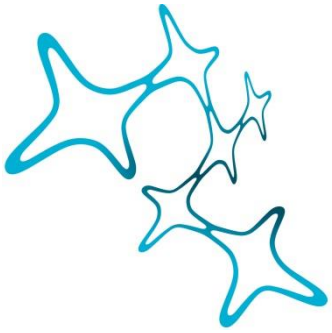
EXPLORING NEURONAL CORRELATES OF OBSESSIVE-COMPULSIVE DISORDER

NOVEL APPROACHES USING BRAIN STIMULATION AND FMRI

Daniela Rodriguez Manrique



Graduate School of
Systemic Neurosciences

LMU Munich

Dissertation der
Graduate School of Systemic Neurosciences
Ludwig-Maximilians-Universität München

June 2024

Supervisor
Prof. Dr. Kathrin Koch
Abteilung für Neuroradiologie
NeuroKopfZentrum
Klinikum rechts der Isar der TUM

First Reviewer: Prof. Dr. Kathrin Koch
Second Reviewer: Dr. Paul Taylor
External Reviewer: Prof. Dr. Christoph Herrmann

Date of Submission: 26th June, 2024
Date of Defense : 24th October, 2024

Table of Contents

Abstract

Obsessive compulsive disorder (OCD) is complex in its symptoms and comorbidities. Conventional pharmacological therapies continue to only benefit half of those affected. This dissertation investigates the neuronal correlates in OCD in two samples of OCD patients recorded with different fMRI sequences. One study assesses differences in spontaneous brain activity as measured by low frequency oscillations (LFOs) using percentage of amplitude fluctuation (PerAF) in patients. The other study investigates the effect of transcranial direct current stimulation (tDCS) on inhibition performance- a capacity known to be strongly impaired in OCD - and underlying brain activity. We found decreased LFOs in the bilateral cingulate gyrus, the right temporal gyrus, bilateral thalamus and right insula. These areas were largely in line with the largest multi-site OCD resting state connectivity analysis in OCD to date. Additionally, tDCS at the preSMA, which typically exhibits hypoactivation during inhibition in OCD patients, was able to elicit an improved inhibition performance. tDCS intervention also showed an increased BOLD activation in the cingulate gyrus, the bilateral middle frontal gyrus, inferior frontal gyrus, supramarginal gyrus and cerebellum. In summary, this dissertation provides an improved method, capturing LFOs using a more reliable, reproducible and less biased calculation of percentage of amplitude fluctuation (PerAF) for investigating resting state neuronal correlates of OCD. In addition, the dissertation demonstrated how single session tDCS modulates brain regions implicated in OCD neuropathology and transiently rescues accompanying behavioural deficits. tDCS should be considered for future OCD treatment options. Together both studies guide the literature on novel methods aimed at precisely capturing neuronal correlates of OCD neuropathology.

Abbreviations

Abbreviation	Definition
ACC	Anterior Cingulate Cortex
ALFF	Amplitude of low frequency fluctuations
BOLD	Blood Oxygen Level Dependent
CBT	Cognitive Behavioural Therapy
CSTC	Cortico-Striato-Thalamo-Cortical
DF	Degrees of Freedom
dlPFC	Dorsolateral prefrontal cortex
DMN	Default Mode Network
EF	Electric Field
EPI	Echo Planar Imaging
FC	Functional Connectivity
FD	Framewise Displacement
fALFF	Fractional amplitude of low frequency fluctuations
fMRI	Functional Magnetic Resonance Imaging
HCs	Healthy Controls
HRF	Haemodynamic Response Function
IFG	Inferior frontal gyrus
MB	Multiband
MNI	Montreal Neurological Institute
mPerAF	Mean percentage amplitude of fluctuations
MPRAGE	Magnetization-Prepared Rapid Acquisition Gradient Echo
MRI	Magnetic Resonance Imaging

