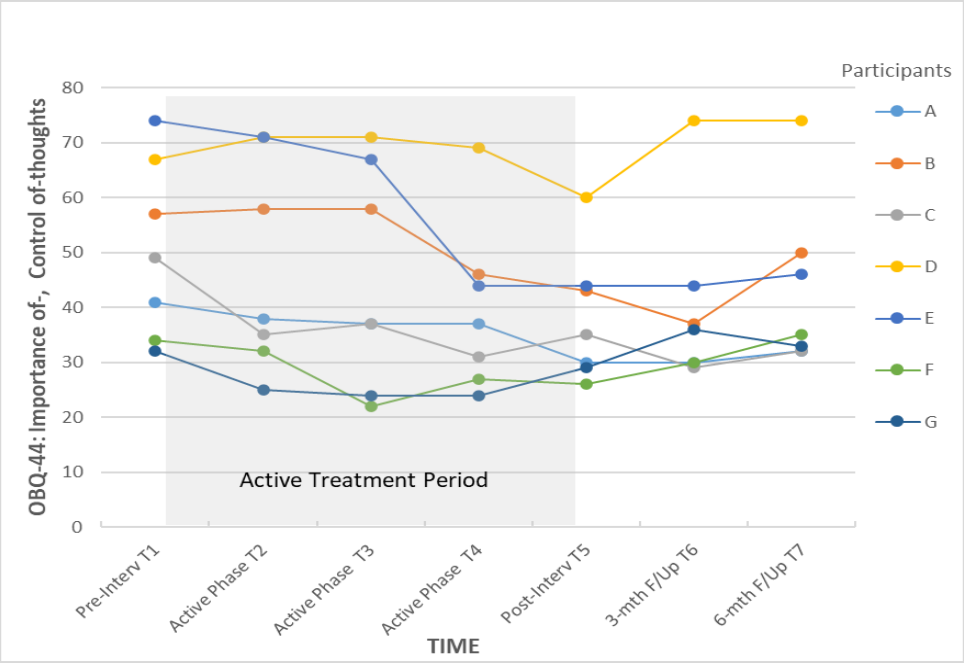
Note: Y-BOCS = Yale Brown Obsessive Compulsive Scale; SoR = Stages of Response which provides a description of the magnitude of change. This table demonstrates the clinical outcome levels as measured by the stages of response for each individual across time.

Secondary Outcome Measures

OBQ-44. There was a significant reduction in the OBQ-44 total scores from pre-intervention (*M* = 231.00, *SE* = 14.85) to post-intervention (*M* = 182.50, *SE* = 6.61). This difference, 48.50, 95% CI [13.10, 83.90], was significant, *t*(5) = 3.52, p = .02, *d* = 1.44 large effect size. The OBQ-44 total score reduction was not maintained at the 3-month and 6-month-follow-up. There was no significant difference across any time points for subscale 1(Inflated responsibility/ perceived threat of harm) *p* = .14, and subscale 2 (Perfectionism/ intolerance of Uncertainty) *p* = .08. There was a significant reduction in scores on subscale 3 (Importance and control of thoughts) between pre-intervention (*M* = 50.57, *SE* = 6.12) and post-intervention (*M* = 38.14, *SE* = 4.48). The mean difference was 12.43, 95% CI [4.39, 20.47], *t*(6) = 3.78, *p* = .01, and represented a large effect size, *d* = 1.43. This was not maintained at the 3-month and 6-month-follow-up *p* >.05 (see Figure 3 for trend).

Figure 3

Importance and control of thoughts subscale scores over time



Note: OBQ-44 = Obsessive Beliefs Questionnaire; T = time; Interv = intervention; mth = month; F/Up = follow-up.

DASS-21. DASS-21 total score significantly reduced from pre-intervention (*M* = 17.33, *SE* = 1.38) to post-intervention (*M* = 11.00, *SE* = 1.63). The mean difference was 6.33, 95% CI [1.90, 10.77], *t*(5) = 3.67, *p* = .01, with a large effect size *d* = 1.50. The change was not maintained at follow-up. There were no significant differences between pre- and post-intervention scores on the DASS-21 subscales (S1 – 'Depression'; S2 – 'Anxiety'; S3 – 'Stress') or 'Total Scores' *p* >.05.

Q-LES-Q. There was no significant change between pre-intervention scores (*M* = 66.57, *SE* = 5.09) and post-intervention scores (*M* = 75.71, *SE* = 2.51), *t*(6) = -2.16, *p* = .07, for the Q-LES-Q.

Discussion

To the best of our knowledge, this is the first evaluation of concurrent tDCS and ERP for treatment refractory OCD. Seven treatment refractory participants completed the study. After 10 sessions of ERP combined with 2mA stimulation over the left OFC and pre-SMA (20-minutes per session), four participants met the criteria for remission and two qualified as partial responders. At the three-month follow-up, three of the four remained in remission, and three had relapsed. However, by the 6-month follow-up period, treatment gains were lost by all but one participant who remained in remission. One participant remained treatment refractory throughout the study (G). This case series provides support for the further evaluation of a dual protocol approach combining ERP and tDCS for OCD.

These findings are consistent with previous studies involving tDCS targeting OFC and pre-SMA. They are also consistent with contemporary theory suggesting that deficits in inhibitory learning may underlie poor response to exposure-based approaches. We had anticipated that using tDCS to modulate the neural areas (OFC

and pre-SMA) activated during ERP would enhance inhibitory learning, induce neuroplasticity, and improve the effectiveness of ERP. While the current findings did indicate that the dual protocol approach was associated with symptom change in this treatment refractory group, the underlying mechanism(s) of change remains unclear. Due to participant burden and the practical challenges of working with this clinical population, we did not directly measure inhibitory learning or neuroplasticity. Furthermore, as this was a case series with limited participant numbers, we did not include a tDCS control condition to account for placebo effects. A true randomised controlled study of this dual-protocol approach is needed and should include measures of potential underlying mechanisms of change (e.g., inhibitory learning).

Whilst the results indicate that tDCS-ERP significantly reduces symptoms in treatment refractory OCD, the treatment gains were not maintained over time. Gains were diminished at three-month follow-up and lost in all but one participant by six-month post-treatment. Although it is encouraging that there was an initial treatment response, there is a clear need to establish a maintenance or treatment tapering schedule that will allow for gains to be retained longer term. Furthermore, our findings highlight the clear need for future tDCS research to include longer-term follow-ups to examine whether gains observed in active treatment phases and short-term follow-up are maintained longer term. Appropriate follow-up periods would also allow researchers to establish not only whether any immediate gains are maintained, but whether those participants who do not demonstrate immediate gains show delayed gains (delayed change).

One participant in the current study (G) did not respond to the intervention and was considered an outlier. Whilst participant G did present with the highest Y-BOCS (31-severe) and the earliest onset of OCD (10-years-of-age), their baseline

level of non-response was not the highest in the group. Participant G engaged well during the pre-screening and baseline monitoring period. Once treatment commenced, however, their self-reported level of distress between sessions increased and level of engagement in exposure exercises declined. During the study Participant G reported relationship difficulties at home, resulting in instability in their living arrangements. In session 8, G also reported a significant history of abuse that had not been disclosed during the intake interviews. A collaborative decision was made to complete the treatment sessions but with time taken to provide additional support and strategies to stabilise G's declining mood. Participant G was referred on for a psychiatric review and continued psychological support. At the three-month follow-up period, G revealed they had been hospitalised for major depression and had become homeless, which could account for the rise in symptom severity on all outcome measures at that time point. At the 6-month follow-up period, participant G reported being in stable accommodation and had re-engaged with community support services for their ongoing care, although their symptoms remained in the severe range.

The observed reduction the OBQ-44 total scores and the *Importance and control of thoughts* subscale was noted to coincide with reductions in the YBOCS scores. This is notable given changes in these scores have been demonstrated to partially mediate changes in obsessive compulsive symptoms during cognitive behavioural treatment for OCD (Diedrich et al., 2016), yet our treatment did not directly aim to change these cognitions. Treatments directly targeting obsessive beliefs, such as those proposed by the metacognitive model of OCD (see Rees & Anderson, 2013), have been associated with large treatment effects in a range of trials to date. It is plausible that incorporating the direct challenging of obsessional

beliefs at the metacognitive level would also improve gains further and may assist with longer term maintenance of gains.

Strengths

In light of the limitations examined in study one, one of the strengths of the case series is that the methodology is based on our previously published protocol paper to ensure our treatment approach is replicable. The inclusion of baseline data is a strength of this study as it demonstrates pre-intervention symptom stability and identifies that any change that occurred was likely due to the intervention. Although challenging to coordinate, the 6-month follow-up is a particular strength of this study as it allowed us to see that the improvements were not maintained. Had the study ceased immediately following intervention, our results and interpretation would have suggested that ERP with tDCS is an effective treatment for OCD in treatment refractory OCD. Few previous trials of tDCS for OCD have included follow-up data (see Green et al., 2024). Da Silva's (2016)case study (N=2) reported no significant change in symptoms in one patient, and a significant improvement in the other at the completion of treatment (45% reduction in Y-BOCS), which was maintained six months later. The two RCTs identified as having significant results in a systematic review (Green et al., 2024) included a one-month follow-up (Akbari et al., 2022) and no follow-up (Gowda et al., 2019), so it cannot be determined whether any treatment gains were maintained. The findings of the present study highlight a need for the longer-term monitoring of OCD symptoms following any intervention involving tDCS in future trials.

Limitations

There are several limitations with this case series. The study did not include any clinician-rated measures of severity, either by the therapist or a blinded assessor.

The small sample size, lack of measures of brain function, and the lack of sham-control condition limit the interpretation of the outcomes of this study. We cannot partial out the effects of time, nor the possibility of spontaneous recovery and/or placebo effects for the tDCS component, expectancy effects, therapist effects, or that change was the result of having more ERP rather than tDCS, given the lack of an appropriate control and in light of previous evidence of the effectiveness of ERP in promoting OCD belief change (see Overton & Menzies, 2005).

Whilst the inclusion of only treatment refractory patients is invaluable to this subgroup, this limits the generalisability of the results to the general OCD population. Whilst the Y-BOCS is the most widely and frequently used instrument to quantify the ongoing severity of OCD symptoms, it may not be sensitive to subtle changes (such as a decrease from 5 h to 3 h per day of rituals), which may translate into a considerable reduction in distress. Finally, all treatment sessions were delivered by the first author, so we cannot control for therapist effects.

Future Directions

There are several directions for future research to determine whether tDCS adds anything to ERP for treatment-refractory OCD. This would ideally involve an appropriately powered double-blind randomised sham-controlled trail with extended follow-up periods. A review of maintenance protocols also needs to be conducted in tDCS studies to determine whether treatment gains are being maintained once the treatment has stopped; whether ongoing maintenance sessions are required to retain remission; and the composition of the maintenance sessions (e.g., ERP alone, tDCS alone, or a dual approach). A limited number of studies involving in-home tDCS for MDD have included a tapered approach in their design (see Alonzo et al., 2019; Cappon et al., 2022). However, these studies lacked an appropriate follow-up period

to determine if any long-term change occurred. Further, none of the trials included a comparator arm (i.e., tapered vs non-tapered approach), making it difficult to establish whether additional sessions made any difference. Future studies should include multiple arms and longer follow-up periods.

