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Effects of Transcranial Direct Current Stimulation on Resting State Functional Connectivity in Obsessive Compulsive Disorder

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In loving memory of Andreas Schönberg,
may your mind be free.

Abstract

Obsessive-compulsive disorder (OCD) is a debilitating psychiatric condition characterized by intrusive thoughts and repetitive behaviors that impair daily functioning. Alterations in resting state functional connectivity (rsFC) have frequently been reported in patients with OCD and have been implied in clinical symptoms underlying the disorder. Transcranial direct current stimulation (tDCS) as a neuromodulator has emerged as a potential treatment for an array of psychiatric disorders including OCD, potentially via its moderating effect on rsFC.

The aim of this study was to investigate the effects of concomitant tDCS on rsFC fMRI over the pre-SMA in patients with OCD. We hypothesize that active tDCS in comparison to sham tDCS, will lead to changes in rsFC in patients with OCD.

In this double blind, sham-controlled, randomized cross-over study, forty-nine patients with OCD received both sham and real tDCS (one week apart). The tDCS anode was placed over the right pre-supplementary motor area (pre-SMA) and 20-minutes of 2mA active tDCS or sham control was applied to the patient whilst undergoing simultaneous functional MRI. Resting-state fMRI scans were acquired immediately following the tDCS. Changes in rsFC were assessed using seed-to-voxel connectivity analysis using four pivotal regions associated with inhibitory control as ROIs: the pre-SMA, supplementary motor area (SMA), primary motor cortex (M1), and inferior frontal gyrus (IFG), all on the right hemisphere.

The results showed that tDCS compared to sham revealed a significant decrease in rsFC, employing stringent control settings (voxel threshold $p< 0.001$ uncorrected and cluster threshold $p < 0.05$, cluster size p-FDR corrected) in one-sided tests. The main findings revealed: 1) hypoconnectivity between the right SMA and right occipital pole; 2) hypoconnectivity between the right M1 and right occipital pole and cortex as well as to the left temporal pole; 3) hypoconnectivity between the right IFG and postcentral gyrus, precuneus cortex, lingual gyrus, and occipital fusiform gyrus.

These findings suggest that tDCS over the pre-SMA can modulate rsFC in patients with OCD, specifically by decreasing connectivity between central nodes of inhibitory control and the motor network, somatosensory areas and visual network. These connectivity decreases might be one of the mechanisms underlying the therapeutic effects of repeated tDCS stimulation in patients with OCD. Further studies are needed to investigate the influence of tDCS stimulation characteristics

(such as, e.g., electrode placement, number of stimulation sessions) on rsFC and its therapeutic efficiency.

Zusammenfassung

Die Zwangsstörung (OCD) ist ein beeinträchtigender psychiatrischer Zustand, der durch aufdrängende Gedanken und sich wiederholende Verhaltensweisen gekennzeichnet ist, welche die tägliche Funktionsfähigkeit beeinträchtigen. Veränderungen in der Ruhezustands-funktionellen Konnektivität (rsFC) wurden häufig bei Patienten mit OCD berichtet und werden in klinischen Symptomen, die der Störung zugrunde liegen, vermutet. Die transkranielle Gleichstromstimulation (tDCS) als Neuromodulator hat sich als potenzielle Behandlungsmethode für verschiedene psychiatrische Störungen, einschließlich OCD, herausgebildet, möglicherweise durch ihre moderierende Wirkung auf die rsFC.

Das Ziel dieser Studie war es, die Auswirkungen der gleichzeitigen Anwendung von tDCS auf die rsFC-fMRT über dem prä-supplementär-motorischen Areal (prä-SMA) bei Patienten mit OCD zu untersuchen. Unsere Hypothese lautet, dass aktive tDCS im Vergleich zu Schein-tDCS zu Veränderungen in der rsFC bei Patienten mit OCD führen wird.

In dieser doppelblinden, scheinkontrollierten, randomisierten Cross-over-Studie erhielten neunundvierzig Patienten mit OCD sowohl Schein- als auch echte tDCS (eine Woche auseinander). Die tDCS-Anode wurde über dem rechten prä-supplementären motorischen Bereich (pre-SMA) platziert, und während gleichzeitiger funktioneller MRT wurde 20 Minuten lang 2 mA aktive tDCS oder Schein-Kontrolle auf den Patienten angewendet. Ruhezustand-fMRT-Scans wurden unmittelbar nach der tDCS aufgenommen. Veränderungen in der rsFC wurden unter Verwendung der Seed-to-Voxel-Konnektivitätsanalyse mit vier entscheidenden Regionen, die mit inhibitorischer Kontrolle in Verbindung stehen, als ROIs bewertet: prä-SMA, supplementärer motorischer Bereich (SMA), primärer motorischer Cortex (M1) und inferiorer frontaler Gyrus (IFG), alle auf der rechten Hemisphäre.

Die Ergebnisse zeigten, dass tDCS im Vergleich zu Schein tDCS, eine signifikante Abnahme der rsFC aufwies, unter Verwendung strenger Fehlerkontrolle (Voxel-Schwelle $p < 0{,}001$ unkorrigiert und Cluster-Schwelle $p < 0{,}05$, Cluster-Größe p-FDR-korrigiert) in einseitigen Tests. Die Hauptergebnisse waren: 1) Hypokonnektivität zwischen dem rechten SMA und dem rechten Okzipitalpol; 2) Hypokonnektivität zwischen dem rechten M1 und dem rechten Okzipitalpol und Kortex sowie dem linken Temporalpol; 3) Hypokonnektivität zwischen dem rechten IFG und

dem postzentralen Gyrus, dem Precuneus-Kortex, dem lingualen Gyrus und dem Okzipital-Fusiform-Gyrus.

Diese Ergebnisse legen nahe, dass tDCS über dem prä-SMA die rsFC bei Patienten mit OCD modulieren kann, insbesondere durch die Verringerung der Konnektivität zwischen zentralen Areale der inhibitorischen Kontrolle und dem motorischen Netzwerk, den somatosensorischen Bereichen und dem visuellen Netzwerk. Diese Konnektivitätsabnahmen könnten eines der Mechanismen sein, die den therapeutischen Effekten wiederholter tDCS-Stimulation bei Patienten mit OCD zugrunde liegen. Weitere Studien sind erforderlich, um den Einfluss von tDCS-Stimulationsmerkmalen (wie z.B. Elektrodenplatzierung, Anzahl der Stimulations-Sitzungen) auf die rsFC und ihre therapeutische Effizienz zu untersuchen.

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Abbreviations

ADHD – Attention deficit/hyperactivity disorder

APA – American Psychiatric Association

BOLD – Bold oxygen level dependent

CBT – Cognitive behavioral therapy

CN – Cerebellar network

CSTC – Cortico-striato-thalamo-cortical

DLPFC – Dorso-lateral prefrontal cortex

DMN – Default mode network

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders 5th Revision

DTI – Diffusion tensor imaging

ECN – Executive control network

fMRI – Functional magnetic resonance imaging

HAM-D – Hamilton depression rating scale

HMAT – Human motor area template

IBN – Intrinsic brain network

IFG – Inferior frontal Gyrus

FPN – Frontoparietal network

ICD-11 – International Classification of Disease and Related Health Problems 11th Revision

LTD – Long-term depression

LTP – Long-term potentiation

LMU – Ludwig-Maximillian University Munich

M1 – Primary motor cortex

MNI – Montreal Neurological Institute

MPRAGE – Magnetisation prepared rapid acquisition by gradient echo

MRI – Magnetic resonance imaging

NIBS – Non-invasive brain stimulation

NMDA – Methyl-D-aspartate

OCD – Obsessive compulsive disorder

OFC – Orbitofrontal cortex

pre-SMA – Pre-supplementary motor area

PTSD – Post traumatic stress disorder

ROI – Region of interest

rsFC – Resting state functional connectivity

rs-fMRI – Resting state functional magnetic resonance imaging

SN – Salience network

SMA – Supplementary motor area

SMN – Somatomotor network

SSRI – Selective serotonin reuptake inhibitors

tDCS – Transcranial direct current stimulation

TE – Echo time

TMS – Transcranial magnetic stimulation

TR – Repetition time

TUM – Technical University Munich

Y-BOCS – Yale Brown Obsessive Compulsive Scale

1. INTRODUCTION

1.1 Obsessive Compulsive Disorder

Obsessive compulsive disorder (OCD) is a debilitating psychiatric condition that has a rich history and has preoccupied clinicians for centuries. Historical accounts depicting clinical characteristics of obsessions and compulsions date back to the 15th century when it was entwined with the notions of witchcraft, as seen in the "Malleus Maleficarum" or Shakespeare's Macbeth in the 17th century (Fornaro et al., 2009). French psychiatrist J. Esquirol first described OCD in the early 19th century, and the German psychiatrist and neurologist Karl Westphal further established it as a separate mental disorder with his publication "Zwangsvorstellungen" in 1877 (Oberbeck et al., 2013). Today, OCD is one of the most common psychiatric disorders (Stein et al., 2020) and is defined by the International Classification of Diseases, 11th Edition (ICD-11) by the World Health Organisation, and the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), by the American Psychiatric Association (APA).