OCD	Obsessive-Compulsive Disorder
OFC	Orbitofrontal Cortex
PerAF	Percentage amplitude of fluctuations
PFC	Prefrontal Cortex
PreSMA	Pre-Supplementary Motor Area
ROI	Region of Interest
rs-fMRI	Resting-State Functional Magnetic Resonance Imaging
RT	Reaction Time
rTMS	repetitive Transcranial Magnetic Stimulation
serotonin	5-hydroxytryptamine
SSRIs	Selective Serotonin Reuptake Inhibitors
T1	Longitudinal relaxation time
T2*	Spin-spin relaxation time
tDCS	Transcranial Direct Current Stimulation
TE	Echo Time
tES	Transcranial Electric Stimulation
TMS	Transcranial Magnetic Stimulation
TR	Repitition Time
vmPFC	Ventromedial prefrontal cortex
Voxel	Volumetric Pixel
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

1.0 General Introduction

1.1 Obsessive-Compulsive Disorder

Obsessive-Compulsive Disorder (OCD) has a prevalence of 2.3% in Europe (Wittchen & Jacobi, 2005). Patients experience a reoccurring cycle of obsessions, grounded in personal fears and anxieties, triggering patients to execute compulsions that lead to a reduction in said anxieties. Compulsions can be incredibly diverse and encompass either checking behaviours, such as washing hands, or mental exercises such as counting to specific numbers (American Psychiatric Association & Association, 2013). These satisfy patients' afflicted obsessions. Obsessions are intrusive thoughts, which are often at odds with the patients' self-perception and morality. Obsessive thoughts become pervasive in the patients' mind, forcing them to allocate increasing time and energy to mitigate them. Eventually, this reoccurring cycle debilitates the patients' ability to cope with everyday tasks, compromising their quality of life and causing substantial disability (Mancebo et al., 2008; Storch et al., 2009). Given the diversity in expression of symptoms between patients, we can expect a similar level of multiplicity in their neuronal pathology.

The basal ganglia, a cluster of subcortical nuclei, is important in the facilitation of goal-directed actions and development of habits (Gremel & Costa, 2013). It is comprised of the ventral striatum which includes the nucleus accumbens and the olfactory tubercle, as well as the dorsal striatum, which includes the caudate nucleus and putamen (Lanciego et al., 2012). The subthalamic nucleus (STN), internal globus pallidus (GPi), external globus pallidus (GPe), and substantia nigra pars reticulata (SNr) are considered basal ganglia nuclei (Lanciego et al., 2012). Originally, OCD was described using the orbitofrontal-striatal model. The model depicts overactivity in the direct pathway where thalamus input is relayed through the orbitofrontal cortex (OFC) to the striatum, which typically is involved in movement execution (Modell et al.,

1989). In addition, a simultaneous underactivity in the indirect pathway, which projects back to the OFC from the basal ganglia, is hypothesised. The indirect pathway, also labelled the inhibitory pathway, works as a negative feedback loop to the direct pathway and inhibits actions (Lanciego et al., 2012). In OCD the feedback loop between these two is altered, causing hyperactivity in the obsessive (direct) pathway (Menzies et al., 2008). The hyper activation of the direct and hypoactivation of the indirect pathways are depicted in figure 1. There is ample evidence of OFC's role in aspects of inhibitory control, emotional processing, and rewards which play a role in OCD symptoms (Balasubramani et al., 2020; Elliott & Deakin, 2005; Hikosaka & Watanabe, 2004; Schoenbaum et al., 2002). Positron emission tomography studies additionally found increased glucose metabolic activity in the bilateral OFC, basal ganglia, and the thalamus of OCD patients (Gargano et al., 2023; Nordahl et al., 1989; Swedo et al., 1989). Increased glucose metabolic activity is indicative of increased neural activity in patients, as neurons require glucose for adenosine triphosphate (ATP) and neurotransmitter production (Mergenthaler et al., 2013).

The relatively "simple" orbitofrontal-striatal model has since been expanded in the literature to include OCD hyperactivity in the cortico-striato-thalamo-cortical (CSTC) circuit (Fettes et al., 2017). Increased activity in the caudate nucleus (within the striatum) inhibits GPi neurons resulting in intensified thalamus activity. The GPi neurons are GABAergic and typically dampen thalamus activity, as shown in figure 1 (Zheng & Monti, 2022). For this reason, OCD primate models are induced through bicuculline (a competitive GABA antagonist) injection to the GPi, mimicking decreased GPi neuronal activity in OCD (Baup et al., 2008). We can further observe that within the CSTC loop OCD patients exhibit connectivity differences between the GPi and GPe (Calza et al., 2019). As mentioned in the previous paragraph, the GPi induced heightened thalamus activity additionally increases OFC activity. This conversely further intensifies the activity in the caudate nucleus via the cingulate gyrus. Some work suggests

hyperactivity of the caudate nucleus in OCD (Baxter Jr et al., 1988; Benkelfat et al., 1990; Guehl et al., 2008). However, some papers argue the effect of caudate excitability could also stem from the pre-supplementary motor area (preSMA) and inferior frontal gyrus (IFG) projections, which also influence caudate nucleus hyperactivity (Jahfari et al., 2011; Xu et al., 2016).