Conclusion

This study provides support for the ongoing evaluation of tDCS in conjunction with ERP for treatment refractory OCD, with six of the seven participants achieving remission or partial response across the active treatment. However, there is a clear need for improved maintenance protocols so that gains are not lost longer term, and for the inclusion of a sham condition to determine whether tDCS outcomes are a placebo effect. This study highlights the importance of longer-term follow-up in all future tDCS trial design.

Chapter 7. Thesis Discussion

Overall Summary of the Research Findings

The overarching aim of this research was to explore tDCS as an adjunct approach to current evidence-based treatments for treatment refractory OCD. First, a systematic review was conducted to identify the current research base of RCTs involving tDCS for OCD, evaluate the quality of the reporting using the CONSORT criteria for the reporting of RCTs of nonpharmacologic treatment, and to examine the outcomes of tDCS for OCD in RCTs. Second, a protocol was developed for a double-blind randomised sham-controlled trial of tDCS for OCD to examine the therapeutic potential of tDCS for OCD symptoms. Third, an online survey was conducted to examine consumer perspectives on the acceptability of tDCS as an emerging treatment approach for OCD. Finally, whilst we were unable to run an RCT due to the COVID pandemic, a case series was conducted to evaluate a dual protocol approach of ERP combined concurrently with tDCS for treatment refractory OCD.

The first study revealed there is limited evidence to support the use of tDCS for OCD, and that amongst the RCTs included in the evaluation there were low levels of overall compliance with the CONSORT standards. This highlights a need for improvement in reporting of studies involving tDCS for OCD. There are many claims in the literature of tDCS being a promising approach for OCD, but our systematic review of RCTs revealed that only two trials found significant between-group (active vs sham) differences for OCD outcomes. One of these studies was very limited in its reporting of outcomes, further hindering the interpretability of a potential impact of tDCS. The trial that showed significant pre- to post-treatment differences in Y-BOCS and demonstrated more robust (compared to the other trials)

reporting of the trial design, involved anodal stimulation of the pre-SMA (Gowda et al., 2019). Despite the lack of supporting outcomes in well controlled designs, trials of tDCS for OCD continue to make positive and misleading statements citing the results of case studies and non-RCTs as supporting evidence for its therapeutic potential.

In terms of study reporting, most protocols were described at a level that allowed the reader to gain a basic understanding of how a trial took place. However, more detailed reporting is required for researchers and clinicians to not only determine the quality and clinical significance of a trial, but also for replication. Furthermore, the limitations in the study designs combined with the heterogeneity in stimulation sites precluded a meta-analysis that would produce any valid or reliable outcomes. There is a clear need for improved reporting standards and for an appropriately powered RCT to account for potential placebo effects. To address the issues identified in study one, a published protocol was developed for a double-blind randomised sham-controlled trial of tDCS for OCD to examine the therapeutic potential of tDCS for OCD symptoms.

We attempted to conduct a double-blind randomised sham/control trial involving anodal stimulation of pre-SMA and cathodal stimulation of OFC but were unable to recruit participants into the trial. After 18 months of recruitment efforts, we decided to discontinue recruiting efforts and not conduct this RCT. Recruitment was no doubt impacted by the COVID-19 pandemic with multiple stop-starts due to community lockdowns, but also the original design of the RCT itself was problematic and a barrier to recruitment. In accord with a true RCT, we intended to perform both anodal and sham (control) tDCS. Ethical guidelines required us to explicitly inform potential participants that they may or may not receive active

(anodal tDCS) treatment. Whilst there was no promise that active tDCS would reduce OCD symptoms, the concept of receiving no active treatment came at a perceived high cost of attending the clinic for 15 one-hour sessions over a six-month period, compounded by the very nature of OCD being a 'doubter's disease'. We suspect that many potential participants did not want to commit to such time-consuming treatment at the risk of being randomly assigned into a control group receiving sham tDCS. Aside from the fear of contamination, we suspect there was also an element of doubt about the intervention itself (e.g., is tDCS safe, will it work?). This was supported by the findings of study three (survey), which demonstrated that most participants would not be willing to try tDCS unless there was more evidence that it was safe and effective. What also emerged from this study was a correlation between symptom severity/duration and the acceptability of tDCS. Those who have had OCD for a long period of time and tried multiple treatments but still experienced severe symptoms, indicated that they would be willing to try tDCS if it was available. These findings, along with the lack of recruitment into the planned RCT, informed the design of study four which offered all participants the dual approach of ERP with tDCS.

The results of study four (case series) were promising. The remission rate in the current study from pre to post treatment was 57%, including the outlier, or 67% without. This is comparable to remission rates noted in prior meta-analytic studies reporting on ERP outcomes for non-treatment resistant OCD populations (e.g., 59% in Ost et al, 2022). Given the current sample had not responded to ERP and medications in prior trials, this is a notable finding. The remission rate for pre to follow up, however, was 14% (with outlier) or 16% (without) in the current trial, which is not comparable with 57% remission rates noted at follow up in Ost et al.

(2022). This highlights the need to consider how future studies might promote better maintenance of gains following tDCS and ERP. It may be that treatment tapering, or on-demand booster sessions could assist with maintenance of gains. Future research should also consider means to address the limitations of the current study. The lack of a control condition is a major limitation of the case series, as it is not clear whether change occurred due to having more ERP (repeated), the intensive delivery of ERP (3 times per week), the addition of tDCS, or expectation that the combined approach would work. ERP in an outpatient setting is most commonly conducted once a week due to feasibility, affordability, and the limited number of trained therapists, so the current study ERP delivery did mark a change from the usual delivery of the psychotherapeutic treatment elements.

The results from the four studies presented in this PhD support the need for an alternative approach to current evidence-based treatments for those with OCD who do not respond or are seeking an alternative treatment option. The findings demonstrate that the quality of reporting of tDCS studies needs to be improved and that there is a need for the longer-term monitoring of OCD symptoms following any intervention involving tDCS. Those studies that reported treatment gains did not include an adequate follow-up period to demonstrate whether gains were maintained over time.

Lessons Learned and Future Directions

Rethinking the RCT Recruitment and Design

The design of the planned RCT was problematic and a barrier to recruitment. We had initial enquiries from many people, but they then did not want to participate in the RCT when they discovered they could be in a control group. Whilst there was no promise that active tDCS would reduce OCD symptoms, the concept of receiving

no treatment came at a perceived high cost of attending the clinic for 15 one-hour sessions over a six-month period. When we realised the design was a barrier to recruitment, the time constraints of the PhD timeline did not afford a late change to the planned RCT. The advent of COVID-19 meant we had already been subject to 18-months of lockdowns and restrictions that hindered the progress of this PhD, specifically the planned RCT. Ideally, the design of the planned RCT would have been adjusted and recruitment would (hopefully) have been more successful. However, a modified version of the RCT was beyond the scope of this PhD.

Future trials should consider a multiple armed dual approach of ERP with tDCS (active vs sham) and should include extended follow-up periods to monitor whether symptom change is maintained over time. There is also a clear need to establish whether a maintenance or treatment tapering schedule is warranted. This would indicate whether a tapering protocol would allow for gains to be retained longer term and how tapering might be designed to optimise treatment gains. A consideration for a future trial would be to explore the effectiveness of a tapered versus non tapered approach.

Multiple arms would also help to answer whether changes in OCD specific beliefs (e.g., importance and control of thoughts) was attributed to tDCS or ERP. Such changes can often occur implicitly, as while engaging in ERP individuals (Overton & Menzies, 2005) are effectively challenging previously held beliefs by observing the lack of predicted consequences even when these are not explicitly discussed in session. Nevertheless, the current case series demonstrate higher rates of recovery than those noted in previous research of existing treatment which goes some way in indicating potential benefits of the augmented treatment.

Whilst a reduction in symptom severity was observed in most cases in the case series, we cannot identify what the mechanisms of change may have been. We intended to explore inhibitory control and cognitive flexibility in the planned RCT to examine whether these two aspects of cognition are involved in changes in OCD symptoms following intervention. Further, pre- and post-intervention brain imaging may indicate changes in neural structures and/or activation and whether they correlate with symptom change following the combined approach. In a study of response inhibition in OCD, Thorsen et al. (2020) used a stop-signal task (SST) to examine the relationship between response inhibition and OCD symptom improvement following intensive ERP (the Bergen 4-day treatment program). The study included an age-gender-education matched control group (i.e., no OCD) who did not receive any intervention. Interestingly, pre-intervention testing revealed no significant difference between the OCD group and control group for the SST, suggesting that response inhibition was intact in the OCD group. The authors suggested that differences in inhibition response times, such as those reported by Norman et al. (2019), only become evident when very large numbers of participants are involved. Thorsen et al. (2020) reported that post-treatment improvement of OCD symptoms was not related to performance on the SST, but this is unsurprising given that pre-intervention SST performance in this group was 'normal' and there were no significant pre-post changes in SST. This study also examined cortical activation and connectivity using 3T functional magnetic resonance imaging, and it was reported that pre-post changes in cortical activation and connectivity were also unrelated to improvements in OCD symptoms. Although these findings seem to suggest that inhibitory control may not be related to improvement of OCD symptoms following ERP, the picture remains unclear. Inhibitory control is a multi-faceted and complex

concept, and to some degree involves higher order cognitive (executive) functioning and impulsivity. The measurement of inhibitory control is similarly complex and is unlikely to be captured by any one measure. The cognitive and cortical mechanisms underlying successful ERP treatment of OCD are unclear and require further detailed examination in larger-scale studies.

Future research may be guided by emerging neurobiological frameworks. There is some (albeit limited) neuroimaging evidence to suggest that OCD pathology may extend beyond the CSTC model to include the ACC and amygdala, but their contributions remain unclear and there are mixed findings in the neuroimaging data. Further research is needed to develop a neurobiological model that considers the potential contributions of the ACC and amygdala to OCD.

Finally, although the Y-BOCS is the most widely and frequently used instrument to quantify the ongoing severity of OCD symptoms, it may not be sensitive to subtle changes (such as a decrease from 5 h to 3 h per day of rituals) which potentially translates into a considerable reduction in distress. The use or development of a more sensitive assessment of OCD symptoms may be informative in future trials, particularly those aiming to establish correlations between symptoms and mechanisms of change.

The Survey Instrument

Study two (survey) relied on self-reporting of (i) an OCD diagnosis, and (ii) completion of the OCI-R to confirm the presence and severity of obsessive-compulsive symptoms. An independent confirmed diagnosis by a practitioner, would have strengthened the generalisations of the study findings to the wider OCD community. The presence of comorbidities such as major depression and other anxiety disorders and their severity were also not measured, which may have

impacted the findings relating to treatment acceptability and preferences. Ideally, the data would be collected from treatment-seeking individuals at the point of having completed a diagnostic assessment and were considering their treatment options. Future survey studies could also include other non-invasive brain stimulation approaches, such as transcranial magnetic stimulation. The survey in our study used a surgical approach (DBS) as a comparator. However, DBS is not comparable to tDCS, pharmacotherapy, and psychotherapy for OCD.