1.1.2 Definition and Diagnostic Criteria

OCD is a complex condition characterized by distinct features outlined in the "Obsessive-Compulsive and Related Disorders" by the ICD-11 and DSM-5. The ICD-11 describes obsessions as "repetitive and persistent thoughts (e.g., contamination), or impulses/urges (e.g., washing) that are experienced as intrusive or unwanted and are commonly associated with anxiety" (World Health Organisation, 2021). In order to minimize or suppress such obsessions, they are commonly followed by compulsions, defined as "repetitive behaviors or rituals" (e.g., washing, counting), "including mental acts" (e.g., praying) that an individual feels driven to carry out in order to relieve themselves of inner tension. Obsessions and compulsions typically present themselves together and seldom occur as an obsession or compulsion alone (Shavitt et al., 2014). To fulfill the diagnostic criteria, obsessions and compulsions must be time-consuming (taking more than one hour per day), significantly interfere with daily life, and may not be attributable to substances or other medical conditions (American Psychiatric Association, 2022).

Furthermore, both classification systems outline specifiers as well as additional subtypes of OCD. The ICD-11 and DSM-5 use specifiers to refer to the degree to which patients have insights into their beliefs. The DSM-5 differentiates whether a patient has good or fair insight, poor insight,

absent insight, or delusions beliefs. Individuals who lack insight and firmly believe in the validity of their OCD beliefs must be accurately diagnosed and differentiated from individuals suffering from a psychotic disorder.

While the typical content of obsessions and compulsions vary among individuals, there are central themes that present themselves globally in OCD. These include symptoms of contamination obsessions and compulsive cleaning; symmetry obsessions and repetitive ordering and counting; forbidden or taboo thoughts such as sexual, aggressive, and religious obsessions; fear of harming oneself or others; and checking related compulsions (Stein et al., 2019). Figure 1. shows a schematic representation of the five most common symptom dimensions.

Symptom Dimension	Obsessions	Compulsions
Contamination	Concerns about germs, dirt, fear of illness	Washing, showering and cleaning
Symmetry	Concerns about symmetry and oder	Ordering, counting, arranging, straightening
Unacceptable thoughts	Intrusive sexual, religious or agressive thoughts	Mental rituals, confessing, praying
Hoarding	Hoarding and need to save	Hoarding behaviours
Harm-related	Concerns about harming others or oneself	Checking

Figure 1. OCD symptom dimensions.
Modified from Stein et al., (2019).

1.1.3 Comorbidities and Differential Diagnosis

Distinguishing OCD from developmentally normative preoccupations, such as demonstrated in children, personality traits, or other cultural or individual variations, is essential (ICD-11). Obsessions and compulsions must induce notable distress and functional impairment to be accurately diagnosed as a clinical disorder. In turn, OCD often leads to a range of comorbidities that impact occupational, academic, and interpersonal functioning as well as overall well-being (Koran et al., 1996). The most common comorbidities affecting OCD patients were anxiety disorders (76%), mood disorders (63%), impulse-control disorders (56%), and substance use disorders (39%). Additionally, tic disorders are highly prevalent, particularly in males with early-

onset OCD (Ruscio et al., 2010). Given the overlapping symptomology among these disorders, comprehensive clinical assessments, such as the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), are critical for distinguishing OCD from related conditions and ensuring appropriate treatment (Goodman et al., 1989). According to Zwanzger & Schneider (2017), critical differential diagnoses include the following.

- Anankastic Personality Disorder (ICD-11)
- Depressive Disorders
- Psychotic Disorders
- Gilles-de-la-Tourette-Syndrome
- Other obsessive compulsions and related disorders, e.g. Trichotillomania

1.1.4 Epidemiology

It is estimated that the lifetime prevalence of OCD is 2-3% and typically manifests around the age of 20 years (Ruscio et al., 2010). While females are slightly more prone to developing OCD, males are affected at an earlier age, with nearly 25% affected before the age of 10 (Ruscio et al., 2010). On average, individuals with OCD were reported to suffer from the disorder for a mean of nine years, according to the NCS-R data by Ruscio et al. (2017). In addition, their data presented that the average time a day occupied by obsessions was 6 hours and 5 hours engaging in compulsions (Ruscio et al. 2017). As a result, OCD has far-reaching public health consequences that impact various aspects of patients' lives, including relationships, social functioning, and overall quality of life.

1.1.5 Etiology & Neurobiology of OCD

Genetics

The etiology and neurobiology of OCD are not fully understood; however, biological and psychosocial factors appear to contribute to multifactorial psychopathology. Consistent evidence alludes to OCD having a strong familial and genetic component, supported by family and twin studies (Pauls, 2010). A recent meta-analysis showed that the phenotypic heritability of OCD was approximately 50%, and the likelihood of OCD was 7.2 times greater in families with a history of

OCD than in control families (Blanco-Vieira et al., 2023). Moreover, twin studies have shown that monozygotic twin correlations are approximately 0.52 to 0.43 compared to 0.27 and 0.20 in dizygotic twins, suggesting that the development of OCD has both a genetic and environmental component (Blanco-Vieira et al., 2023; Taylor, 2011; van Grootheest et al., 2005). Environmental factors, such as adverse childhood events, drug use, and stressful life events, contribute to an increase in risk factors (Fontenelle et al., 2008).

Neurobiology

The utilization of modern neuroimaging has helped identify anatomical and functional neurobiological underpinnings that support the phenomenology of OCD. Disease models that have been implicated in the etiology of OCD include cortico-striatal-thalamo-cortical circuits (CSTC), neurotransmitter hypothesis, and cognitive dysfunction (Chamberlin et al., 2005; Jalal et al., 2022).

Over the last decade, the primary focus in understanding the neuropathology of OCD has centered on the imbalance within the CSTC circuits of the brain (Chamberlain et al., 2005; Milad & Rauch, 2012). This imbalance is believed to be a potential underlying factor contributing to the cognitive deficits frequently observed in individuals with OCD (Fineberg et al., 2018). The CSTC circuit originates in the frontal-cortical regions and extends to the striatum, which projects to the thalamus and ultimately back to the cortex (Jalal et al., 2023). The pathways within these circuits comprise a direct and an indirect pathway that exerts opposing effects on the thalamus, leading to increased cortical excitation through the direct pathway or decreased cortical excitation through the indirect pathway. A review by Jalal et al. (2023) outlined that the direct and indirect pathways of the CSTC circuit are dysfunctional in patients with OCD, leading to an overactive direct loop with heightened excitatory effects on the thalamus. This results in a weakening of thalamic inhibition and a reduced filter function of the basal ganglia in relation to cortical information. Subsequently giving rise to repetitive and stereotypical maladaptive patterns of behaviors and thoughts that occur through these positive feedback loops (Jalal et al., 2023). Although the results have been slightly inconsistent, structural abnormalities within the CSTS circuits have shown reduced volumes in the orbitofrontal cortex (OFC) (Atmaca et al., 2007) and striatum (Menzies et al., 2008). Additionally, findings from a meta-analysis by Gürsel et al. (2018) using resting-state fMRI in OCD showed evidence of abnormal interaction between the prefrontal-parietal-limbic networks and CSTC loops in OCD.

Furthermore, the key neurotransmitters of the CSTC circuit, serotonin, dopamine, and glutamate, have received significant attention for their role in the etiology due to their pronounced responsiveness to specific pharmacotherapies in managing OCD symptoms (Jalal et al., 2022).

Cognitive Dysfunction

Moreover, the cognitive deficits observed in individuals with OCD include impairments in cognitive flexibility, working memory, planning, and response inhibition (Stein et al., 2020). Response inhibition refers to the capacity for executive control over specific motor or cognitive processes and is likely to be compromised in patients with OCD (Chamberlain et al., 2005; Rosenberg et al., 1997). The inability of patients to stop such distressing intrusive thoughts or repetitive motoric behaviors is highly suggestive of an inhibitory failure (Chamberlain et al., 2005). Although the findings have been inconsistent, this has been demonstrated by task paradigms, such as stop-signal tasks, in patients with OCD (Mar et al., 2022). More specifically, response inhibition has shown to occur in a network of brain regions involving the pre-SMA, the motor cortex including the precentral gyrus and the right inferior frontal gyrus (IFG) (Sharp et al., 2010). In line with these findings, several studies have reported that in healthy subjects, neuromodulation of the pre-SMA has improved response inhibition in task paradigms (Hsu et al., 2011). However, to the best of our knowledge, no comparible studies have been carried out in individuals with OCD.

1.1.6 Current Treatment Approaches

Current evidence supports the use of cognitive behavioral therapy (CBT) as a first-line treatment, often in combination with selective serotonin reuptake inhibitors (SSRIs). CBT commonly focuses on the use of exposure and response prevention, developed by Meyer (1966), in which patients are exposed to triggering situations and encouraged to not respond with compulsive rituals after confrontation. Findings from a meta-analysis conducted by Skapinakis et al. (2016) are consistent with previous guidelines that recommend SSRIs as a treatment for OCD. They demonstrated that citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline were equally effective and showed no superiority over others. In addition, all resulted in a reduction in Y-BOCS scores by 3.49, showing significant efficacy compared to placebo. The tricyclic antidepressant clomipramine is also approved for treatment; however, it has a higher side effect profile than SSRIs

(Skapinakis et al., 2016). Furthermore, a multidimensional therapeutic approach, including psychoeducation, relaxation techniques, and physical activity, is crucial for symptom improvement.