The CSTC circuit unquestionably does not function in isolation in the brain. Therefore, different studies have extended the areas involved to include hyperactivity in the anterior cingulate cortex (ACC) (Fitzgerald et al., 2005; Menzies et al., 2008; van de Veerdonk et al., 2023). On a macrolevel, the three-network hypothesis emerged: involving hypoconnectivity within and between the frontoparietal network (FPN), salience network and default mode network (DMN) and associated deficiencies in switching between habit and goal-directed activities (Gursel et al., 2018; Menon, 2011). The hypoconnectivity specifically involves the ventromedial prefrontal cortex (vmPFC) and ACC, critical areas of the DMN, and communicating with the caudate nucleus during goal-directed tasks (Banca et al., 2015; Tricomi et al., 2009). Simultaneously increased activity in the OFC, amygdala and putamen, related to excessive habit formation, was observed by other studies (Banca et al., 2015; Gillan et al., 2014; Gillan et al., 2011; Thorsen et al., 2018). Another approach to investigating OCD relevant regions is looking at volumetric and density alterations in the disorder. Structural studies have been able to confirm grey matter density in the thalamus and lenticular nucleus (comprised of the putamen and GP) of OCD patients (Radua & Mataix-Cols, 2009; Radua et al., 2010; Rotge et al., 2010). Volume abnormalities in the ACC were also observed in OCD patients, albeit not being specific to OCD and observed in other psychiatric disorders (Rotge et al., 2010). In overview, there is a large amount of evidence for functional alterations in cortico-striato-thalamic regions and networks that likely play a relevant role in the pathogenesis of the disorder. Most critical are the hyperfunction of the direct pathway and under function of the indirect pathway. In addition,

preSMA and IFG hypofunction also influence the striatum and vice versa. Finally, OCD patients show impairments in resting-state network switching, which are partially mediated by the ACC. These impairments are accompanied by increased habit formation and alterations in goal directed behaviours.

Nevertheless, despite CSTC areas having established themselves in the literature related to OCD, there is confirmation bias associated with region of interest (ROI) studies, as this can exclude other implicated regions and exacerbate differences in study results. Furthermore, it is difficult to isolate OCD-specific abnormalities, as co-morbidities are relatively common. Thorsen et al. (2018) reported that comorbidity with mood and anxiety disorders influenced OCD-control activity during emotional processing. Most commonly, generalised anxiety disorder and mood disorders, including unipolar depression or bipolar depression, coincide in 75.8% and 63.3% of patients respectively (Ruscio et al., 2010). Less common are also coexisting personality disorders, which in combination with bipolar disorder make OCD treatment more challenging (Hollander et al., 2002; Pallanti et al., 2011; Perris et al., 2019).