Expanding Reliability and Generalisability

The reliance on self-reporting of an OCD diagnosis in study two (survey), limits the generalisability of the findings to the wider OCD community. The interpretation of the outcomes of the case series were limited by the lack of a sham-control condition, and all ERP with tDCS sessions being delivered by the first author. The effects of time, expectancy of treatment effect, therapist effect, and the possibility of spontaneous recovery and/or placebo effects for the tDCS component could also not be partialled out. Further, the small sample size, and inclusion of only treatment refractory patients limits the generalisability of the results to the general OCD population.

Implications of tDCS Beyond the Laboratory

Based on the evidence to date, there is currently no justification for using tDCS over evidence-based treatments for OCD beyond research purposes in the laboratory. There is also a need for larger controlled clinical trials and better research on whether there are any long-term adverse effects. Although the use of tDCS in a research setting is accepted as safe (Day et al., 2023), the specific montage used in this and other research (cathodal pre-frontal and anodal SMA) has not been specifically explored for any long-term, detrimental effects. This raises the concern

over the widespread marketing and commercial sales of consumer tDCS devices in Australia. There appear to be no national regulations regarding the safety and effectiveness of tDCS devices outside of the research setting. tDCS is increasingly being used in a commercial setting for cognitive enhancement and for clinical conditions including addiction, chronic pain, epilepsy, fibromyalgia, migraine, stroke, post operative acute pain and schizophrenia (to name a few). This is despite consumer tDCS devices now being subject to European Union regulation for the purposes of risk management and clinical evaluation regarding safety (Carter et al., 2018).

Summary and Conclusion

This thesis sought to examine the effectiveness and acceptability of tDCS for OCD. The key findings were that (1) the level of reporting needs to be improved; (2) despite numerous claims that tDCS is a promising treatment option for the future, there is little evidence to support such claims; and (3) future studies need to include sham/controlled trials and longer-term follow-up periods. The findings of this research have added to the body of literature pertaining to tDCS for OCD, in particular being the first research to combine tDCS with ERP in a dual protocol approach. However, based on the evidence, tDCS should not be integrated into standard psychological care and remains a treatment for further study.

References

Abramovitch, A., Abramowitz, J. S., Riemann, B. C., & McKay, D. (2020). Severity benchmarks and contemporary clinical norms for the Obsessive-Compulsive Inventory-Revised (OCI-R). *Journal of Obsessive-Compulsive and Related Disorders*, *27*, 100557. https://doi.org/https://doi.org/10.1016/j.jocrd.2020.100557

Abramowitz, J., Taylor, S., & McKay, D. (2009). Obsessive-compulsive disorder. *The Lancet*, *374*, 491-499. https://doi.org/0.1016/S0140-6736(09)60240-3

Abramowitz, J. S. (2006). The psychological treatment of obsessive—compulsive disorder. *The Canadian Journal of Psychiatry*, *51*, 407-416. https://doi.org/10.1177/070674370605100702

Abramowitz, J. S., Franklin, M. E., Schwartz, S. A., Furr, J. M. J. J. o. c., & psychology, c. (2003). Symptom presentation and outcome of cognitive-behavioral therapy for obsessive-compulsive disorder. *71*(6), 1049. https://doi.org/10.1037/0022-006X.71.6.1049

Acevedo, N., Castle, D., Bosanac, P., & Rossell, S. (2023). Phenomenological Changes Associated with Deep Brain Stimulation for Obsessive Compulsive Disorder: A Cognitive Appraisal Model of Recovery. *Brain Sci*, *13*(10). https://doi.org/10.3390/brainsci13101444

Adams, T. G., Cisler, J. M., Kelmendi, B., George, J. R., Kichuk, S. A., Averill, C. L., Anticevic, A., Abdallah, C. G., & Pittenger, C. (2022). Transcranial direct current stimulation targeting the medial prefrontal cortex modulates functional connectivity and enhances safety learning in obsessive-compulsive disorder: Results from two pilot studies. *Depression and anxiety*, *39*(1), 37-48. https://doi.org/10.1016/j.brs.2021.09.008

Adler, C. M., McDonough-Ryan, P., Sax, K. W., Holland, S. K., Arndt, S., & Strakowski, S. M. (2000). fMRI of neuronal activation with symptom provocation in unmedicated patients with obsessive compulsive disorder. *Journal of psychiatric research*, *34*, 317-324. https://doi.org/10.1016/S0022-3956(00)00022-4

Akbari, S., Hassani-Abharian, P., & Tajeri, B. (2022). The effect of transcranial direct current stimulation (tDCS) on cerebellum in reduction of the symptoms of obsessive-compulsive disorder. *Neurocase*, *28*(2), 135-139. https://doi.org/10.1080/13554794.2021.1936073

Alonso, P., Cuadras, D., Gabriëls, L., Denys, D., Goodman, W., Greenberg, B. D., Jimenez-Ponce, F., Kuhn, J., Lenartz, D., & Mallet, L. (2015). Deep brain stimulation for obsessive-compulsive disorder: a meta-analysis of treatment outcome and predictors of response. *PloS one*, *10*(7), e0133591. https://doi.org/10.1371/journal.pone.0133591

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/https://doi.org/10.1016/j.jad.2019.04.041

Altman, D. G., Schulz, K. F., Moher, D., Egger, M., Davidoff, F., Elbourne, D., Gøtzsche, P. C., Lang, T., & Group, C. (2001). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Annals of internal medicine*, *134*(8), 663-694. https://doi.org/10.7326/0003-4819-134-8-200104170-00012

American Psychological Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. American Psychiatric Association.

American Psychological Association. (2022). *Diagnostic and statistical manual of mental disorders (5th ed., text rev.)*. American Psychiatric Association. https://doi.org/10.1176/appi.books.9780890425787

Andrews, G., Bell, C., Boyce, P., Gale, C., Lampe, L., Marwat, O., Rapee, R., & Wilkins, G. (2018). Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of panic disorder, social anxiety disorder and generalised anxiety disorder. *Australian & New Zealand Journal of Psychiatry*, *52*(12), 1109-1172. https://doi.org//doi.org/10.1177/0004867418799453

Antony, M. M., Bieling, P. J., Cox, B. J., Enns, M. W., & Swinson, R. P. (1998). Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. *Psychological Assessment*, *10*(2), 176. https://doi.org/10.1037/1040-3590.10.2.176

Arora, T., Bhowmik, M., Khanam, R., & Vohora, D. (2013). Oxcarbazepine and fluoxetine protect against mouse models of obsessive compulsive disorder through modulation of cortical serotonin and CREB pathway. *Behavioural brain research*, *247*, 146-152. http://dx.doi.org/10.1016/j.bbr.2013.02.038

Bation, R., Mondino, M., Le Camus, F., Saoud, M., & Brunelin, J. (2019). Transcranial direct current stimulation in patients with obsessive compulsive disorder: a randomized controlled trial. *European Psychiatry*, *62*, 38-44. https://doi.org/10.1016/j.eurpsy.2019.08.011

Bation, R., Poulet, E., Haesebaert, F., Saoud, M., & Brunelin, J. (2016). Transcranial direct current stimulation in treatment-resistant obsessive–compulsive disorder: An open-label pilot study. *Progress in Neuro-Psychopharmacology*

and Biological Psychiatry, *65*, 153-157. https://doi.org/10.1016/j.pnpbp.2015.10.001

Beck, A. T. (1970). Cognitive therapy: Nature and relation to behavior therapy. *Behavior therapy*, *1*(2), 184-200.

Benkelfat, C., Nordahl, T. E., Semple, W. E., King, A. C., Murphy, D. L., & Cohen, R. M. (1990). Local cerebral glucose metabolic rates in obsessive-compulsive disorder: patients treated with clomipramine. *Archives of general psychiatry*, *47*(9), 840-848. https://doi.org/10.1001/archpsyc.1990.01810210048007

Benninger, D. H., Lomarev, M., Lopez, G., Wassermann, E. M., Li, X., Considine, E., & Hallett, M. (2010). Transcranial direct current stimulation for the treatment of Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry*, *81*, 1105-1111. https://doi.org/10.1136/jnnp.2009.202556

Boeding, S. E., Paprocki, C. M., Baucom, D. H., Abramowitz, J. S., Wheaton, M. G., Fabricant, L. E., & Fischer, M. S. (2013). Let me check that for you: Symptom accommodation in romantic partners of adults with Obsessive–Compulsive Disorder. *Behaviour research and therapy*, *51*(6), 316-322. https://doi.org/https://doi.org/10.1016/j.brat.2013.03.002

Bourne, S. K., Eckhardt, C. A., Sheth, S. A., & Eskandar, E. N. (2012). Mechanisms of deep brain stimulation for obsessive compulsive disorder: effects upon cells and circuits. *Frontiers in integrative neuroscience*, *6*, 29. https://doi.org/10.3389/fnint.2012.00029

Boutron, I., Altman, D. G., Moher, D., Schulz, K. F., & Ravaud, P. (2017). CONSORT statement for randomized trials of nonpharmacologic treatments: a 2017 update and a CONSORT extension for nonpharmacologic trial

abstracts. *Annals of internal medicine*, *167*(1), 40-47. https://doi.org/10.7326/M17-0046

Brander, G., Pérez-Vigil, A., Larsson, H., & Mataix-Cols, D. (2016). Systematic review of environmental risk factors for Obsessive-Compulsive Disorder: A proposed roadmap from association to causation. *Neuroscience & Biobehavioral Reviews*, *65*, 36-62. https://doi.org/https://doi.org/10.1016/j.neubiorev.2016.03.011

Brunelin, J., Mondino, M., Bation, R., Palm, U., Saoud, M., & Poulet, E. (2018). Transcranial direct current stimulation for obsessive-compulsive disorder: A systematic review. *Brain sciences*, *8*, 37-48. https://doi.org/10.3390/brainsci8020037

Cappon, D., den Boer, T., Jordan, C., Yu, W., Lo, A., LaGanke, N., Biagi, M. C., Skorupinski, P., Ruffini, G., & Morales, O. (2022). Safety and feasibility of tele-supervised home-based transcranial direct current stimulation for major depressive disorder. *Frontiers in aging neuroscience*, *13*, 765370. https://doi.org/10.3389/fnagi.2021.765370

Carlisle, B., Kimmelman, J., Ramsay, T., & MacKinnon, N. (2015). Unsuccessful trial accrual and human subjects protections: an empirical analysis of recently closed trials. *Clinical trials*, *12*(1), 77-83. https://doi.org/10.1177%2F1740774514558307

Carter, A., Rogasch, N. C., & Paul, B. (2018). Regulating consumer use of transcranial direct current stimulation devices. https://www.mja.com.au/system/files/issues/209_01/10.5694mja17.00778.pdf

Chamberlain, S. R., Blackwell, A. D., Fineberg, N. A., Robbins, T. W., & Sahakian, B. J. (2005). The neuropsychology of obsessive compulsive disorder: The

importance of failures in cognitive and behavioural inhibition as candidate endophenotypic markers. *Neuroscience & Biobehavioral Reviews*, *29*, 399-419. https://doi.org/10.1016/j.neubiorev.2004.11.006