While many patients experience a significant improvement in overall well-being through targeted psychological support and pharmacotherapy, studies have shown that approximately 40-60% of patients with OCD do not adequately respond to conventional treatment (Pallanti & Quercioli, 2006; Skapinakis et al., 2016), relapse, or may be resistant to traditional approaches (Denys et al., 2010). In rare cases, alternative treatment approaches may be considered in complicated cases or therapy-refractory OCD. These include invasive neurosurgical techniques and deep brain stimulation of targeted areas of the striatum (Denys et al., 2010; Luyten et al., 2016). More recently, non-invasive neuromodulation techniques, including transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), have been gaining attention as techniques offering promising perspectives for safe and effective adjuvant treatment modalities for psychiatric disorders, including OCD. Failure to respond to treatment is associated with significant social disability and reduced quality of life. Thus, new emerging techniques deserve close attention to further the spectrum of treatment options.

1.2 Transcranial Direct Current Stimulation

1.2.1 TDCS Mechanisms of Action

Non-invasive brain stimulation (NIBS) techniques, such as TMS and tDCS, have been the focus of many neurocognitive and neuroimaging studies over the last decade. Both TMS and tDCS have shown to consistently modulate localized brain activity and promote neuroplasticity by temporarily inducing changes in neuronal excitability (Nitsche & Paulus, 2000, 2001, 2011; Nitsche et al., 2008). They are well-tolerated, safe, and cost-effective methods that have been shown to improve cognitive functioning and offer great potential for therapeutic applications in various neurological and psychiatric conditions (Kuo & Nitsche, 2012; Lefaucher et al., 2014, 2020). TMS applies magnetic pulses to specific brain regions, generating an electrical field capable of depolarizing superficial axons and initiating activation of cortical neural networks (Lefaucher et al., 2014). In contrast, tDCS uses a mild direct electrical current (1-2 mA) via two electrodes, causing the underlying cortical tissue to become polarized, thereby causing a shift in the underlying resting membrane potential (Stagg et al., 2018). Neurophysiological investigations have shown that anodal

stimulation typically increases neuronal excitability, whereas cathodal stimulation decreases it, causing either mild depolarization or hyperpolarization (Arul-Anandam & Loo, 2009). When stimulation is applied for a short duration, in the range of 10-20 minutes, after-effects have been shown to last approximately 1.5 hours (Nitsche & Paulus, 2001; Nitsche et al., 2003). Conversely, repetitive stimulation, such as daily sessions, has shown to induce synaptic changes by altering the strength of the synaptic transmission. This repetitive stimulation leads to similar neuroplastic effects, such as long-term potentiation (LTP) and long-term depression (LTD), which are associated with the N-methyl-D-aspartate (NMDA) receptors of glutamatergic synapses and calcium channels, as well as protein synthesis (Nitsche et al., 2003). Furthermore, a study conducted by Zheng et al. (2011) showed that anodal stimulation led to a substantial increase in regional cerebral blood flow during and after stimulation. In contrast, cathodal stimulation resulted in a more modest increase in blood flow during and after the stimulation session.

1.2.2 Applications in Neuropsychiatric Disorders

Beyond its neurophysiological effects, tDCS also has the capacity to influence cognitive functions, including working memory and learning processes (Kuo & Nitsche, 2012; Shin et al., 2015). This opens up opportunities to address cognitive issues related to psychiatric disorders and offers alternative or supplementary therapeutic options. TDCS has been shown to have potential in the treatment of strokes (Hummel & Cohen, 2006), Alzheimer's disease (Ferrucci et al., 2008), chronic pain (Fregni et al., 2007), and has been successful in improving symptoms in neuropsychiatric illnesses, including major depressive disorder (Moffa et al., 2020), bipolar depression (Sampaio-Junior et al., 2018), and schizophrenia (Brunelin et al., 2012). More recently, there has been promising evidence suggesting that tDCS could be effective in the treatment of OCD (Brunelin et al., 2018).

1.2.3 Effects of tDCS on OCD

The presence of abnormal activity and connectivity within CSTC circuits, as observed in individuals with OCD, provides a solid rationale for the application of tDCS neuromodulation to target these neural networks (Shivakumar et al., 2019). Neurophysiological and neuroimaging investigations have implicated both hyper- and hypo-activities within the (pre-) supplementary motor area (SMA), anterior cingulate cortex, orbitofrontal-striatal circuits, and basal ganglia in the

pathophysiology of OCD (Brunlein et al., 2018; Hou et al., 2012; Menzies et al., 2008). Thus, given the dominant etiological model and neurocircuitry underlying OCD, it has been hypothesized that targeting these areas of the brain via activation (anodal) or inhibition (cathodal) tDCS stimulation may lead to a reduction in obsessive-compulsive symptoms (Fregni et al., 2021). Thus far, few tDCS studies have focused on targeting the DLPFC, while most have focused on stimulating the SMA/pre-SMA and OFC.

1.2.4 Rational for Stimulating the pre-SMA

The pre-SMA is located in the dorsomedial frontal cortex and is an integral component of a critical network of brain regions that play a fundamental role in response inhibition. Response inhibition involves the ability to suppress thoughts and actions essential for daily functioning (Nachev et al., 2008) and is often measured using behavioral task paradigms such as the stroop or stop-signal task (SST), to measure certain facets of impulsivity and compulsivity (van Velzen et al., 2014). Deficits in inhibitory control have significant implications for well-being and are associated with various psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), Trichotillomania, and OCD. Neuroimaging studies have contributed to our understanding of the pre-SMA's role in response inhibition and its relevance in OCD. However, beyond understanding the neural basis of this process, there is growing interest in the practical applications of this knowledge. Notably, the pre-SMA is increasingly being recognized as a promising target for tDCS stimulation, offering potential relief from OCD symptoms.

To the best of our knowledge, no studies to date have investigated the effects of tDCS over the pre-SMA on inhibitory control in patients with OCD (and is the subject of current investigation in our department, as a continuation of this study). However, there is compelling evidence supporting the potential of NIBS, including tDCS over the pre-SMA, to enhance inhibtion prerfomance in healthy individuals. Hsu etl. (2011) demonstrated that anodal tDCS over the pre-SMA improved response inhibition in SST. Moreover, Yu et al. (2015), employed a combination of tDCS and fMRI, and found that anodal tDCS over the pre-SMA improved stopping speed in the SST, and correlated with an increase in BOLD response in the ventromedial prefrontal cortex. Given these findings, we propose that by applying tDCS over the pre-SMA in individuals with OCD, we may effectively target key neuronal areas associated with inhibitroy control, a primary neurocognitive dysfunction underlying the symptoms of the disorder.

To date, several studies have investigated the effects of tDCS on symptom improvment in OCD. Despite the heterogeneity in tDCS protocols, the effects of tDCS over the pre-SMA have shown promise. D'Urso et al. (2016) were among the first to conduct a randomized controlled partial crossover design study, demonstrating that cathodal tDCS over the pre-SMA significantly improved OCD symptoms. An open-label study by Harika-Germaneua et al. (2020) further supported this finding, showing that combined cathodal stimulation over the bilateral supplementary motor area (SMA) and anodal tDCS over the right supraorbital area led to a significant decrease in YBOCS scores in treatment-resistant OCD patients, up to 3 months of follow-up. In a recent randomized controlled trial, Silva et al. (2021) confirmed the efficacy of tDCS, showing that cathodal tDCS of the SMA and anodal tDCS on the left deltoid led to a significant decrease in OCD symptoms in comparison with sham when assessed using Y-BOCS scores. However, tDCS did not significantly affect comorbid symptoms of depression or anxiety. In contrast to the previous electrode montages, Gowda et al. (2019) investigated the efficacy of add-on anodal tDCS to the pre-SMA and cathodal right supra-orbital area in patients with SSRI-resistant OCD. Their results showed that active tDCS significantly decreased symptoms in contrast to the sham group. Furthermore, a large case series by Thamby et al. (2021) reinforced the growing body of evidence supporting the potential of tDCS applied to the pre-SMA in the treatment of OCD.

In summary, the potential of pre-SMA modulation through tDCS in the context of OCD raises important questions regarding the underlying mechanisms of action, warranting further investigation. Building upon this foundation, studies on functional connectivity and resting-state functional magnetic resonance imaging (rs-fMRI) studies may shed light on how tDCS exerts its potential effects on individuals with OCD.

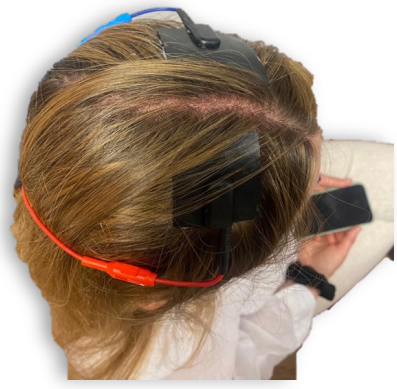


Figure 2. TDCS electrode montage positioning.
Anode over right pre-SMA.