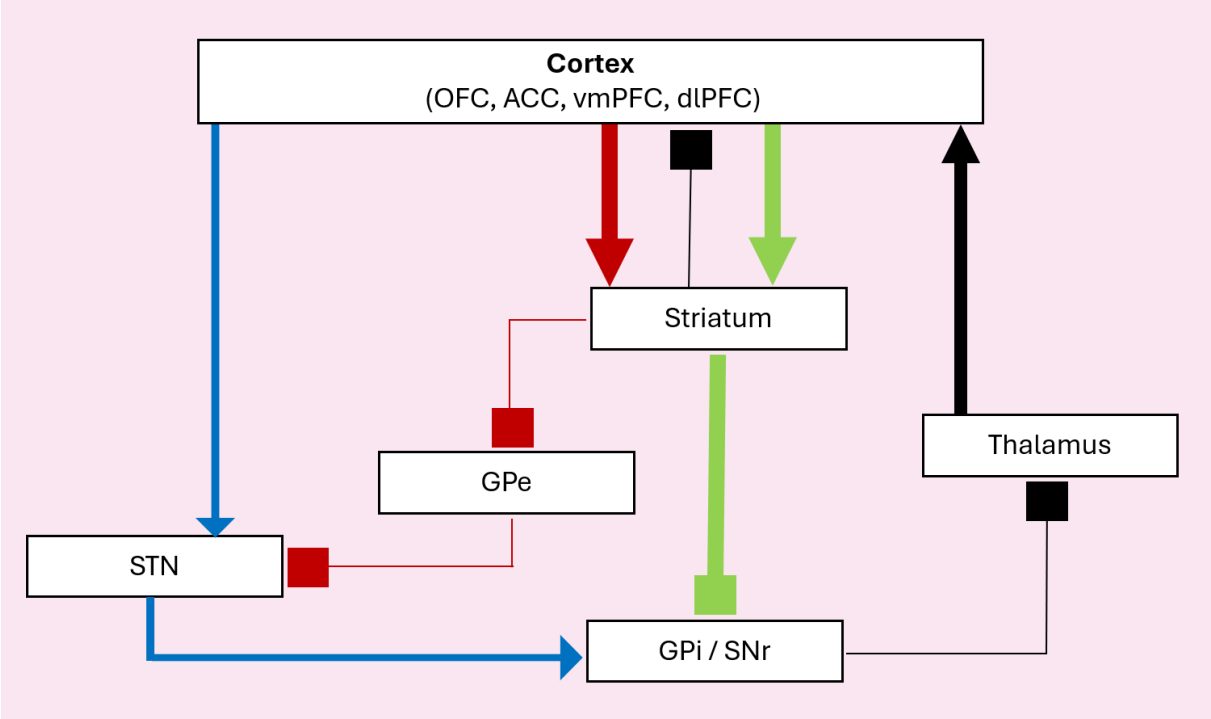


Figure 1: Summary of cortio-stratal-thalamo-cortical alterations in OCD. Cortical regions relevant for OCD pathophysiology include regions of the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), ventromedial prefrontal cortex (vmPFC) and dorsolateral prefrontal cortex (dlPFC). The direct pathway is net excitatory (green) and tends to facilitate behaviour, whereas the indirect pathway (red) is net inhibitory and tends to restrain behaviour. Hyperactivity in the obsessive (direct) pathway has been identified as a feature of OCD symptoms. This hyperactivity is denoted by a thick line of excitatory input from the cortex to the striatum. The striatum in turn has increased inhibitory tone (thick line) on the internal globus pallidus (GPi) and substantia nigra pars reticulata complex (SNr), which causes decreased inhibition (thin black line) of the thalamus. The thalamus is thereby disinhibited and increases its excitatory input (thick black line) to the cortex. This modulation disrupts the negative feedback loop, increasing obsessions and compulsions of OCD patients. The "hyperdirect" pathway (blue arrows) bypasses the striatum and synapses directly on the subthalamic nucleus (STN). Modulating this pathway has gained in prominence as a mechanism for therapeutic intervention, as the STN is a popular region for deep brain stimulation. Squares highlight that these neuronal connections are inhibitory, whereas arrows show they are excitatory.

1.2 Pharmacological Interventions

Currently the first line of treatment for OCD patients are selective serotonin reuptake inhibitors (SSRIs) (Del Casale et al., 2019). These pharmacological agents bind and inhibit the presynaptic plasma membrane transporter (SERT), thereby increasing serotonin availability in the synaptic cleft (Zhou et al., 2009). This increases the likelihood of serotonin binding to postsynaptic (5HT1A) serotonin receptors, resulting in increased neuronal firing. A hypothesis for their efficacy is not only the improvement in the availability of neurotransmitters, but also an accompanying increment of brain-derived neurotrophic factor (BDNF) which causes