Cheng, Q., Huang, J., Xu, L., Li, Y., Li, H., Shen, Y., Zheng, Q., & Li, L. (2019). Analysis of Time-Course, Dose-Effect, and Influencing Factors of Antidepressants in the Treatment of Acute Adult Patients With Major Depression. *International Journal of Neuropsychopharmacology*, *23*(2), 76-87. https://doi.org/10.1093/ijnp/pyz062

Coffman, B. A., Clark, V. P., & Parasuraman, R. (2014). Battery powered thought: Enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation. *NeuroImage*, *85*, 895-908. https://doi.org/10.1016/j.neuroimage.2013.07.083

Craske, M. G., Liao, B., Brown, L., & Vervliet, B. (2012). Role of inhibition in exposure therapy. *Journal of Experimental Psychopathology*, *3*, 322-345. https://journals.sagepub.com/doi/pdf/10.5127/jep.026511

Craske, M. G., Treanor, M., Conway, C. C., Zbozinek, T., & Vervliet, B. (2014). Maximizing exposure therapy: An inhibitory learning approach. *Behaviour research and therapy*, *58*, 10-23. https://doi.org/10.1016/j.brat.2014.04.006

Craske, M. G., Treanor, M., Zbozinek, T. D., & Vervliet, B. (2022). Optimizing exposure therapy with an inhibitory retrieval approach and the OptEx Nexus. *Behaviour research and therapy*, *152*, 104069. https://doi.org/https://doi.org/10.1016/j.brat.2022.104069

Craske, M. G., Waters, A. M., Bergman, R. L., Naliboff, B., Lipp, O. V., Negoro, H., & Ornitz, E. M. (2008). Is aversive learning a marker of risk for anxiety

disorders in children? *Behaviour research and therapy*, *46*(8), 954-967. https://doi.org/10.1016/j.brat.2008.04.011

D'Urso, G., Brunoni, A. R., Mazzaferro, M. P., Anastasia, A., de Bartolomeis, A., & Mantovani, A. (2016). Transcranial direct current stimulation for obsessive–compulsive disorder: A randomized, controlled, partial crossover trial. *Depression and anxiety*, *33*(12), 1132-1140. https://doi.org/doi:10.1002/da.22578

D'Urso, G., Brunoni, A. R., Anastasia, A., Micillo, M., de Bartolomeis, A., & Mantovani, A. (2016). Polarity-dependent effects of transcranial direct current stimulation in obsessive-compulsive disorder. *Neurocase*, *22*(1), 60-64. https://doi.org/10.1080/13554794.2015.1045522

da Conceição Costa, D. L., de Campos, A. P., de Bragança Pereira, C. A., Torres, A. R., Dos Santos, A. C., Requena, G., Ferrão, Y. A., Do Rosário, M. C., Miguel, E. C., & Simpson, H. B. (2022). Latency to treatment seeking in patients with obsessive-compulsive disorder: Results from a large multicenter clinical sample. *Psychiatry research*, *312*, 114567. https://doi.org/10.1016/j.psychres.2022.114567

da Silva, R. d. M. F., Brunoni, A. R., Goerigk, S., Batistuzzo, M. C., Costa, D. L. d. C., Diniz, J. B., Padberg, F., D'Urso, G., Miguel, E. C., & Shavitt, R. G. (2021). Efficacy and safety of transcranial direct current stimulation as an add-on treatment for obsessive-compulsive disorder: a randomized, sham-controlled trial. *Neuropsychopharmacology*, *46*(5), 1028-1034. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8115679/

da Silva, R. d. M. F., Brunoni, A. R., Miguel, E. C., & Shavitt, R. G. (2016). Transcranial direct current stimulation for treatment-resistant obsessive-

compulsive disorder: report on two cases and proposal for a randomized, sham-controlled trial. *Sao Paulo medical journal*, *134*(5), 446-450. http://www.scielo.br/pdf/spmj/v134n5/1806-9460-spmj-134-05-00446.pdf

Daniel, M., Buchholz, S. W., Schoeny, M., Halloway, S., Kitsiou, S., Johnson, T., Vispute, S., Kapp, M., & Wilbur, J. (2022). Effects of the COVID-19 pandemic on recruitment for the working women walking program. *Res Nurs Health*, *45*(5), 559-568. https://doi.org/10.1002/nur.22258

Datto, C. J. (2000). Side effects of electroconvulsive therapy. *Depression and anxiety*, *12*(3), 130-134. https://doi.org/10.1002/1520-6394(2000)12:3<130::AID-DA4>3.0.CO;2-C

Day, P., Twiddy, J., & Dubljević, V. (2023). Present and emerging ethical issues with tDCS use: A summary and review. *Neuroethics*, *16*(1), 1. https://doi.org/10.1007/s12152-022-09508-9

De Avila, R. C. S., Do Nascimento, L. G., Porto, R. L. d. M., Fontenelle, L., Filho, E. C. M., Brakoulias, V., & Ferrão, Y. A. (2019). Level of insight in patients with obsessive–compulsive disorder: an exploratory comparative study between patients with “good insight” and “poor insight”. *Frontiers in Psychiatry*, *10*, 413. https://doi.org/10.3389/fpsyt.2019.00413

de Wit, S. J., de Vries, F. E., van der Werf, Y. D., Cath, D. C., Heslenfeld, D. J., Veltman, E. M., van Balkom, A. J., Veltman, D. J., & van den Heuvel, O. A. (2012). Presupplementary motor area hyperactivity during response inhibition: a candidate endophenotype of obsessive-compulsive disorder. *American Journal of Psychiatry*, *169*, 1100-1108. https://doi.org/10.1176/appi.ajp.2012.12010073

Dedoncker, J., Baeken, C., De Raedt, R., & Vanderhasselt, M.-A. (2020). Combined transcranial direct current stimulation and psychological interventions: state of the art and promising perspectives for clinical psychology. *Biological Psychology*, 107991. https://doi.org/10.1016/jbiopsycho.2020.107991

Deepak, D. (2017). *Effect of Adjunctive Transcranial Direct Current Stimulation to Supplementary Motor Area and Dorsolateral Prefrontal Cortex in Obsessive Compulsive Disorder: A Randomized Double Blind Sham-controlled Study* (Publication Number 27543700) [D.P.M., Central Institute of Psychiatry (India)]. Ann Arbor MI. https://www.proquest.com/dissertations-theses/effect-adjunctuive-transcranial-direct-current/docview/2379686934/se-2?accountid=10382

Derksen, M., Feenstra, M., Willuhn, I., & Denys, D. (2020). Chapter 44 - The serotonergic system in obsessive-compulsive disorder. In C. P. Müller & K. A. Cunningham (Eds.), *Handbook of Behavioral Neuroscience* (Vol. 31, pp. 865-891). Elsevier. https://doi.org/https://doi.org/10.1016/B978-0-444-64125-0.00044-X

DeVeaugh-Geiss, J. (1994). Pharmacologic therapy of obsessive compulsive disorder. *Advances in Pharmacology*, *30*, 35-52. https://doi.org/10.1016/S1054-3589(08)60171-4

Diedrich, A., Sckopke, P., Schwartz, C., Schlegl, S., Osen, B., Stierle, C., & Voderholzer, U. (2016). Change in obsessive beliefs as predictor and mediator of symptom change during treatment of obsessive-compulsive disorder–a process-outcome study. *BMC Psychiatry*, *16*, 1-10. https://doi.org/10.1186/s12888-016-0914-6. PMID: 27388205; PMCID: PMC4937602.

Dinn, W. M., Aycicegi-Dinn, A., Göral, F., Karamursel, S., Yildirim, E. A., Hacioglu-Yildirim, M., Gansler, D. A., Doruk, D., & Fregni, F. (2016). Treatment-resistant obsessive-compulsive disorder: Insights from an open trial of transcranial direct current stimulation (tDCS) to design a RCT. *Neurology, Psychiatry and Brain Research*, *22*(3-4), 146-154. http://dx.doi.org/10.1016/j.npbr.2016.08.003

Dold, M., Aigner, M., Lanzenberger, R., & Kasper, S. (2013). Antipsychotic augmentation of serotonin reuptake inhibitors in treatment-resistant obsessive-compulsive disorder: a meta-analysis of double-blind, randomized, placebo-controlled trials. *International Journal of Neuropsychopharmacology*, *16*(3), 557-574. https://doi.org/10.1093/ijnp/pyv047

dos Santos-Ribeiro, S., de Salles Andrade, J. B., Quintas, J. N., Baptista, K. B., Moreira-de-Oliveira, M. E., Yücel, M., & Fontenelle, L. F. (2018). A systematic review of the utility of electroconvulsive therapy in broadly defined obsessive-compulsive-related disorders. *The Primary Care Companion for CNS Disorders*, *20*(5), 24760. https://doi.org/10.4088/PCC.18r02342

Eisen, J. L., Sibrava, N. J., Boisseau, C. L., Mancebo, M. C., Stout, R. L., Pinto, A., & Rasmussen, S. A. (2013). Five-year course of obsessive-compulsive disorder: Predictors of remission and relapse. *The Journal of Clinical Psychiatry*, *74*(3), 233. https://doi.org/10.4088/JCP.12m07657

Ellis, A. (1962). *Reason and emotion in psychotherapy*. Carol Publishing Group. https://doi.org/http://link.library.curtin.edu.au/p?pid=CUR_ALMA2179922010001951

Farrell, L. J., Nabinger de Diaz, N. A., Mathieu, S., McKenzie, M. L., Miyamoto, T., Donovan, C. L., Waters, A. M., March, S., Bothma, N., Kroon, R., Simcock, G., Ware, R. S., Selles, R. R., Storch, E. A., & Ollendick, T. (2022). FAST CBT for pediatric OCD: A multiple-baseline controlled pilot trial of parent training in exposure and response prevention delivered via telehealth [Original Research]. *Frontiers in Psychology*, *13*. https://doi.org/10.3389/fpsyg.2022.1009735

Fawcett, E. J., Power, H., & Fawcett, J. M. (2020). Women are at greater risk of OCD than men: a meta-analytic review of OCD prevalence worldwide. *The Journal of Clinical Psychiatry*, *81*(4), 13075. https://www.psychiartrist.com/jcp/ocd-prevalence-and-gender/

Fergus, T. A., & Carmin, C. N. (2014). The validity and specificity of the short-form of the Obsessive Beliefs Questionnaire (OBQ). *Journal of Psychopathology and Behavioral Assessment*, *36*, 318-328. https://doi.org/10.1007/s10862-013-9398-6

Fineberg, N. A., Cinosi, E., Smith, M. V., Busby, A. D., Wellsted, D., Huneke, N. T., Garg, K., Aslan, I. H., Enara, A., & Garner, M. (2023). Feasibility, acceptability and practicality of transcranial stimulation in obsessive compulsive symptoms (FEATSOCS): A randomised controlled crossover trial. *Comprehensive psychiatry*, *122*, 152371. https://doi.org/10.1192/j.eurpsy.2022.54

Fineberg, N. A., Dell'Osso, B., Albert, U., Maina, G., Geller, D., Carmi, L., Sireau, N., Walitza, S., Grassi, G., & Pallanti, S. (2019). Early intervention for obsessive compulsive disorder: An expert consensus statement. *European*

Neuropsychopharmacology, *29*(4), 549-565. https://doi.org/10.1016/j.euroneuro.2019.02.002

Fineberg, N. A., Reghunandanan, S., Simpson, H. B., Phillips, K. A., Richter, M. A., Matthews, K., Stein, D. J., Sareen, J., Brown, A., & Sookman, D. (2015). Obsessive–compulsive disorder (OCD): Practical strategies for pharmacological and somatic treatment in adults. *Psychiatry research*, *227*(1), 114-125. https://doi.org/10.1016/j.psychres.2014.12.003

Foa, E., Franklin, M., & Kozak, M. (1998). Psychosocial treatments for obsessive-compullsive disorder: Literature Review. In R. Swinson, M. Antony, S. Rachman, & M. Richter (Eds.), *Obsessive-compulsive disorder: Theory, research, and treatment* (pp. 258-276). Guildford Press.