1.3 Functional Connectivity of OCD

1.3.1 Resting-State fMRI

The human brain can be observed as an intricate network in which various cortical regions are engaged in constant communication with each other. Rs-fMRI is a method used to evaluate the brain's intrinsic activity that occurs when a subject is at rest and in the absence of any specific stimuli (Biswal et al., 1995). When a patient undergoes a rs-fMRI, they are instructed to close their eyes, not focus on any thoughts, and to stay awake. The following brain activity is analyzed by measuring spontaneous low-frequency (< 0.1 HZ) fluctuations in blood-oxygen-level dependent (BOLD) (Fox & Raichle, 2007). Through visualizing changes in BOLD signal at rest, using fMRI, we can better understand how spatially distant brain regions interact and contribute to cognitive processes (Poldrack et al., 2011).

Furthermore, functional connectivity, as first described by Biswal et al. (1995), is a measurement that describes temporal correlations between spatially distinct brain regions over time (Biswal et al., 1995). Using functinal connectivity fMRI, many investigations have recognized large-scale intrinsic brain networks (IBN) that are highly correlated not only during task activation but also during rest. One of the most well-researched IBNs is the default-mode network (DMN), which is highly active during a wakeful resting state and is involved in daydreaming, emotional thinking and self-referential thought (Stern et al., 2012). In addition to the DMN, other resting-state networks have been identified, including the salience network (SN), auditory network, executive control network (ECN), frontoparietal network (FPN), cerebellar network (CN), and somatomotor network (SMN). Recent investigations have shown that disruptions in rsFC within these IBNs may be linked to altered network functioning in various disease states. This suggests that rsFC f MRI, as a marker of brain function, may offer valuable insight into abnormalities in neural circuits contributing to psychiatric disorders (Stern et al., 2012).

1.3.2 Resting-State fMRI in OCD

RsFC fMRI has been used to elucidate the involvement of dysregulation within the CSTC network in the neural underpinnings of OCD (Liu et al., 2022). Emerging evidence suggests that broader cortical dysfunction within several other neuronal circuits is likely to be related to cognitive deficits

and compulsive symptoms in OCD (Stern et al., 2012). Recent reviews have highlighted that abnormalities in the fronto-limbic, sensorimotor, dorsal cognitive, ventral affective, and ventral cognitive circuits play a role in the clinical aspects of OCD (Shepard et al., 2021; Stein et al., 2019). The observed changes in rsFC within these networks are assumed to be closely linked to the clinical symptoms present in OCD. Abnormal activation characterized by both hypoactivity and hyperactivity has been reported in the prefrontal cortex, cingulate gyrus, and pre-SMA (Pinto et al., 2022). More specifically, the role of response inhibition and "cognitive flexibility," which has been linked to networks incldluing the pre-SMA, motor cortex, and IFG has been proposed as a critical target for the underlying mechanisms of OCD characteristics and has served as a target for neuromodulation techniques using tDCS as shown in a recent metanalysis by Pinto et al. (2022). Although studies have shown significant improvement in symptoms following tDCS in patients with OCD, the findings have been very heterogeneous, which may be attributed to the use of different seeds or ROIs, small sample sizes, and electrode montage. Thus, further investigations are needed to further understand the mechanisms by which tDCS unfolds its treatment effects in patients with OCD.

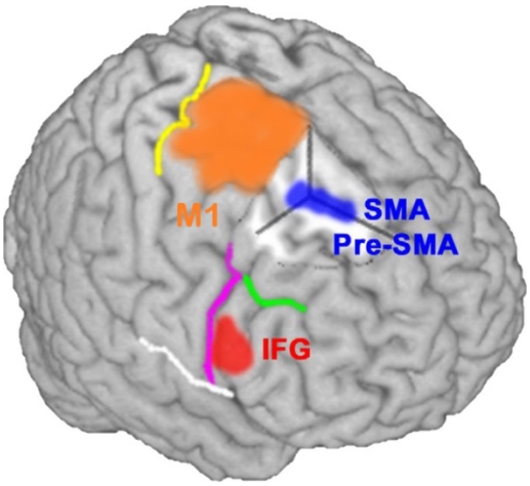


Figure 3. Cortical substrates involved in response inhibition.

This schematic representation shows key areas implicated in response inhibition namley, pre-supplementary motor area (pre-SMA), somatomotor area (SMA) and the right inferior frontal gyrus (IFG). The primary motor area (M1) is also highlighted as a key area involved it motor response. The right sided pre-SMA, SMA, M1 and IFG as indicated in the image, have been carefully selected as our regions of interest (ROI) and used as seed in our resting state functional connectivity (rsFC) analysis.
Figure modified from Chambers et al. (2009). p.663

2. Aim of Thesis

RsFC-fMRI has been an effective tool for elucidating the underlying mechanisms by which altered connectivity may contribute to the pathophysiology of OCD. Non-invasive neuromodulation techniques, such as tDCS, have exhibited promising results in symptom reduction of various psychiatric diseases, including OCD. However, the precise mechanism by which tDCS modulates brain activity and functional connectivity in patients with OCD remains unclear. To the best of our knowledge, no study has been conducted on patients with OCD who have undergone concomitant rsFC fMRI and tDCS over the pre-SMA.

Therefore, this investigation aimed to carry out the simultaneous acquisition of rsFC-fMRI together with tDCS over the pre-SMA to shed light on potential alterations in functional connectivity in patients with OCD following neurostimulation. We conducted a seed-to-voxel analysis using the right pre-SMA, right M1, right SMA and right IFG as predetermined regions of interest (ROIs) associated with inhibitory control, a major characteristic exhibited in OCD (see FIGURE 3).

3. Methods

3.1 Resting State Functional Connectivity

The following information aims to provide an overview of the methodology involved in resting state functional connectivity (rsFC), building upon the content presented in the introduction. RsFC utilizes fMRI to observe low-frequency fluctuations (0.01-0.1 Hz) in blood-oxygen-level-dependent (BOLD) signals while the brain is at rest, allowing for the examination of intrinsic brain activity (Biswal et al., 1997). Research by Biswal and collegues (1997) were the first to discover synchronous low-frequency fluctuations in the brain's resting state, demonstrating notable temporal correlations within and between anatomically distant brain regions, pointing to their interconnectivity during periods of rest (Biswal et al., 1997). Previously, it was assumed that these low-frequency oscillations may reflect artifacts produced by cardiac and resperatory patterns. However, evidence has shown that these resting-state fMRI signals arise from patterns that occur between brain regions that share both functional and neuroanatomical overlap such as areas within the motor, visual and auditory networks (van Heuvel & Hulshoff, 2010). This suggests that at rest, interconnected brain regions form functional networks and exhibit ongoing spontaeous neuronal activity (van Heuvel & Hulshoff, 2010). In the last decade, rsFC has become a powerful tool for mapping functional connections within the brain in both states of health and disease. Furthermore, rsFC anaylsis has gained significant attention as a research methodology to assist in the understanding of the mechanisms underlying neurological and psychiatric diseases.

There are several ways in which functional connectivity may correlate between different brain regions as outline by Poldrack et al. (2011). First, it can be attributed to a direct causual influence from one area to another, known as effective connectivity (FIGURE 2a.). Second, connectivity might result from a third region mediating between two others (FIGURE 2b.). Lastly, two regions could jointly influence on one area, known as stimulus-riven transients (FIGURE 2c.). This highlights the importance of taking caustion when interpreting results from functional connectivity analysis (Poldrack et al. (2011).

While there are various methodological approachs for analyzing functional connectivity, the seed-to-voxel correlation method is one of the most common forms of connectivity analysis, and is utilized in this study. Seed-to-voxel anaylsis uses predefined regions of interest (ROI) known as "seeds" which are often anatomically defined using a brain atlas or identified through prior fMRI studies. The fMRI timeseries data is extracted from the seed through averaging the BOLD signal

across all voxels within the seeds during rest, and is then correlated with the time series of every other voxel in the brain.

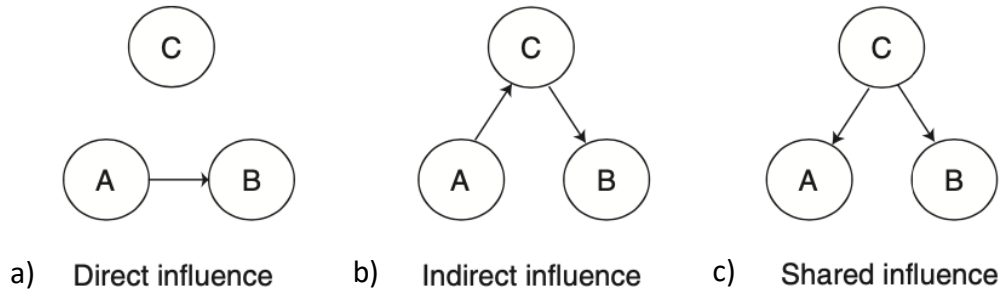


Figure 4. Functional connectivity correlations.
Figure from Poldrack et al., (2022). p. 131

3.2 Participants

Forty-nine participants diagnosed with OCD, aged between 18-65 (16 male, 33 female), were included in this study (Table 1.). Recruitment took place at various locations including the Klinik Windach – Klinik für Psychosomatische Medizin und Psychotherapie, Tagesklinik Westend, Schön Klinik Roseneck – Haus Rosenheim, and through the distribution of flyers at the LMU Kinikum- Klinik für Psychiatrie und Psychotherapie, and the Technical University Munich (TUM) and Ludwig-Maximillian University Munich (LMU) campuses.