dendrite formation in serotonin synapses (Goddard et al., 2008). This is believed to bolster synaptic plasticity, instrumental for establishing new coping mechanisms (Goddard et al., 2008). PET studies on major depression disorder (MDD) show that downregulation of 5HT1A autoreceptors takes 8 weeks (Gray et al., 2013). Accordingly, SSRI´s have been shown to take effect about 8 weeks after starting medication in MDD. For OCD patients, however, a first effect seems to be perceivable even later. There is however little understanding on why OCD efficacy to SSRIs takes longer compared to MDD patients (Koran et al., 2007). Additionally, a higher SSRI dose is necessary for OCD patients (Fineberg et al., 2007; Hollander et al., 2002; Stein et al., 1992). SSRIs are preferred due to their tolerability and efficacy. They are additionally widely prescribed for many other disorders such as MDD, anxiety disorders, bipolar depression, post-traumatic stress disorder, panic disorder and many others which make them compatible with patient's comorbidities. Their versatility has facilitated the study of their side-effects and safety in diverse settings.

Frequently, SSRIs are prescribed in combination with therapy. The two most popular types are cognitive behavioural therapy (CBT) and exposure and response prevention, where patients are forced to confront their obsessions and fears related to them. Both therapies are rated at similar efficacies (Ost et al., 2015). Del Casale et al. (2019) reported best results when combining CBT or exposure and response prevention with SSRI in their meta-analysis. In any case, the issue of refractory OCD persists. Estimates vary and depend on the heterogeneity of the sample (Hollander et al., 2002; van Roessel et al., 2023) and the duration of the study but between 20% to as many as 60% of patients continue to be in remission after 10 years (Bloch et al., 2013). Patients are typically recommended to try two different SSRIs before exploring alternative dopamine antagonists, glutamatergic interventions, and anti-inflammatory interventions, which have safety and side-effect concerns (van Roessel et al., 2023). For culmination of the reasons stated above, investigation into alternative non-pharmacological treatments is rising and brain

stimulation methods are increasingly being regarded as a potential second-line treatment option in OCD patients.

1.3 OCD And Inhibition

There have been a variety of efforts into defining psychopathological mechanisms in OCD which are fundamental to the disorder and do not distinguish between individual obsessions and compulsions. One attempt at this was a few recent studies investigating poor insight as a meaningful measure for severity of disorder to which pharmacological response and task performance can be attributed (Broekhuizen et al., 2023; Catapano et al., 2010; Koch & Rodriguez-Manrique, 2023). Another such ascription is inhibition. As described above obsessions represent recurrent and persistent thoughts or impulses which are perceived by the patients as unwanted, intrusive and hard to inhibit. Compulsions are defined as repetitive behaviours or mental thoughts which patients are unable to inhibit. Hence, a deficit in inhibition is considered as a core psychopathological mechanism of OCD. The deficit is assumed to be relevant for the disorder, independent of the individual symptom profile and to represent a crucial impairment underlying both obsessions and compulsions.

From an experimental perspective, inhibition is the ability to suppress prepotent behavioural responses and is related to goal-directed behaviour which is likewise frequently impaired in the disorder of OCD (Chambers et al., 2009). OCD patients have deficits in tasks of inhibitory control, including motor response inhibition, cognitive inhibition, reflex inhibition and verbal inhibition (Menzies et al., 2008). Additionally, inhibition deficits seem to also be present in paediatric OCD patients, showing it is ubiquitous to the disorder and its reliability as a measure (Britton et al., 2010; Woolley et al., 2008). Neuroimaging studies in OCD patients have linked deficiencies in response inhibition of OCD patients to altered recruitment of CSTC circuits (van Velzen et al., 2014). The hyperactivity in the ACC, OFC and thalamus is hypothesised to be

compensatory for CSTC decreased activity in OCD patients (figure 1) (Maltby et al., 2005). During a variety of inhibition and inference control tasks OCD patients have exhibited altered CSTC connectivity, specifically as decreased activation of the right SMA and preSMA (Fitzgerald et al., 2005; Page et al., 2009; Roth et al., 2007; Rubia et al., 2011; Woolley et al., 2008). However, the literature is not homologous in its observations, some studies exhibited this decreased activation in the left SMA and/or preSMA during inhibition performance (Page et al., 2009; Rubia et al., 2010). De Wit and colleagues (2012) contrarily reported left preSMA hyperactivation in unmedicated OCD patients and their unaffected siblings compared to HCs. Activation values additionally negatively correlated with stop-signal response time (SSRT) in the Stop-signal task. The stop-signal task is displayed in figure 2. Of interest is also the increased activity in the right preSMA only of siblings compared to HCs. Indicating that in OCD patients' activity in the right preSMA was not significantly different from HCs, going against previous study findings. It ought to be noted that OCD patients' and their siblings' SSRTs did not differ from each other in this study. The altered activation in the PreSMA was attributed to compensatory mechanisms, related to neural processing inefficiencies in the preSMA itself. One could reason a genetic predisposition causes preSMA inefficiency, thus manifesting in siblings. Siblings then employ compensatory mechanisms that are no longer attained in the OCD patients.