Foa, E. B. (2010). Cognitive behavioral therapy of obsessive-compulsive disorder. *Dialogues in clinical neuroscience*, *12*(2), 199-207. https://doi.org/https://doi.org.10.31887/DCNS.2010.12.2/efoa

Foa, E. B., & Franklin, M. E. (2000). Psychotherapies for obsessive-compulsive disorder: A review. *Obsessive-compulsive disorder*, *4*, 93-146. https://doi.org/10.1002/0470846496.ch3

Foa, E. B., Huppert, J. D., & Cahill, S. P. (2006). Emotional processing theory: An update. In B. O. Rothbaum (Ed.), *Pathological anxiety: Emotional processing in etiology and treatment*. Guilford Press.

Foa, E. B., Huppert, J. D., Leiberg, S., Langner, R., Kichic, R., Hajcak, G., & Salkovskis, P. M. (2002). The Obsessive-Compulsive Inventory: Development and validation of a short version. *Psychological Assessment*, *14*, 485-496. https://doi.org/10.1037/1040-3590.14.4.48

Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: Exposure to corrective information. *Psychological Bulletin*, *99*(1), 20-35. https://doi.org/10.1037/0033-2909.99.1.20

Foa, E. B., Liebowitz, M. R., Kozak, M. J., Davies, S., Campeas, R., Franklin, M. E., Huppert, J. D., Kjernisted, K., Rowan, V., & Schmidt, A. B. (2005). Randomized, placebo-controlled trial of exposure and ritual prevention, clomipramine, and their combination in the treatment of obsessive-compulsive disorder. *American Journal of Psychiatry*, *162*(1), 151-161. https://doi.org/10.1176/appi.ajp.162.1.151

Fontenelle, L. F., Coutinho, E. S., Lins-Martins, N. M., Fitzgerald, P. B., Fujiwara, H., & Yuecel, M. (2015). Electroconvulsive therapy for obsessive-compulsive disorder: a systematic review. *The Journal of Clinical Psychiatry*, *76*(7), 6341. https://doi.org/10.4088/JCP.14r09129

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. (2021). Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation in neurological and psychiatric disorders. *International Journal of Neuropsychopharmacology*, *24*(4), 256-313. https://academic.oup.com/ijnp/article/24/4/256/5876418

Fregni, F., El-Hagrassy, Mirret M, Pacheco-Barrios, Kevin, Carvalho, Sandra, Leite, Jorge, Simis, Marcel, et al. . (2021). Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation in neurological and psychiatric disorders. *International Journal of*

Neuropsychopharmacology,, *24*, 256-313. https://doi.org/10.1093/ijnp/pyaa051

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): A tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology*, *117*(4), 845-850. https://doi.org/https://doi.org/10.1016/j.clinph.2005.12.003

García-Soriano, G., Rufer, M., Delsignore, A., & Weidt, S. (2014). Factors associated with non-treatment or delayed treatment seeking in OCD sufferers: a review of the literature. *Psychiatry research*, *220*(1-2), 1-10. https://doi.org/10.1016/j.psychres.2014.07.009

George, M. S., Padberg, F., Schlaepfer, T. E., O'Reardon, J. P., Fitzgerald, P. B., Nahas, Z. H., & Marcolin, M. A. (2009). Controversy: Repetitive transcranial magnetic stimulation or transcranial direct current stimulation shows efficacy in treating psychiatric diseases (depression, mania, schizophrenia, obsessive-complusive disorder, panic, posttraumatic stress disorder). *Brain stimulation*, *2*(1), 14-21. https://doi.org/10.1016/j.brs.2008.06.001

Gershkovich, M., Wheaton, M. G., & Simpson, H. B. (2017). Management of treatment-resistant obsessive-compulsive disorder. *Current Treatment Options in Psychiatry*, *4*(4), 357-370. https://doi.org/10.1007/s40501-017-0127-8

Gillihan, S. J., Williams, M. T., Malcoun, E., Yadin, E., & Foa, E. B. (2012). Common pitfalls in exposure and response prevention (EX/RP) for OCD. *Journal of Obsessive-Compulsive and Related Disorders*, *1*(4), 251-257. https://doi.org/https://doi.org/10.1016/j.jocrd.2012.05.002

Gonçalves, Ó. F., Carvalho, S., Leite, J., Fernandes-Gonçalves, A., Carracedo, A., & Sampaio, A. (2016). Gray matter morphological alteration in obsessive compulsive disorder: evidence for an inhibitory control and emotional regulation disorder. *Principles and Practice of Clinical Research*, *2*(2). https://doi.org/10.2180/ppcrj.2016.22.1

Goodman, W. K., Price, L. H., Delgado, P. L., Palumbo, J., Krystal, J. H., Nagy, L. M., Rasmussen, S. A., Heninger, G. R., & Charney, D. S. (1990). Specificity of serotonin reuptake inhibitors in the treatment of obsessive-compulsive disorder: comparison of fluvoxamine and desipramine. *Archives of general psychiatry*, *47*(6), 577-585. https://doi.org/10.1001/archpsyc.1990.01810180077011

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Delgado, P., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown obsessive compulsive scale: II. Validity. *Archives of general psychiatry*, *46*(11), 1012-1016. https://doi.org/10.1001/archpsyc.1989.01810110054008

Goodman, W. K., Price, L. H., Rasmussen, S. A., Mazure, C., Fleischmann, R. L., Hill, C. L., Heninger, G. R., & Charney, D. S. (1989). The Yale-Brown obsessive compulsive scale: I. Development, use, and reliability. *Archives of general psychiatry*, *46*(11), 1006-1011. https://doi.org/doi:10.1001/archpsyc.1989.01810110048007

Gowda, S. M., Narayanaswamy, J. C., Hazari, N., Bose, A., Chhabra, H., Balachander, S., Bhaskarapillai, B., Shivakumar, V., Venkatasubramanian, G., & Reddy, Y. J. (2019). Efficacy of pre-supplementary motor area transcranial direct current stimulation for treatment resistant obsessive

compulsive disorder: a randomized, double blinded, sham controlled trial. *Brain stimulation*, *12*(4), 922-929. https://doi.org/10.1016/j.brs.2019.02.005

Green, P. E., Loftus, A., & Anderson, R. A. (2020). Protocol for Transcranial Direct Current Stimulation for Obsessive-Compulsive Disorder. *Brain sciences*, *10*(12), 1008. https://doi.org/10.3390/brainsci10121008

Green, P. E., Loftus, A. M., & Anderson, R. A. (2024). Transcranial Direct Current Stimulation for Obsessive Compulsive Disorder: A systematic review and CONSORT evaluation. *Journal of the International Neuropsychological Society*. Manuscript doi: 10.1017/S1355617724000602

Greenberg, B. D., Rauch, S. L., & Haber, S. N. (2010). Invasive circuitry-based neurotherapeutics: stereotactic ablation and deep brain stimulation for OCD. *Neuropsychopharmacology*, *35*(1), 317-336. https://doi.org/10.1038/npp.2009.128

Haciomeroglu, B. (2020). The role of reassurance seeking in obsessive compulsive disorder: the associations between reassurance seeking, dysfunctional beliefs, negative emotions, and obsessive- compulsive symptoms. *BMC Psychiatry*, *20*(1), 356. https://doi.org/10.1186/s12888-020-02766-y

Hallett, M. (2007). Transcranial Magnetic Stimulation: A Primer. *Neuron*, *55*(2), 187-199. https://doi.org/http://dx.doi.org/10.1016/j.neuron.2007.06.026

Hansen, N. (2012). Action mechanisms of transcranial direct current stimulation in Alzheimer's disease and memory loss. *Frontiers in Psychiatry*, *3*, 48. https://doi.org/10.3389/fpsyt.2012.00048

Harika-Germaneau, G., Gosez, J., Bokam, P., Guillevin, R., Doolub, D., Thirioux, B., Wassouf, I., Germaneau, A., Langbour, N., & Jaafari, N. (2024). Investigating Brain Structure and tDCS Response in Obsessive-Compulsive

Disorder. *Journal of psychiatric research*. https://doi.org/10.1016/j.jpsychires.2024.06.053

Harika-Germaneau, G., Heit, D., Drapier, D., Sauvaget, A., Bation, R., Chatard, A., Doolub, D., Wassouf, I., Langbour, N., & Jaafari, N. (2024). Treating refractory obsessive compulsive disorder with cathodal transcranial direct current stimulation over the supplementary motor area: a large multisite randomized sham-controlled double-blind study. *Frontiers in Psychiatry*, *15*, 1338594. https://doi.org/10.3389/fpsyt.2024.1338594

Harrison, B. J., Soriano-Mas, C., Pujol, J., Ortiz, H., López-Solà, M., Hernández-Ribas, R., Deus, J., Alonso, P., Yücel, M., & Pantelis, C. (2009). Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Archives of general psychiatry*, *66*(11), 1189-1200. https://doi.org/jamanetwork.com/

Hasan, A., Schneider, M., Schneider-Axmann, T., Ruge, D., Retz, W., Rösler, M., Falkai, P., & Wobrock, T. (2013). A similar but distinctive pattern of impaired cortical excitability in first-episode schizophrenia and ADHD. *Neuropsychobiology*, *67*(2), 74-83. https://doi.org/10.1159/000343912

Hazari, N., Narayanaswamy, J. C., Chhabra, H., Bose, A., Venkatasubramanian, G., & Reddy, Y. J. (2016). Response to transcranial direct current stimulation in a case of episodic obsessive compulsive disorder. *The journal of ECT*, *32*(2), 144-146. https://doi.org/10.1097/YCT.0000000000000309

Hindle, J. V., Petrelli, A., Clare, L., & Kalbe, E. (2013). Nonpharmacological enhancement of cognitive function in Parkinson's disease: A systematic review. *Movement Disorders*, *28*, 1034-1049. https://doi.org/10.1002/mds.25377

Hoehn-Saric, R., Ninan, P., Black, D. W., Stahl, S., Greist, J. H., Lydiard, B., McElroy, S., Zajecka, J., Chapman, D., & Clary, C. (2000). Multicenter double-blind comparison of sertraline and desipramine for concurrent obsessive-compulsive and major depressive disorders. *Archives of general psychiatry*, *57*(1), 76-82. https://doi.org/10.1001/archpsyc.57.1.76

Hood, S. D., Broyd, A., Robinson, H., Lee, J., Hudaib, A.-R., & Hince, D. A. (2017). Effects of tryptophan depletion on selective serotonin reuptake inhibitor-remitted patients with obsessive compulsive disorder. *Journal of Psychopharmacology*, *31*(12), 1615-1623. https://doi.org/10.1177/0269881117736916