All participants met the ICD-11 criteria for OCD and exhibited a Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score of ≥8. Inclusion criteria comprised right-handedness and stable pharmacological treatment, excluding the intake of benzodiazepines within 24 hrs of the study. Exclusion criteria encompassed neurological disorders (including epilepsy and seizures), psychiatric comorbidities (e.g. schizophrenia, PTSD, and personality disorders), incompatibility with MRI scanners (e.g., intracranial implants, pacemakers or defibrillators), and pregnancy. Written consent was obtained from all participants before the day of the study.

To assess symptom severity and comorbidities, participants completed various questionnaires both before and after the study, including the YBOCS, YBOCS checklist, and HAM-D. This project received approval from the Ethics Committee Klinikum Rechts der Isar, Faculty of Medicine at the Technical University of Munich (Project Number 124/20 S).

Table 1. Demographics and clinical data.

Variable	OCD patients
Number of participants	49
Sex (male/female)	16/33
Age at scanning, M ± SD	31.7 ± 11.3
Duration of OCD, M ± SD	16.6 ± 11.0
Medication (yes/no)	33/16
YBOCS total, M ± SD	19.9 ± 5.7
Y-BOCS obsessions, M ± SD	9.9 ± 3.1
Y-BOCS compulsions, M ± SD	10 ± 3.8
HAM-D, M ± SD	19.4 ± 9.7

Note: A single individual may concurrently experience a mix of different medications and simultaneous health conditions.
Abbreviations: OCD = obsessive-compulsive disorder, Y-BOCS = Yale-Brown Obsessive Compulsive Scale

3.4 Study Design

This study was conducted at Klinikum rechts der Isar, and employed a double-blind, randomized, sham-controlled, cross-over design. Each patient engaged in the study on two distinct days, separated by a 7-day interval to mitigate any potential carryover effects.
For Group A, patients underwent tDCS-sham on day 1 and tDCS-stimulation on day 7, concurrent with fMRI scans. Conversely, Group B experienced the reverse, with tDCS stimulation on day 1 and tDCS-sham on day 7, also during simultaneous fMRI (see Fig. X).
Ensuring thorough adherence to the study protocol, participants signed the study agreement at two designated instances, including on the day of the study. Prior to MRI scanning, patients completed an MRI patient consent form and a comprehensive questionnaire outlining inclusion/exclusion criteria. Additionally, a detailed patient history, co-morbidities, and current/past medication records were obtained through a patient questionnaire. To assess current symptom severity, patients utilized a Likert-Scale prior to scanning, as well as assessments using both YBOCS and YBOCS Symptom-Checklist. Depression symptoms were evaluated using the Hamilton Depression Rating Scale (HAM-D).

All patients underwent a total of 50-60 min of MRI scanning, 20 min of tDCS whilst patients engaged in two task paradigms (results excluded from this paper), followed by 10 min of resting

state imaging. Post-tDCS and scanning, patients were assessed on symptom severity and potential side effects resulting from the tDCS.

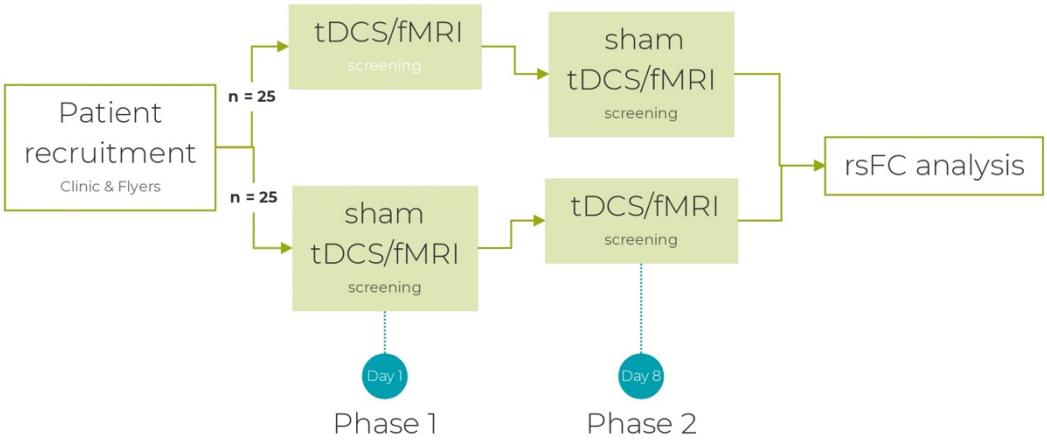


Figure 5. Study design.

Abbreviations: fMRI = functional magnetic resonance imaging, rsFC = resting state functional connectivity, tDCS = transcranial direct current stimulation

3.5 tDCS

The tDCS device utilized in this study was the NeuroConn DC-Stimulator MR, specifically designed for compatibility with MRI. To ensure the safety of simultaneous tDCS and MRI scanning, the experimental set-up inside and outside the scanner adhered strictly to the guidelines provided by NeuroConn.

For electrode placement optimization targeting the pre-SMA, we employed electrical field calculations using SimNIBS (see FIGURE 6). The optimal electrode placement for stimulating the pre-SMA was determined using an EEG 10-20 cap. The anodal stimulation site, (right pre-SMA) was located over the center point of the FC1 with a 3x3 rubber electrode; the cathode was placed over the center point of the FC2 using a 4x4 rubber electrode. Prior to electrode application, the patient's hair and scalp were prepared using Ten20 electrode paste to improve skin conductivity underneath the electrodes. Hair thickness was recorded and defined as 0=bald, 1=thin, 2=thick. The tDCS was configured at a current of 2 mA, with a fade-in and fade-out duration of 15s, and

variable duration of either 30 s or 1200 s, contingent on the group condition. Impedance was maintained below 15 ohms once the 2 mA threshold was reached.

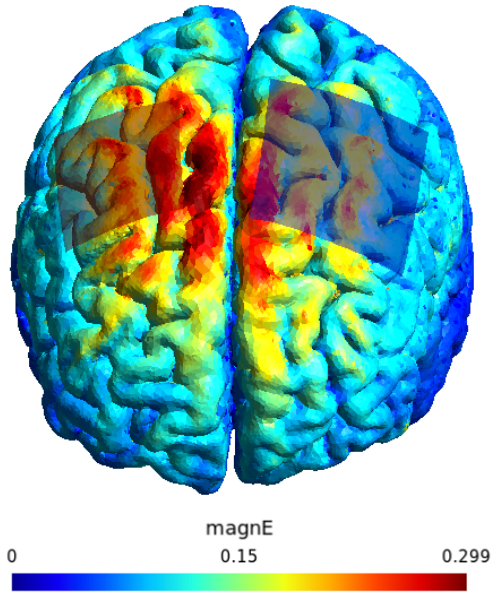


Figure 6. Modeling of electric field magnitude.

Using Simnibs, the optimal tDCS electrode placement was calculated using electrical field magnitude on a standard subject brain mesh. MagnE shows the electrical field magnitude (V/m) on the grey matter surface. Anode (left, smaller) and cathode (right, larger) depicted as grey squares. A 2mA anidak current with 3x3 cm anode at FC1 and 4x4 cathode at FC2 position was modelled. The EEG 10-20 positions were obtained from MNI electrode definitions with SimNIBS.

3.6 fMRI Data Acquisition

MRI image data was acquired using a 3.0 Tesla Philips Ingenia scanner (Philips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil at Klinikum Rechts der Isar, Munich Germany. A survey scan was run to plan and optimize field of view for subsequent image acquisition.

High resolution anatomical T1-weighted images were obtained using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with the following scanning parameters: 230 slices; sagittal orientation; 368 x 317 matrix; 0.7 mm isotropic resolution; echo time (TE) = 5.1 ms; repetition time (TR) = 11 ms ; flip angle = 8°.

T2 weighted functional MRI resting-state functional images were acquired using an echo-planar-imaging (EPI) sequence with the following parameters: 64 transverse slices; slice thickness = 3

mm; whole brain coverage, 3 x 3 x 3 mm^2 resolution ; TE = 30 ms; TR = 1000 ms; flip angle = 60°; field of view (FOV) = 192 x 192 x 118.5 mm, 64 transverse slices ; matrix size = 64 x 62; A series of 660 whole-brain volumes were recorded. The participants were instructed to keep their head still, close their eyes but not sleep.

Whitin the same imaging session, a DTI sequence, two task-based T2 sequences, and a FLAIR sequence were acquired.

3.7 fMRI Preprocessing and Analysis

FMRI data were preprocessed using CONN Functional Connectivity toolbox. Results included in this manuscript come from analyses performed using CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012) (RRID:SCR_009550) release 22.a (Nieto-Castanon & Whitfield-Gabrieli, 2022) and SPM (Penny et al., 2011) (RRID:SCR_007037) release 12.7771. See appendix for individual list of references.