Differences in preSMA inhibition-activation findings can also be attributed to the specific type of task (van Velzen et al., 2014). There are several inhibition tasks used in studies, including the Stroop task used in our study (figure 2). Additionally, the age, medication status and duration of illness of the sample has an influence (van Velzen et al., 2014). Nonetheless, an extensive meta-analysis has reasserted the ubiquitous inhibition deficits of OCD, as it found patients showed longer SSRTs without a significant difference in mean reaction time (Mar et al., 2022). OCD patients showed impaired task error processing and inhibition performance overall

relative to healthy controls (HCs) (Norman et al., 2019). The meta-analysis additionally found that patients showed hyperactivation of the preSMA, dorsal ACC and anterior lateral PFC (Norman et al., 2019). There is a clear consensus in the literature on the involvement of inhibition deficits in psychopathological mechanisms in OCD. Therefore, inhibition tasks are often utilised as a proxy of disease severity.

Let us examine what inhibition looks like in a healthy brain to better contextualise the OCD studies. Chambers and colleagues (2009) found the IFG and preSMA to be most crucial for response inhibition. There are contrasting studies emphasising the role of either the preSMA (Chambers et al., 2007) or IFG (Floden & Stuss, 2006) in inhibitory function. One study was able to integrate these two standpoints, as it found that fast inhibitors showed increased connectivity between the right IFG and caudate, whereas slow inhibitors showed increased connectivity between the preSMA and right caudate (Jahfari et al., 2011). It is unclear however, if the excitatory influence of the preSMA on the primary motor cortex or the later occurring inhibitory right IFG effect on the primary motor cortex was responsible for interference effects (Jahfari et al., 2011). Sebastian and colleagues (2013) resume that action withholding and action cancellation both recruit IFG and preSMA, while the more "simple" interference inhibition solely recruits IFG activation. In addition Chen and colleagues (2009) found that selectively suppressing the preSMA with TMS showed an increased in SSRT which further argues for its core role in the mechanisms of inhibition. Different brain regions are recruited depending on the specific inhibition task. A simple version of the Go/No-go task will likely show preSMA activity and tasks that require working memory demands are more likely to additionally show right dorsolateral PFC activity (Mostofsky et al., 2003; Simmonds et al., 2008). Our study aimed to encompass a variety of inhibition neural processes and therefore we chose to record both the Stop-signal and Stroop tasks, as depicted on figure 2. Dring the Stop-signal task patients were asked to respond to the direction of the arrow shown. However, in 30% of the

trials a stop signal appears with a delay, which adjusts by ±50 milliseconds depending on the participants' response. In the Stroop task patients are asked to respond to the colour the word is written in and not the colour it spells. The meaning and colour of the word are congruent in 50% of the cases and incongruent in the other 50% of cases. Participants have difficulty shifting between these two conditions.