Jacoby, R. J., & Abramowitz, J. S. (2016). Inhibitory learning approaches to exposure therapy: A critical review and translation to obsessive-compulsive disorder. *Clinical Psychology Review*, *49*, 28-40. https://doi.org/10.1016/j.cpr.2016.07.001

James, I. A., & Blackburn, I.-M. (1995). Cognitive therapy with obsessive–compulsive disorder. *The British Journal of Psychiatry*, *166*(4), 444-450. https://doi.org/10.1192/bjp.166.4.444

Julien, D., O'Connor, K. P., & Aardema, F. (2007). Intrusive thoughts, obsessions, and appraisals in obsessive–compulsive disorder: A critical review. *Clinical Psychology Review*, *27*(3), 366-383. https://doi.org/10.1016/j.cpr.2006.12.004

Katzman, M. A., Bleau, P., Blier, P., Chokka, P., Kjernisted, K., & Van Ameringen, M. (2014). Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. *BMC Psychiatry*, *14*(1), S1. https://doi.org/10.1186/1471-244x-14-s1-s1

Kekic, M., Boysen, E., Campbell, I. C., & Schmidt, U. (2016). A systematic review of the clinical efficacy of transcranial direct current stimulation (tDCS) in psychiatric disorders. *Journal of psychiatric research*, *74*, 70-86. https://doi.org/10.1016/j.jpsychires.2015.12.018

Kim, S. W., Dysken, M. W., & Kuskowski, M. (1990). The Yale-Brown obsessive-compulsive scale: a reliability and validity study. *Psychiatry research*, *34*, 99-106. https://doi.org/doi:10.1016/0165-1781(90)90061-9

Konstantinidou, H., & Evans, C. (2015). Pharmacotherapy and psychotherapy: the challenges of integrating two paradigms. *Psychoanalytic Psychotherapy*, *29*(4), 343-362. http://dx.doi.org/10.1080/02668734.2015.1051096

Kriston, L. (2013). Dealing with clinical heterogeneity in meta-analysis. Assumptions, methods, interpretation. *Int J Methods Psychiatr Res*, *22*(1), 1-15. https://doi.org/10.1002/mpr.1377

Krueger, C., & Tian, L. (2004). A comparison of the general linear mixed model and repeated measures ANOVA using a dataset with multiple missing data points. *Biological Research for Nursing*, *6*(2), 151-157. https://doi.org/10.1177/1099800404267682

Kühne, F., Hobrecker, L. K., Heinze, P. E., Meißner, C., & Weck, F. (2024). Exposure therapy tailored to inhibitory learning principles in a naturalistic setting: an open pilot trial in obsessive-compulsive outpatient care [Brief Research Report]. *Frontiers in Psychology*, *15*. https://doi.org/10.3389/fpsyg.2024.1328850

Kuo, M.-F., Chen, P.-S., & Nitsche, M. A. (2017). The application of tDCS for the treatment of psychiatric diseases. *International Review of Psychiatry*, *29*(2), 146-167. https://doi.org/10.1080/09540261.2017.1286299

Lam, J. N., & Steketee, G. S. (2001). Reducing Obsessions and Compulsions Through Behavior Therapy. *Psychoanalytic Inquiry*, *21*(2), 157-182. https://doi.org/10.1080/07351692109348930

Lawrence, B. J., Gasson, N., Johnson, A. R., Booth, L., & Loftus, A. M. (2018). Cognitive training and transcranial direct current stimulation for mild cognitive impairment in parkinson's disease: A randomized controlled trial. *Parkinson's Disease*, *1*, 1-12. https://doi.org/10.1155/2018/4318475

Lefaucheur, J.-P., Antal, A., Ayache, S. S., Benninger, D. H., Brunelin, J., Cogiamanian, F., Cotelli, M., De Ridder, D., Ferrucci, R., & Langguth, B. (2017). Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clinical Neurophysiology*, *128*(1), 56-92. http://dx.doi.org/10.1016/j.clinph.2016.10.087

Leonard, H. L., Swedo, S. E., Rapoport, J. L., Koby, E. V., Lenane, M. C., Cheslow, D. L., & Hamburger, S. D. (1989). Treatment of obsessive-compulsive disorder with clomipramine and desipramine in children and adolescents: a double-blind crossover comparison. *Archives of general psychiatry*, *46*(12), 1088-1092. https://doi.org/10.1001/archpsyc.1989.01810120030006

Ley, P., & Florio, T. (1996). The use of readability formulas in health care. *Psychology, Health & Medicine*, *1*, 7-28. https://doi.org/10.1080/13548509608400003

Lins-Martins, N. M., Yücel, M., Tovar-Moll, F., Rodrigues, E. C., & Fontenelle, L. F. (2015). Electroconvulsive therapy in obsessive-compulsive disorder: a chart review and evaluation of its potential therapeutic effects. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *27*(1), 65-68. https://doi.org/10.1176/appi.neuropsych.13080184

Lissek, S., Powers, A. S., McClure, E. B., Phelps, E. A., Woldehawariat, G., Grillon, C., & Pine, D. S. (2005). Classical fear conditioning in the anxiety disorders: A meta-analysis. *Behaviour research and therapy*, *43*, 1391-1424. https://doi.org/10.1016/j.brat.2004.10.007

Loftus, A. M., Yalcin, O., Baughman, F. D., Vanman, E. J., & Hagger, M. S. (2015). The impact of transcranial direct current stimulation on inhibitory control in young adults. *Brain and Behavior*, *5*(5), e00332. https://doi.org/10.1002/brb3.332

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour research and therapy*, *33*, 335-343. https://doi.org/10.1016/0005-7967(94)00075-U

Mantovani, A., Lisanby, S. H., Pieraccini, F., Ulivelli, M., Castrogiovanni, P., & Rossi, S. (2006). Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive–compulsive disorder (OCD) and Tourette's syndrome (TS). *International Journal of Neuropsychopharmacology*, *9*(1), 95-100. https://doi.org/10.1017/S1461145705005729

Mar-Barrutia, L., Real, E., Segalás, C., Bertolín, S., Menchón, J. M., & Alonso, P. (2021). Deep brain stimulation for obsessive-compulsive disorder: a systematic review of worldwide experience after 20 years. *World journal of psychiatry*, *11*(9), 659. https://doi.org/10.5498/wjp.v11.i9.659

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

Mastellone, M. (1974). Aversion therapy: a new use for the old rubber band. *Journal of Behavior Therapy and Experimental Psychiatry*(5), 311-312. https://doi.org/10.1016/0005-7916(74)90086-X

Mataix-Cols, D., Rauch, S. L., Baer, L., Eisen, J. L., Shera, D. M., Goodman, W. K., Rasmussen, S. A., & Jenike, M. A. (2002). Symptom stability in adult obsessive-compulsive disorder: data from a naturalistic two-year follow-up study. *American Journal of Psychiatry*, *159*(2), 263-268. https://doi.org/10.1176/appi.ajp.159.2.263

Maziero, M. P., Macaya, D., Shavitt, R. G., Diniz, J. B., Miguel, E. C., Silva, R. M. F. d., & Costa, D. L. d. C. (2022). Management of Patients With Obsessive-Compulsive Disorder: Focus on Pharmacotherapy. *Psychiatric Annals*, *52*(4), 143-151. https://doi.org/10.3928/00485713-20220315-01

McCulloch, C. E., & Neuhaus, J. M. (2005). Generalized linear mixed models. *Encyclopedia of Biostatistics*, *4*, 1049. https://doi.org/10.1002/0470011815.b2a10021

McDougle, C., Goodman, W., Price, L., Delgado, P., Krystal, J., Charney, D., & Heninger, G. (1989). Neuroleptic addition in fluvoxaminerefractory OCD. *Amer Psychiatr Assoc New Res Abstract# NR350*. https://doi.org/10.1176/ajp.147.5.652

McHugh, R. K., Whitton, S. W., Peckham, A. D., Welge, J. A., & Otto, M. W. (2013). Patient preference for psychological vs. pharmacological treatment of psychiatric disorders: a meta-analytic review. *The Journal of Clinical Psychiatry*, *74*(6), 595. https://doi.org/doi:10.4088/JCP.12r07757

McIntyre, C. C., & Hahn, P. J. (2010). Network perspectives on the mechanisms of deep brain stimulation. *Neurobiology of Disease*, *38*(3), 329-337. https://doi.org/10.1016/j.nbd.2009.09.022

Meichenbaum, D. (1975). Self-instructional methods. *Helping people change*, 357-391.

Meyer, J. M., Farrell, N. R., Kemp, J. J., Blakey, S. M., & Deacon, B. J. (2014). Why do clinicians exclude anxious clients from exposure therapy? *Behaviour research and therapy*, *54*, 49-53. https://doi.org/10.1016/j.brat.2014.01.004

Meyer, V., & Levy, R. (1973). *Modification of behavior in obsessive-compulsive disorders, in Issues and Trends in Behavior Therapy* (U. Adams. H. E, P., Springfield, I.L., Thomas, C. C., Ed.).

Meyer, V., Levy, R., & Schnurer, A. (1974). *A behavioral treatment of obsessive compulsive disorders, in Obsessional States.* (H. R. Beech, Ed.).

Milad, M. R., & Rauch, S. L. (2012). Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. *Trends in cognitive sciences*, *16*(1), 43-51. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4955838/pdf/nihms799012.pdf

Mirza, M., Siebert, S., Pratt, A., Insch, E., McIntosh, F., Paton, J., Wright, C., Buckley, C. D., Isaacs, J., & McInnes, I. B. (2022). Impact of the COVID-19 pandemic on recruitment to clinical research studies in rheumatology. *Musculoskeletal Care*, *20*(1), 209. https://doi.org/10.1002/msc.1561

Moher, D., Hopewell, S., Schulz, K. F., Montori, V., Gøtzsche, P. C., Devereaux, P. J., Elbourne, D., Egger, M., & Altman, D. G. (2012). CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group

randomised trials. *International Journal of Surgery*, *10*(1), 28-55. https://doi.org/https://doi.org/10.1016/j.ijsu.2011.10.001

Moritz, S., Külz, A., Voderholzer, U., Hillebrand, T., McKay, D., & Jelinek, L. (2019). "Phobie à deux" and other reasons why clinicians do not apply exposure with response prevention in patients with obsessive–compulsive disorder. *Cognitive behaviour therapy*, *48*(2), 162-176. https://doi.org/10.1080/16506073.2018.1494750

Mowrer, O. (1960). Learning theory and behavior.