Preprocessing: Functional and anatomical data were preprocessed using a flexible preprocessing pipeline (Neito- Castanon, 2020) including realignment with correction of susceptibility distortion interactions, outlier detection, direct segmentation and MNI-space normalization, and smoothing. Functional data were realigned using SPM realign & unwarp procedure (Andersson et al. 2001), where all scans were coregistered to a reference image (first scan of the first session) using a least squares approach and a 6 parameter (rigid body) transformation (Friston et al., 1995), and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Potential outlier scans were identified using ART (Whitfield-Gabriele et al., 2011) as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations (Power et al., 2014; Nieto-Castanon- submitted), and a reference BOLD image was computed for each subject by averaging all scans excluding outliers. Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure (Calhoun et al., 2017) using SPM unified segmentation and normalization algorithm (Ashburner & Friston, 2005; Ashburner, 2007) with the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 6 mm full width half maximum (FWHM).

Denoising: In addition, functional data were denoised using a standard denoising pipeline (Neito-Castanon, 2020) including the regression of potential confounding effects characterized by filtered white matter timeseries (5 CompCor noise components), filtered CSF timeseries (5 CompCor noise components), filtered motion parameters and their first order derivatives (12 factors) (Friston et al., 1996), outlier scans (below 64 factors) (Power et al., 2014), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries (Hallquist et al, 2013) between 0.017 Hz and 0.1 Hz. CompCor (Behzadi et al., 2007; Chai et al., 2012) noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 135.8 to 154.5 (average 151.6) across all subject (Neito-Castanon, submitted).

First-level analysis SBC_01: Seed-based connectivity maps (SBC) were estimated characterizing the spatial pattern of functional connectivity with a seed area. Seed regions included 4 ROIs. These were selected based on relevant motor areas involved in inhibtiory control. The following ROIs were carefully selected: pre-SMA, SMA, M1, and IFG. There were defined using Human Motor Area Template (HMAT) (mayka et al., 2006).
Functional connectivity strength was represented by bivariate regression coefficients from a weighted general linear model (weighted-GLM (Neito-Castanon, 2020), estimated separately for each seed area and target voxel, modeling the association between their BOLD signal timeseries.

Group-level analyses: were performed using a General Linear Model (GLM (Neito-Castanon, 2020). For each individual voxel a separate GLM was estimated, with first-level connectivity measures at this voxel as dependent variables (one independent sample per subject and one measurement per task or experimental condition, if applicable), and groups or other subject-level identifiers as independent variables. Voxel-level hypotheses were evaluated using multivariate parametric statistics with random-effects across subjects and sample covariance estimation across multiple measurements. Inferences were performed at the level of individual clusters (groups of contiguous voxels). Cluster-level inferences were based on parametric statistics from Gaussian Random Field theory (Worsley et al., 1996; Nieto-Castanon, 2020). Results were thresholded using a combination of a cluster-forming $p < 0.001$ voxel-level threshold, and a familywise corrected p-FDR < 0.05 cluster-size threshold (Chumbley et al., 2010).

Following preprocessing, 3 subjects were excluded from the SBC due to the validity of scans following scrubbing resulting in n= 46 patients being included in our final analysis.

4. Results

Seed-based connectivity analyses were conducted to investigate potential alterations in rsFC patterns among OCD patients following both active tDCS and sham interventions. The regions of interest (ROIs) selected for this study included the right pre-SMA, right SMA, right M1 and right IFG.

Following preprocessing, 3 patients were excluded due to invalidity of scans after scrubbing. Our findings revealed a significant decrease in rsFC in n=46 patients using advanced control settings (voxel threshold $p < 0.001$ uncorrected and cluster threshold $p < 0.05$, cluster size p-FDR corrected) in both two-sided and one-sided tests.

One of the most robust findings involved altered hypoconnectivity from the primary motor network (SMA and M1) to the visual network post-tDCS as shown in Table 1 and FIGURE 4. Specifically, the one sided-tests revealed a reduction in rsFC from the right SMA to one cluster including the right occipital pole, right superior lateral occipital cortex, and right inferior lateral occipital cortex (FIGURE 4a). Additionally, the right M1 seed exhibited decreased rsFC to two clusters. The first cluster included the right occipital pole, right superior lateral occipital pole (FIGURE 4b), and the second cluster included the left temporal pole (FIGURE 4c). The right IFG seed demonstrated reduced rsFC to two clusters. The first cluster was made up of the right pre-central gyrus, right and left post-central gyrus and precuneus cortex (FIGURE 4d). The second cluster included the right and left lingual gyrus, and left occipital fusiform gyrus (FIGURE 4e).

Notably, these results were obtained using advanced family-wise error control settings with a voxel threshold $p < 0.001$ uncorrected and cluster threshold $p < 0.05$, cluster size p-FDR corrected. There were no statistically significant changes in rs-FC with these settings when using the pre-SMA as a seed.

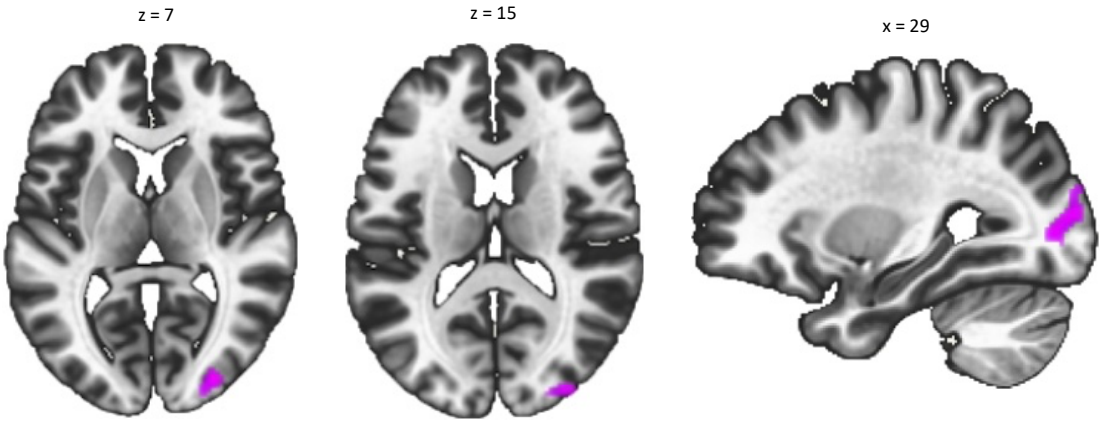
Table 2. One-sided results showing rsFC following active tDCS

Seed	Cluster	Location	K*e*	x	y	z	Size p-FDR
Right pre-SMA	-	-	-	-	-	-	-
Right SMA	1	right occipital pole, right superior lateral occipital cortex, right inferior lateral occipital cortex	227	36	-88	18	0.004649
Right M1	1	right occiptial pole, right superior lateral occipital pole	276	26	-88	18	0.001479
	2	left temporal pole	133	-46	16	-32	0.032897
Right IFG	1	right pre-central gyrus, right and left post-central gyrus, precuneous cortex	395	10	-46	70	0.000065
	2	left lingual gyrus, left occipital fusiform gyrus	161	-22	-72	6	0.011036

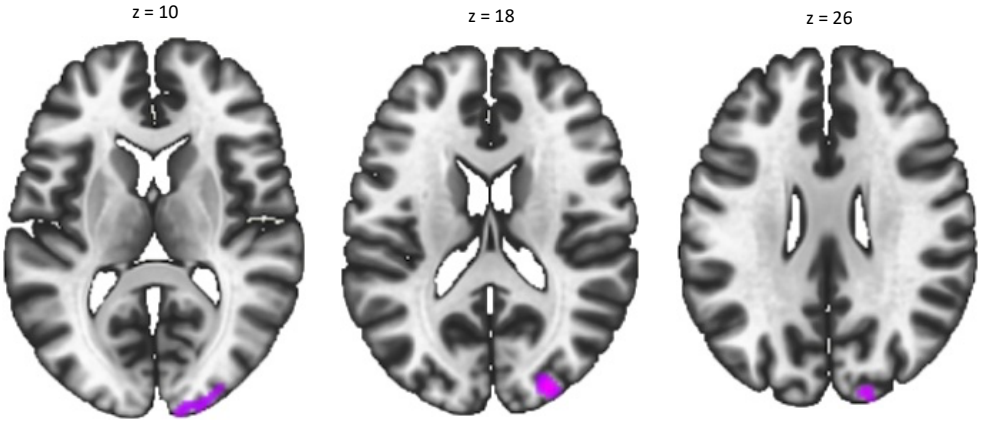
Note: n= 46; peak coordinates are given in MNI space

Abbreviations: *Ke,* cluster extent; MNI, Montreal Neurological Institute; FDR, false discovery rate.