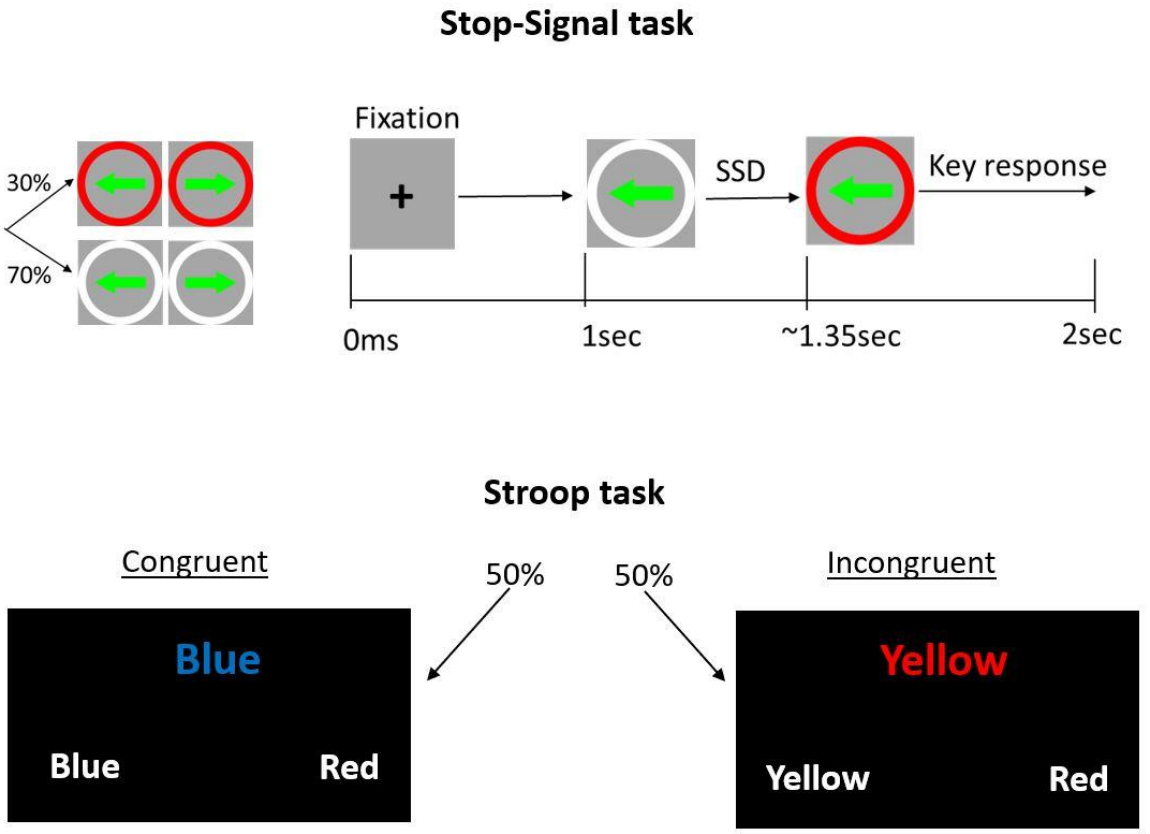


Figure 2: Stop-signal task and Stroop task as performed by OCD patients during the first study.

1.4 Brain Stimulation As An Alternative Therapeutic Tool

Brain stimulation as an alternative therapeutic measure has recently gained a lot of popularity. Improvements in the accuracy of individual white matter tractography mapping and brain surgery navigation have allowed surgeons to target individual fibres when implanting deep brain stimulation electrodes (Haber et al., 2021). The electrode stimulation settings can be

adjusted to hinder maladaptive fibres from firing, successfully relieving symptoms (Visser-Vandewalle et al., 2022). This is a substantial advancement from Jean Talairach's capsulotomy in the 1940s and Lars Leksell's gamma capsulotomy in the 1980s (Leksell et al., 1979; Talairach et al., 1949) which aimed at lesioning maladaptive brain regions or fibres using thermal or gamma knife methods. Both are irreversible and showed efficacy when the right anterior limb of the internal capsule, part of the CSTC pathway was dampened (Lippitz et al., 1999). These methods have also benefited from technological advancements in stereotactic assistance. Regardless, both surgical therapeutic options remain incredibly invasive and are therefore only used in severe refractory OCD.

For the above-mentioned reasons repetitive transcranial magnetic stimulation (rTMS) and transcranial electric stimulation (tES), both safe and non-invasive, have gained popularity in the neuropsychiatric field. TMS elicits hyperpolarisation or depolarisation of surface cortical neurons through short pulsed electric current which create a fast-changing magnetic field. The strength of the electric current is calibrated as the subject-specific motor threshold, where the greatest amplitude and minimum latency of the motor evoked potential can be elicited. The frequency of the pulse among nitric oxide concentration determines whether there is an excitatory (>5 Hz) or inhibitory (<1 Hz) effect in the synapse (Klomjai et al., 2015). The location and duration of the stimulation also influence the effect. rTMS studies in combination with tES studies have contributed to evidence the therapeutic relevance of the sensorimotor network (Xu et al., 2016). The following paragraphs will outline this in more detail.