Myers, S. G., Fisher, P. L., & Wells, A. (2008). Belief domains of the Obsessive Beliefs Questionnaire-44 (OBQ-44) and their specific relationship with obsessive–compulsive symptoms. *Journal of Anxiety Disorders*, *22*, 475-484. https://doi.org/10.1016/j.janxdis.2007.03.012

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience*, *9*(11), 856-869. https://doi.org/10.1038/nrn2478

Najafi, K., Fakour, Y., Zarrabi, H., Heidarzadeh, A., Khalkhali, M., Yeganeh, T., Farahi, H., Rostamkhani, M., Najafi, T., & Shabafroz, S. (2017). Efficacy of transcranial direct current stimulation in the treatment: Resistant patients who suffer from severe obsessive-compulsive disorder. *Indian journal of psychological medicine*, *39*, 573-578. https://doi.org/10.4103/IJPSYM.IJPSYM_388_16

Narayanaswamy, J. C., Jose, D., Chhabra, H., Agarwal, S. M., Shrinivasa, B., Hegde, A., Bose, A., Kalmady, S. V., Venkatasubramanian, G., & Reddy, Y. C. J. (2015). Successful application of add-on transcranial direct current

stimulation (tDCS) for treatment of SSRI resistant OCD. *Brain stimulation, 8,* 655-657. https://doi.org/10.1016/j.brs.2014.12.003

Nardone, R., Bergmann, J., Christova, M., Caleri, F., Tezzon, F., Ladurner, G., Trinka, E., & Golaszewski, S. (2012). Effect of transcranial brain stimulation for the treatment of Alzheimer disease: A review. *International Journal of Alzheimer's Disease*, *2012*, 1-5. https://doi.org/10.1155/2012/687909

NHMRC. (2007). *Guide to the development, implementation and evaluation of clinical practice guidelines*. Retrieved from https://www.nhmrc.gov.au/guidelines-publications/cp30

Nitsche, M. A., Cohen, L. G., Wassermann, E. M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P. S., & Fregni, F. (2008). Transcranial direct current stimulation: State of the art 2008. *Brain stimulation*, *1*, 206-223. https://doi.org/10.1016/j.brs.2008.06.004

Norberg, M. M., Calamari, J. E., Cohen, R. J., & Riemann, B. C. (2008). Quality of life in obsessive-compulsive disorder: An evaluation of impairment and a preliminary analysis of the ameliorating effects of treatment. *Depression and anxiety*, *25*(3), 248-259. https://doi.org/10.1002/da.20298

Nuñez, M., Zinbarg, R. E., & Mittal, V. A. (2019). Efficacy and mechanisms of non-invasive brain stimulation to enhance exposure therapy: A review. *Clinical Psychology Review*, *70*, 64-78. https://doi.org/10.1016/j.cpr.2019.04.001

Olatunji, B. O., Davis, M. L., Powers, M. B., & Smits, J. A. (2013). Cognitive-behavioral therapy for obsessive-compulsive disorder: A meta-analysis of treatment outcome and moderators. *Journal of psychiatric research*, *47*(1), 33-41. https://doi.org/10.1016/j.jpsychires.2012.08.020

Olatunji, B. O., Wolitzky-Taylor, K. B., Willems, J., Lohr, J. M., & Armstrong, T. (2009). Differential habituation of fear and disgust during repeated exposure to threat-relevant stimuli in contamination-based OCD: An analogue study. *Journal of Anxiety Disorders*, *23*, 118-123. https://doi.org/10.1016/j.janxdis.2008.04.006

Ong, C. W., Clyde, J. W., Bluett, E. J., Levin, M. E., & Twohig, M. P. (2016). Dropout rates in exposure with response prevention for obsessive-compulsive disorder: What do the data really say? *Journal of Anxiety Disorders*, *40*, 8-17. http://dx.doi.org/10.1016/j.janxdis.2016.03.006

Öst, L.-G., Havnen, A., Hansen, B., & Kvale, G. (2015). Cognitive behavioral treatments of obsessive–compulsive disorder. A systematic review and meta-analysis of studies published 1993–2014. *Clinical Psychology Review*, *40*, 156-169. https://doi.org/10.1016/j.cpr.2015.06.003

Overton, S. M., & Menzies, R. G. (2005). Cognitive change during treatment of compulsive checking. *Behaviour Change*, *22*(3), 172-184. https://doi.org/10.1375/bech.2005.22.3.172

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., & Brennan, S. E. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *International Journal of Surgery*, *88*, 105906. http://www.prisma-statement.org/PRISMAStatement/PRISMAStatement.aspx

Pallanti, S., & Quercioli, L. (2006). Treatment-refractory obsessive-compulsive disorder: methodological issues, operational definitions and therapeutic lines. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *30*(3), 400-412. https://doi.org/10.1016/j.pnpbp.2005.11.028

Patel, S. R., Galfavy, H., Kimeldorf, M. B., Dixon, L. B., & Simpson, H. B. (2016). Patient preferences and acceptability of evidence-based and novel treatments for obsessive-compulsive disorder. *Psychiatric Services, 68*(3), 250-257. https://doi.org/10.1176/appi.ps.201600092

Patel, S. R., & Simpson, H. B. (2010). Patient preferences for obsessive-compulsive disorder treatment. *The Journal of Clinical Psychiatry, 71*(11), 0-0. https://doi.org/10.4088/JCP.09m05537blu

Perera, M. P. N., Mallawaarachchi, S., Miljevic, A., Bailey, N. W., Herring, S. E., & Fitzgerald, P. B. (2021). Repetitive Transcranial Magnetic Stimulation for Obsessive-Compulsive Disorder: A Meta-analysis of Randomized, Sham-Controlled Trials. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 6*(10), 947-960. https://doi.org/https://doi.org/10.1016/j.bpsc.2021.03.010

Peters, S. K., Dunlop, K., & Downar, J. (2016). Cortico-striatal-thalamic loop circuits of the salience network: a central pathway in psychiatric disease and treatment. *Frontiers in systems neuroscience*, *10*, 104. https://doi.org/10.3389/fnsys.2016.00104

Pinto, B. S., Cavendish, B. A., da Silva, P. H. R., Suen, P. J. C., Marinho, K. A. P., Valiengo, L. d. C. L., Vanderhasselt, M.-A., Brunoni, A. R., & Razza, L. B. (2022). The Effects of Transcranial Direct Current Stimulation in Obsessive–Compulsive Disorder Symptoms: A Meta-Analysis and Integrated Electric Fields Modeling Analysis. *Biomedicines, 11*(1), 80. https://doi.org/10.3390/biomedicines11010080

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

Rachman, S. (1993). Obsessions, responsibility and guilt. *Behaviour research and therapy*, *31*(2), 149-154. https://doi.org/https://doi.org/10.1016/0005-7967(93)90066-4

Rachman, S., & Shafran, R. (1998). Cognitive and behavioral features of obsessive-compulsive disorder In R. P. Swinson, S. Antony, S. Rachman, & M. Richter (Eds.), *Obsessive-compulsive disorder: Theory, research, and treatment* (pp. 51-78). Guildford Press.

Rapinesi, C., Kotzalidis, G. D., Ferracuti, S., Sani, G., Girardi, P., & Del Casale, A. (2019). Brain stimulation in obsessive-compulsive disorder (OCD): a systematic review. *Current neuropharmacology*, *17*(8), 787-807. https://doi.org/10.2174/1570159X17666190409142555

Rauch, S. L., Shin, L. M., Dougherty, D. D., Alpert, N. M., Fischman, A. J., & Jenike, M. A. (2002). Predictors of fluvoxamine response in contamination-related obsessive compulsive disorder: a PET symptom provocation study. *Neuropsychopharmacology*, *27*(5), 782-791. https://doi.org/10.1016/S0893-133X(02)00351-2

Rees, C. S. (2009). *Obsessive-Compulsive Disorder: A Practical Guide To Treatment*. IP Communications.

Rees, C. S., & Anderson, R. A. (2013). A review of metacognition in psychological models of obsessive–compulsive disorder. *Clinical Psychologist*, *17*(1), 1-8. http://doi.org/10.1111/cp.12001

Rehn, S., Eslick, G. D., & Brakoulias, V. (2018). A meta-analysis of the effectiveness of different cortical targets used in repetitive transcranial

magnetic stimulation (rTMS) for the treatment of obsessive-compulsive disorder (OCD). *Psychiatric Quarterly*, *89*, 645-665. https://doi.org/10.1007/s11126-018-9566-7

Riesel, A. (2019). The erring brain: Error-related negativity as an endophenotype for OCD—A review and meta-analysis. *Psychophysiology*, *56*(4), e13348. https://doi.org/https://doi.org/10.1111/psyp.13348

Röhr, S., Arai, H., Mangialasche, F., Matsumoto, N., Peltonen, M., Raman, R., Riedel-Heller, S. G., Sakurai, T., Snyder, H. M., & Sugimoto, T. (2021). Impact of the COVID-19 pandemic on statistical design and analysis plans for multidomain intervention clinical trials: Experience from World-Wide FINGERS. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *7*(1), e12143. https://doi.org/10.1002/trc2.12143

Rosa-Alcázar, A. I., Sánchez-Meca, J., Gómez-Conesa, A., & Marín-Martínez, F. (2008). Psychological treatment of obsessive–compulsive disorder: A meta-analysis. *Clinical Psychology Review*, *28*(8), 1310-1325. https://doi.org/https://doi.org/10.1016/j.cpr.2008.07.001

Rosa, M. A., & Lisanby, S. H. J. N. (2012). Somatic treatments for mood disorders. *37*(1), 102-116. https://www.nature.com/articles/npp2011225

Ruffini, C., Locatelli, M., Lucca, A., Benedetti, F., Insacco, C., & Smeraldi, E. (2009). Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: A controlled investigation. *Primary care companion to the Journal of clinical psychiatry*, *11*, 226-234. https://doi.org/10.4088/PCC.08m00663

Salkovskis, P. M., & Forrester, E. (2002). Responsibility. In *Cognitive approaches to obsessions and compulsions* (pp. 45-61). Elsevier. https://doi.org/10.1016/B978-008043410-0/50005-2

Salkovskis, P. M., & Warwick, H. M. (1985). Cognitive therapy of obsessive–compulsive disorder: Treating treatment failures. *Behavioural and Cognitive Psychotherapy*, *13*(3), 243-255. https://doi.org/10.1017/S0141347300011095

Sathian, B., Asim, M., Banerjee, I., Pizarro, A. B., Roy, B., Van Teijlingen, E. R., do Nascimento, I. J. B., & Alhamad, H. K. (2020). Impact of COVID-19 on clinical trials and clinical research: a systematic review. *Nepal journal of epidemiology*, *10*(3), 878. https://doi.org/10.3126/nje.v10i3.31622

Sauer, K. S., & Witthöft, M. (2022). Inhibitory Learning versus Habituation in an Experimental Exposure Intervention for People With Heightened Health Anxiety: Increase of Distress Tolerance as a Joint Mechanism of Change? *Journal of Experimental Psychopathology*, *13*(4), 20438087221138716. https://doi.org/10.1177/20438087221138716

Saxena, S., Brody, A. L., Maidment, K. M., Dunkin, J. J., Colgan, M., Alborzian, S., Phelps, M. E., & Baxter Jr, L. R. (1999). Localized orbitofrontal and subcortical metabolic changes and predictors of response to paroxetine treatment in obsessive-compulsive disorder. *Neuropsychopharmacology*, *21*(6), 683-693. https://doi.org/10.1016/S0893-133X(99)00082-2

Schoeller, F. (2023). Negative self-schemas drive pathological doubt in OCD. *Front Psychiatry*, *14*, 1304061. https://doi.org/10.3389/fpsyt.2023.1304061