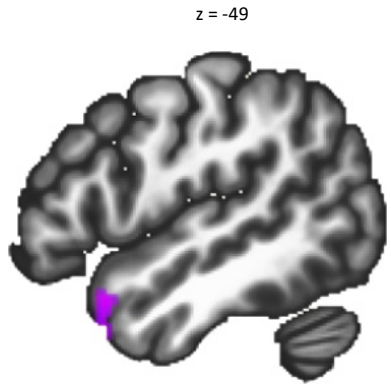
a) ROI: SMA → occipital cortex



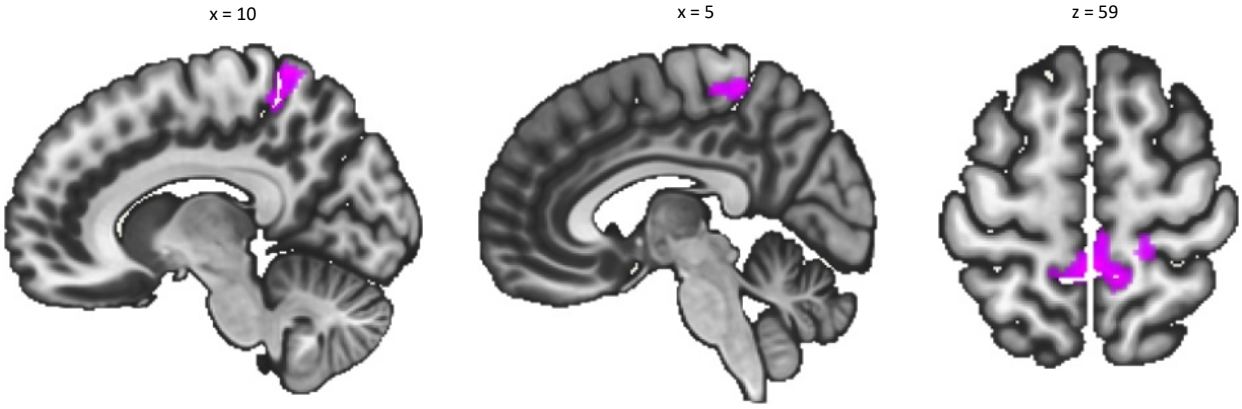
b) ROI: M1 → cluster 1: right occiptial pole, right superior lateral occipital pole



c) ROI: M1 → cluster 2: left temporal pole



d) ROI: IFG → Cluster 1: right pre-central gyrus, right and left post-central gyrus, precuneous cortex



e) ROI: IFG → Cluster 2: left lingual gyrus, left occipital fusiform gyrus

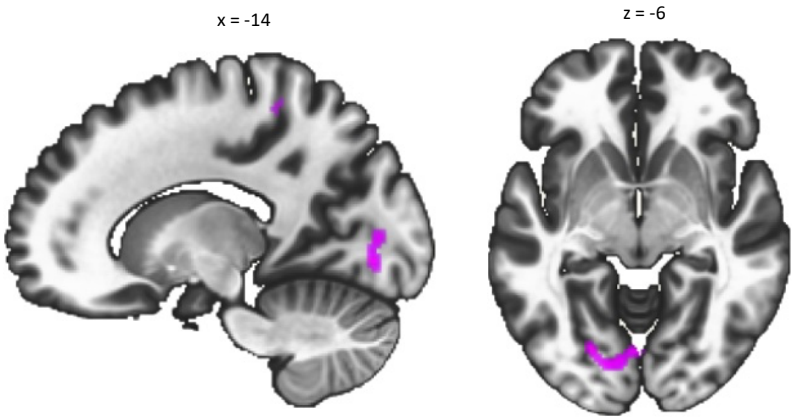


Figure 7. Resting state functional connectivity (rsFC) patterns.

Images show an overall decrease in connectivity following active tDCS in comparison to sham tDCS in patients with obsessive compulsive disorder. Seed-to-voxel rsFC analysis carried out in CONN (voxel threshold $p < 0.001$ uncorrected and cluster threshold $p < 0.05$, cluster size p-FDR corrected).

a) Brain areas, including right occipital pole, right superior lateral occipital cortex, and right inferior lateral occipital cortex showed a decrease in rsFC with the right somatomotor area (SMA). b) Cluster 1: right occiptial pole and right superior lateral occipital pole showed a decrease in rsFC with the right M1. c) cluster 2: left temporal pole showed a decrease in rsFC with the right M1. d) Cluster 1: right pre-central gyrus, right post-central gyrus, left post-central gyrus, precuneous cortex, right pre-central gyrus showed a decrease in rsFC with the right IFG. e) Cluster 2: left lingual gyrus, left occipital fusiform gyrus showed a decrease in rsFC with the right IFG.

5. Discussion

5.1 Resting State Functional Connectivity Patterns following tDCS

The current study aimed to investigate the impact of tDCS, over the pre-SMA, on resting state functional connectivity (rsFC) patterns in individuals with OCD. Forty-nine participants underwent concomitant fMRI and active tDCS in a double-blind, randomized, sham-controlled, cross-over study. Seed-based connectivity analyses were conducted using ROIs associated with inhibitory control, including the right-sided pre-SMA, SMA, M1, and IFG.

Our findings revealed significant alterations in rsFC patterns following active tDCS (TABLE 2). The changes in functional connectivity induced by tDCS over the pre-SMA were observed near the anode stimulation sites and in distant brain regions. We found hypoconnectivity, i.e., specifically reduced rsFC, within and between the motor network, somatosensory areas, critical areas involved in inhibitory control, and the visual cortex. These findings are consistent with previous studies that have demonstrated the ability of tDCS to modulate functional connectivity in various psychiatric disorders, including OCD (Adams et al., 2022; Pinto et al., 2022).

Following active tDCS, our rsFC analysis showed three main findings: 1) hypoconnectivity between the right SMA and a cluster comprising the right occipital pole, as well as the right superior and inferior lateral occipital pole (FGURE 7a.) ; 2) hypoconnectivity between the right primary motor cortex (M1) and two distinct clusters. The first cluster encompasses the right occipital pole and the right superior lateral occipital cortex (FIGURE 7b.), while the second includes the left temporal pole (FIGURE 7c.) ; 3) hypoconnectivity between the right IFG and two clusters. The first cluster involves the right and left postcentral gyrus, precuneous cortex, and right precentral gyrus (FIGURE 7d.). Simultaneously, the second cluster includes both the lingual gyrus (right and left), and the occipital fusiform gyrus (FIGURE 7e.).

5.2 Resting State Functional Connectivity & Response Inhibition

The rationale behind applying tDCS to the pre-SMA in individuals with OCD was to target a key area implicated in motor response inhibition, a critical neurocognitive process underlying the disorder (Chambers et al., 2009; Snyder et al., 2015). While our results did not specifically show

any alternations within the pre-SMA in rsFC seed-to-voxel analysis, the surrounding areas were likely stimulated, as reflected by changes in rsFC within the right SMA, M1, and IFG (TABLE 2). These results suggest that tDCS was effective in stimulating areas involved in motor response inhibition. Converging evidence from neuroimaging studies have consistently implicated the SMA/pre-SMA and the right IFG as critical nodes involved in response inhibition. Furthermore, several studies have shown that the pre-SMA and the right IFG play crucial roles in the CSTC network, facilitating the suppression of motor actions (Chambers et al., 2009). Functional and anatomical connections facilitating the cessation of motor responses have been identified between the pre-SMA and the IFG, as outlined by Chambers et al. (2009). It is postulated that these brain areas send a neural 'stop signal' to the motor cortex via the CSTC pathway to halt or inhibit motor responses (Chambers et al., 2009). This process is critical in OCD, where it is believed that an imbalance within these pathways may contribute to the difficulty in stopping repetitive behaviors that are characteristic of the disorder.

Although our study only involved resting state analysis, a study done by Tomiyama et al. (2022) compared resting-state fMRI and measured response inhibition in 41 medication naïve individuals with OCD in comparison to 49 healthy controls. The study indicated that individuals with OCD had a notable increase in rsFC between the pre-SMA and IFG in comparison to health controls. In addition, heightened connectivity correlated with more significant challenges in suppressing motor actions, as demonstrated by longer stop-signal reaction times (Tomiyama et al., 2022). These findings provide further evidence that targeting areas with tDCS that are involved in motor response inhibition, may lead to changes in rsFC that underly the pathophysiology of OCD. In light of the findings described above, one might suggest that the effects of tDCS over the pre-SMA and surrounding area, as demonstrated by our study, could have contributed to a "normalization" of the otherwise increased rsFC and impaired inhibitory control observed in the individuals with OCD. Consequently, this normalization may have led to an overall decrease in rsFC, as observed by our results. Further studies looking at task-based connectivity analysis using inhibitory control paradigms, combined with rsFC analysis, similar to Tomiyama et al., are currently being investigated in our research group, and will be included in further publications.

5. 3 Resting State Functional Connectivity

Following tDCS, we observed a decrease in connectivity from the right motor cortex, SMA and M1, to the occipital cortex, a topic that will be explored further below. Notably, M1 also showed hypoconnectivity to the left temporal pole following tDCS (FIGURE 1c). The temporal pole, has been associated with high-level cognitive processes, such as autobiographic memory, semantic processing, socio-emotional processing, and visual processing (Herlin et al., 2021), and becomes particularly relevant in this context. Reess et al. (2016) showed that connectomics-based structural network analysis exhibited structural alterations in nodes implicated in the CSTC network and connections within fronto-temporal regions. They reported reduced structural connectivity in various regions, including the temporal poles, in OCD patients compared to healthy controls. Additionally, Moreira et al. (2017) conducted an exploratory multimodal MRI analysis on forty OCD patients, in comparison to forty healthy controls, revealing a significant decrease in functional connectivity in networks connecting the medial orbitofrontal cortex, temporal poles, lingual gyrus and postcentral gyrus. They also observed a volumetric reduction of a cluster encompassing the right medial and superior temporal gyri. While our findings similarly indicated an overall decrease in rsFC from the M1 to the temporal pole, it is essential to consider that these observations were made post-tDCS. Interestingly, the temporal pole has been associated with cognitive efforts to overcome fear (Nili et al., 2010, as cited in Moreira et al., 2017) and implicated in OCD pathophysiology due to its anatomical link and its association with the severity of harm/checking symptoms (van der Heuvel et al., 2009) and dysfunctional beliefs (Alonso et al., 2013). When considering our findings, alongside existing literature, it reinforces the significance of the temporal pole in the context of OCD and the possibility of targeting it with tDCS.