Shanahan, N. A., Velez, L. P., Masten, V. L., & Dulawa, S. C. (2011). Essential role for orbitofrontal serotonin 1B receptors in obsessive-compulsive disorder-like behavior and serotonin reuptake inhibitor response in mice. *Biological*

psychiatry, *70*(11), 1039-1048. https://doi.org/10.1016/j.biopsych.2011.07.032

Sharma, E., & Math, S. B. (2019). Course and outcome of obsessive–compulsive disorder. *Indian Journal of Psychiatry*, *61*(Suppl 1), S43-S50. https://doi.org/10.4103/psychiatry.IndianJPsychiatry_521_18

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 (MINI): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of Clinical Psychiatry*. https://doi.org/10.1016/s0924-9338(99)80239-9

Sherif, M. A., Fotros, A., Greenberg, B. D., & McLaughlin, N. C. R. (2023). Understanding cingulotomy's therapeutic effect in OCD through computer models [Review]. *Frontiers in integrative neuroscience*, *16*. https://doi.org/10.3389/fnint.2022.889831

Silva, R. d. M. F. d., Brunoni, A. R., Goerigk, S., Batistuzzo, M. C., Costa, D. L. d. C., Diniz, J. B., Padberg, F., D'Urso, G., Miguel, E. C., & Shavitt, R. G. (2021). Efficacy and safety of transcranial direct current stimulation as an add-on treatment for obsessive-compulsive disorder: a randomized, sham-controlled trial. *Neuropsychopharmacology*, *46*(5), 1028-1034. https://doi.org/10.1038/s41386-020-00928-w

Simon, D., Adler, N., Kaufmann, C., & Kathmann, N. (2014). Amygdala hyperactivation during symptom provocation in obsessive-compulsive disorder and its modulation by distraction. *Neuroimage Clin*, *4*, 549-557. https://doi.org/10.1016/j.nicl.2014.03.011

Simpson, H. B., Franklin, M. E., Cheng, J., Foa, E. B., & Liebowitz, M. R. (2005). Standard criteria for relapse are needed in obsessive–compulsive disorder. *Depression and anxiety*, *21*, 1-8. https://doi.org/10.1002/da.20052

Skapinakis, P., Caldwell, D. M., Hollingworth, W., Bryden, P., Fineberg, N. A., Salkovskis, P., Welton, N. J., Baxter, H., Kessler, D., & Churchill, R. (2016). Pharmacological and psychotherapeutic interventions for management of obsessive-compulsive disorder in adults: A systematic review and network meta-analysis. *The Lancet Psychiatry*, *3*(8), 730-739. https://doi.org/10.1016/S2215-0366(16)30069-4

Stein, D. J., Montgomery, S. A., Kasper, S., & Tanghoj, P. (2001). Predictors of response to pharmacotherapy with citalopram in obsessive-compulsive disorder. *International Clinical Psychopharmacology*, *16*(6), 357-361. http://journals.lww.com/intclinpsychopharm

Steketee, G., Frost, R., Bhar, S., Bouvard, M., Calamari, J., Carmin, C., Clark, D. A., Cottraux, J., Emmelkamp, P., & Forrester, E. (2003). Psychometric validation of the Obsessive Beliefs Questionnaire and the Interpretation of Intrusions Inventory: Part I. *Behaviour research and therapy*, *41*, 863-878. https://doi.org/10.1016/S0005-7967(02)00099-2

Stern, R. (1978). Obsessive thoughts: the problem of therapy. *The British Journal of Psychiatry*, *133*(3), 200-205. https://doi.org/10.1192/bjp.133.3.200

Steuber, E. R., & McGuire, J. F. (2022). A systematic review of fear learning, extinction learning, and reversal learning in obsessive-compulsive disorder: implications for treatment. *The Journal of Clinical Psychiatry*, *83*(6), 43190. https://doi.org/10.4088/JCP.21r14432

Stevanovic, D. (2011). Quality of Life Enjoyment and Satisfaction Questionnaire–short form for quality of life assessments in clinical practice: A psychometric study. *Journal of Psychiatric and Mental Health Nursing*, *18*, 744-750. https://doi.org/10.1111/j.1365-2850.2011.01735.x

Storen, R., & Corrigan, N. (2020). *COVID-19: A chronology of state and territory government announcements (up until 30 June 2020)*

Parliament of Australia Retrieved from https://parlinfo.aph.gov.au/parlInfo/download/library/prspub/7614514/upload_binary/7614514.pdf

Swedo, S. E., Pietrini, P., Leonard, H. L., Schapiro, M. B., Rettew, D. C., Goldberger, E. L., Rapoport, S. I., Rapoport, J. L., & Grady, C. L. (1992). Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder: revisualization during pharmacotherapy. *Archives of general psychiatry*, *49*(9), 690-694. https://doi.org/10.1001/archpsyc.1992.01820090018003

Szechtman, H., Harvey, B. H., Woody, E. Z., & Hoffman, K. L. (2020). The psychopharmacology of obsessive-compulsive disorder: a preclinical roadmap. *Pharmacological reviews*, *72*(1), 80-151. https://doi.org/10.1124/pr.119.017772

Szechtman, H., & Woody, E. (2004). Obsessive-compulsive disorder as a disturbance of security motivation. *Psychological review*, *111*(1), 111. https://doi.org/10.1037/0033-295X.111.1.111

Thorsen, A. L., van den Heuvel, O. A., Hansen, B., & Kvale, G. (2015). Neuroimaging of psychotherapy for obsessive–compulsive disorder: A

systematic review. *Psychiatry Research: Neuroimaging*, *233*(3), 306-313. https://doi.org/https://doi.org/10.1016/j.pscychresns.2015.05.004

Todder, D., Gershi, A., Perry, Z., Kaplan, Z., Levine, J., & Avirame, K. (2018). Immediate effects of transcranial direct current stimulation on obsession-induced anxiety in refractory obsessive-compulsive disorder: a pilot study. *The journal of ECT*, *34*(4), e51-e57. https://doi.org/10.1097/YCT.0000000000000473

Tolin, D. F., Abramowitz, J. S., Brigidi, B. D., & Foa, E. B. (2003). Intolerance of uncertainty in obsessive-compulsive disorder. *J Anxiety Disord*, *17*(2), 233-242. https://doi.org/10.1016/s0887-6185(02)00182-2

Van Ameringen, M., Simpson, W., Patterson, B., Dell'Osso, B., Fineberg, N., Hollander, E., Hranov, L., Hranov, G., Lochner, C., & Karamustafalioglu, O. (2014). Pharmacological treatment strategies in obsessive compulsive disorder: A cross-sectional view in nine international OCD centers. *Journal of Psychopharmacology*, *28*(6), 596-602. https://doi.org/10.1177/0269881113517955

van Westen, M., Rietveld, E., Figee, M., & Denys, D. (2015). Clinical outcome and mechanisms of deep brain stimulation for obsessive-compulsive disorder. *Current behavioral neuroscience reports*, *2*, 41-48. https://doi.org/10.1007/s40473-015-0036-3

Veale, D., Freeston, M., Krebs, G., Heyman, I., & Salkovskis, P. (2009). Risk assessment and management in obsessive–compulsive disorder. *Advances in Psychiatric Treatment*, *15*(5), 332-343. https://doi.org/10.1192/apt.bp.107.004705

Veale, J. F. (2014). Edinburgh Handedness Inventory–Short Form: a revised version based on confirmatory factor analysis. *Laterality: Asymmetries of Body, Brain and Cognition, 19*(2), 164-177. https://doi.org/10.1080/1357650X.2013.783045

Verbruggen, F., Aron, A. R., Band, G. P., Beste, C., Bissett, P. G., Brockett, A. T., Brown, J. W., Chamberlain, S. R., Chambers, C. D., & Colonius, H. (2019). A consensus guide to capturing the ability to inhibit actions and impulsive behaviors in the stop-signal task. *eLife, 8*, e46323. https://doi.org/10.7554/eLife.46323

Villena-Jimena, A., Gómez-Ocaña, C., Amor-Mercado, G., Núñez-Vega, A., Morales-Asencio, J. M., & Hurtado, M. M. (2018). To what extent do clinical practice guidelines respond to the needs and preferences of patients diagnosed with obsessive–compulsive disorder? *Revista Colombiana de Psiquiatría (English ed.), 47*(2), 98-107. https://doi.org/10.1016/j.rcpeng.2018.03.005

Wells, A. (1995). Meta-cognition and worry: A cognitive model of generalized anxiety disorder. *Behavioural and Cognitive Psychotherapy, 23*, 301-320. https://doi.org/10.1017/S1352465800015897

Williams, M., Chapman, L., Simms, J., & Tellawi, G. (2017). Cross-cultural phenomenology of obsessive-compulsive disorder. In J. Abramowitz, D. McKay, & E. Storch (Eds.), *The Wiley handbook of obsessive compulsive disorder across the lifespan.* (pp. 56-74). Wiley.

Wisniewski, S. R., Fava, M., Trivedi, M. H., Thase, M. E., Warden, D., Niederehe, G., Friedman, E. S., Biggs, M. M., Sackeim, H. A., & Shores-Wilson, K. J. A. J. o. P. (2007). Acceptability of second-step treatments to depressed

outpatients: a STAR* D report. *164*(5), 753-760. https://doi.org/https://ajp.psychiatryonline.org/doi/full/10.1176/ajp.2007.164.5.753

Wolpe, J. (1990). *The practice of behavior therapy*. Pergamon press.

Woody, E. Z., & Szechtman, H. (2013). A biological security motivation system for potential threats: are there implications for policy-making? *Front Hum Neurosci*, *7*, 556. https://doi.org/10.3389/fnhum.2013.00556

World Health Organisation. (1992). *International Statistical Classification of Diseases and Related Health Problems (ICD-10th ed.)*.

World Health Organisation. (2019). 6B20 Obsessive-compulsive disorder. In *International Statistical Classification of Diseases and Related Health Problems* (11th ed.). https://doi.org/https://icd.who.int/

World Health Organisation. (2021). *International Statistical Classification of Diseases and Related Health Problems (ICD-11th ed., text rev.)*. (11th ed.) https://icd.who.int/

World Health Organization. (2020). Naming the coronavirus disease (COVID-19) and the virus that causes it. *Brazilian Journal of Implantology and Health Sciences, 2*(3). https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it

Yekta, M., Rostami, R., & Fayyaz, E. (2015). Transcranial direct current stimulation of dorsolateral prefrontal cortex in patients with obsessive compulsive disorder to improve decision making and reduce obsession symptoms. *Practice in Clinical Psychology*, *3*(3), 185-194. https://sid.ir/en/VEWSSID/J_pdf/50004120150305.pdf

Yoosefee, S., Amanat, M., Salehi, M., Mousavi, S. V., Behzadmanesh, J., Safary, V., Yoonesi, A., & Salehi, B. (2020). The safety and efficacy of transcranial direct current stimulation as add-on therapy to fluoxetine in obsessive-compulsive disorder: a randomized, double-blind, sham-controlled, clinical trial. *BMC Psychiatry*, *20*(1), 1-9. https://doi.org/10.1186/s12888-020-02979-1

Zajonc, R. B. (1968). Attitudinal effects of mere exposure. *Journal of Personality and social Psychology*, *9*(2p2), 1. https://doi.org/10.1037%2Fh0025848