Following tDCS, alterations in the rsFC of the IFG were evident, as shown by an overall decrease in connectivity to the right precentral gyrus, bilateral postcentral gyrus, right precuneus, and distinct regions within the occipital cortex (FIGURE 1d & e). These findings highlight the close connection between the IFG and motor cortex and somatosensory areas and highlight changes in rsFC to the precuneus, a crucial region intricately linked to self-referential thought processes (Yamaguchi & Jitsuishi, 2023). The precuneus is a hub for high-level cognitive functions, including memory, bodily awareness, time perception, and sensory and motor information integration through its structural connections with various brain regions (Yamaguchi & Jitsuishi, 2023). Moreover, the precuneus is an integral structure within the default mode network (DMN). This network has been closely associated with alterations in connectivity implicated in various

psychiatric disorders, including Adams et al., 2022). In the context of OCD, aberrant DMN hyperconnectivity has been reported, correlating with an amplification or perpetuation of internalized thought patterns (Koch et al., 2018). Therefore, the observed hypoconnectivity in rsFC from the IFG to the precuneus following tDCS raises intriguing considerations regarding its potential impact on the overall hyperactivity within the DMN network or specific brain areas associated with OCD as implicated. However, it is crucial to approach these interpretations with caution, recognizing the complexity of neural interactions and the need for further investigations.

The observed hypoconnectivity between all three seeds - SMA, M1, and IFG- to the areas within the occipital lobe is very notable. Similar to the present findings, alterations in rsFC patterns have previously been observed within and between occipital regions in patients with OCD (Moreira et al., 2017; Stern et al., 2017; Reggente et al., 2018; Ravindrann et al., 2020). The study by Moreira et al., 2017 further revealed distinct patterns in OCD patients, including reduced connectivity within the orbitofrontal networks and between sensorimotor areas and enhanced connectivity between the thalamus and occipital cortex. In line with our study, these findings suggest that the neural circuitry of OCD extends beyond traditional models such as the CSTC network, implicating broader network dysfunctions that may contribute to the symptomology of OCD (Moreira et al., 2017). Furthermore, the hyperconnectivity between the thalamus and the occipital cortex in OCD patients may reflect a compensatory mechanism or aberrant visual processing characteristic of the disorder (Kuelz et al., 2004). In another study, Geffen et al. (2022) demonstrated a decreased rsFC or hypoconnectivity between the lateral parietal aspects of the DMN and the occipital cortex, as well as hyperconnectivity between the right lateral parietal region and the right lateral occipital and precuneus. Moreover, the extent of hyperconnectivity was found to correlate positively with the severity of OCD symptoms, suggesting a potential correlation between altered visual processing and the psychopathology of OCD. Interestingly, our results showed connectivity patterns similar to those of Geffen et al. (2022). The IFG had a distinct hypoconnectivity following tDCS to the right and left postcentral gyrus, precuneus cortex, right precentral gyrus, and several areas within the occipital cortex. Although Geffen et al. (2022) saw overall hyperconnectivity between these areas, we would expect to have opposing findings following tDCS.

Further supporting the role of the occipital cortex in OCD, in a task-based functional connectivity study conducted by Ravindran et al. (2020), OCD patients were examined for changes in functional connectivity following emotional provocation using visual stimuli. The study found that across all participants, emotion provocation elicited widespread activation of visual cortices; however,

individuals with OCD demonstrated a hyperactivation between the posterior cingulate gyrus and visual cortical areas during emotion provocation, compared to healthy controls. This enhanced connectivity further substantiates the specific involvement of the visual cortex in the emotional reactivity of patients with OCD. Although the studies highlighted here demonstrate an overall increase in functional connectivity to the visual network, other findings have shown contrary findings, showing a decrease in functional connectivity within similar brain regions (Hou et al., 2014; Moreira et al., 2017). The variability in functional connectivity analysis results primarily reflects the heterogeneous methodological set-ups, such as different electrode montages, scanning protocols, and sample characteristics.

5.5 TDCS on Resting State Functional Connectivity

Surprisingly, our investigation found an overall decrease in rsFC following anodal tDCS in comparison to sham stimulation. This challenges the anticipated increase in connectivity based on existing literature and the known physical properties of anodal stimulation (Arul-Anandam & Loo, 2009). However, similar findings of decreased rsFC following anodal tDCS have been reported, including studies by Antonenko et al. (2017), Adams et al. (2022), and Claaß et al. (2023). Interestingly, Antonenko et al. (2017) reported a concurrent reduction in GABA levels in an older healthy population, which underscores the modulation of neurotransmitters and brain chemistry following tDCS (Antonenko et al., 2017).

The unexpected hypoconnectivity observed in our study, juxtaposed with the documented overactivity in individuals with OCD (Acevedo et al., 2021), sparks curiosity into the underlying effects tDCS has on the rsFC observed here. One could hypothesize that by stimulating the pre-SMA and surrounding areas, i.e., SMA, M1, and IFG with anodal tDCS, one may increase inhibitory control, subsequently elevating motor control and thereby enabling the reduction of an overactive sensory-motor and sensory areas such as the temporal pole and visual network. It is plausible to suggest that in our study, tDCS induced a "downregulation" of sensorimotor hyperactivity, a prevalent observation in critical networks implicated in OCD. This hyperactivity may, in part, be linked to a weakened inhibitory control over the sensorimotor network, consequently contributing to heightened sensory information processing (Ravindran et al., 2019). The observed "downregulation" following tDCS, may contribute to an overall subdued connectivity, leading to a "dampening" or hypoconnectivity of sensory-motor activation as observed in our study.

This interpretation may further be supported by recent studies that used tDCS protocols comparable to our methodology. These demonstrated a reduction in OCD symptoms such as , and an overall decrease in YBOCS scores following tDCS (D' Urso et al., 2016; Harika-Germaneua et al., 2020; Gowda et al., 2019; Silva et al., 2021; Thamby et al., 2021). These findings raise critical questions about the implications of altered connectivity patterns following tDCS on the pathophysiology of OCD, particularly within the neural circuits associated with motor-, inhibitory control and sensory networks. Understanding the nuanced impact of tDCS on these specific areas could provide valuable insights into the neural mechanisms underlying OCD symptoms, potentially paving the way for more precise and effective therapeutic interventions.

6. Limitations

While our study offers valuable insights into the effects of tDCS on rsFC patterns in individuals with OCD, several limitations need to be considered when interpreting the results. First, a sample size of forty-nine participants is relatively small. It may raise concerns regarding robustness and generalizability, as we only included right-handed individuals and tested patients representing a small demographic population. Second, understanding our results poses a fundamental challenge when distinguishing between the impacts of anodal and cathodal stimulation in tDCS. Even in experimental designs where different electrode positions are compared, each combination of anode-cathode positions can be regarded as a different bipolar tDCS modality (Keeser et al., 2011). Additionally, electric field distribution in the brain, as indicated by physical models, suggests that our findings may only apply to the specific parameters and electrode positions used in our study (Keeser et al., 2011; Sadleir et al., 2010). Third, our selected electrode montage stimulated the pre-SMA and the surrounding areas, including the SMA, M1, and IFG. This broader stimulation area could have influenced the observed rsFC patterns. Future studies may benefit from exploring more focal stimulation approaches, such as high-definition tDCS (Sallard et al., 2018) or multifocal tDCS (Adams et al., 2022). Fourth, the absence of a comparison with healthy controls limits our ability to compare rsFC patterns with a baseline following tDCS and should be the aim of future studies. Lastly, our study exclusively focused on the resting state. It is essential to point out that whilst the resting state measures the brain at rest, it does not take into account internal visual focus, introspective thoughts (visual and auditory), and other cognitive states that could contribute additional to our understanding of tDCS-induced rsFC changes.

7. Conclusion

In conclusion, the present study demonstrated that tDCS over the pre-SMA can modulate rsFC in patients with OCD. Specifically, tDCS over the pre-SMA decreased rsFC between 1) the right SMA and a cluster in the right occipital pole; 2) between the right M1 and clusters in the right occipital pole, right superior lateral occipital cortex, and left temporal pole.; 3) between the right IFG and clusters involving the bilatereal postcentral gyrus, precuneous cortex, and right precentral gyrus. Simultaneously, the second cluster includes both the lingual gyrus (right and left), and the occipital fusiform gyrus. Decreasing functional connectivity within and between these areas may give rise to the potential mechanism responsible for the positive impacts observed following repeated tDCS as a potential treatment modality for OCD. Therefore, our findings encourage future studies to explore larger sample sizes and incorporate task-based functional connectivity imaging, further advancing our understanding of tDCS' therapeutic potential for the treatment of OCD.

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11. Appendix

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