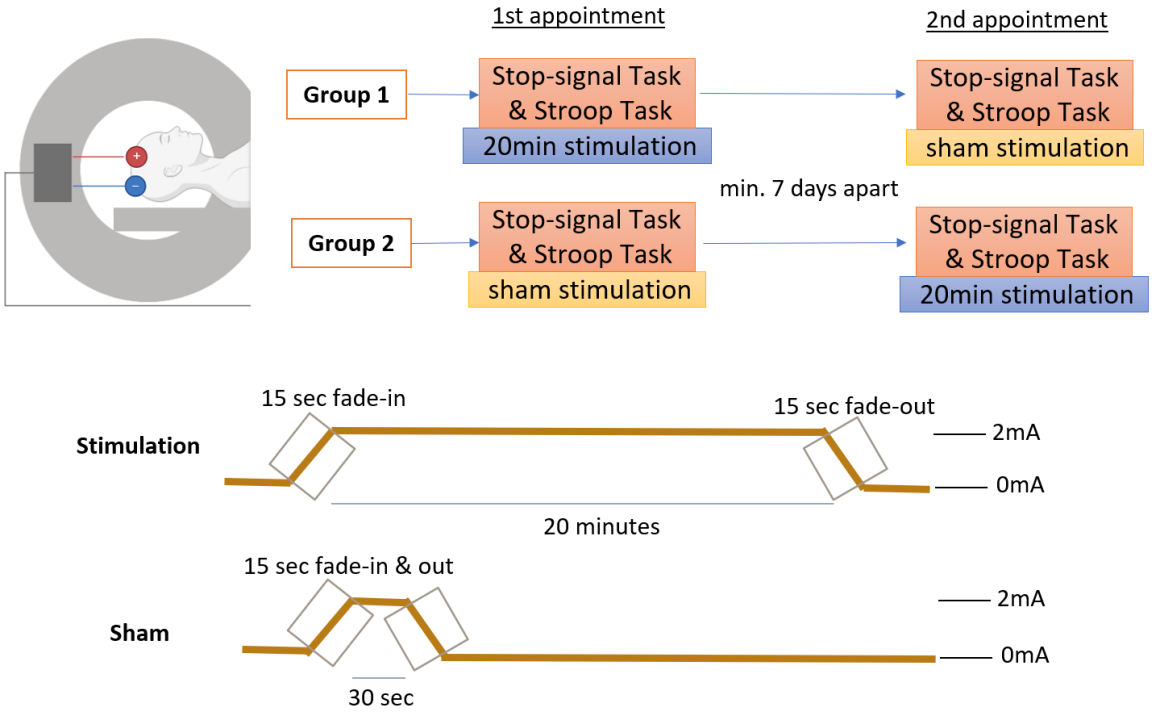


Figure 3: Study design showing the two conditions participants of the first study had to complete. Sec = seconds, min. = minimum.

1.4.1 Transcranial Direct Current Stimulation

Transcranial direct current stimulation (tDCS), one increasingly popular form of tES, contrarily to TMS is not capable of eliciting an evoked potential, as the electric field (EF) it produces is too weak. However, it does modify neuronal membrane polarity and thereby action potential threshold, which has wide-reaching effects (Thair et al., 2017). Two electrodes are placed on the scalp and the current flows from the anode (positive) to the (negative) cathode. Anodal and cathodal tDCS have differing effects, which depend on the brain region being targeted and electric field (EF) produced by the electrodes (Hassanzahraee et al., 2020; Jacobson et al., 2012; Saturnino, Siebner, et al., 2019). Neck, cheek and supraorbital electrode montages have previously been used but are at higher risk of causing skin sensations such as tingling and irritation, as well as cranial muscle pain (Kricheldorff et al., 2022; Paneri et al., 2016). These

sensations are due to increased sensitivity on the face and neck, complicating blinding of the sham condition. These montages have however, also served advantageously to assess tolerability of different current strengths and adverse effects such as skin erythema for the same sensitivity reasons (Woods et al., 2016). Observe figure 3 to examine our sham condition, which had the same current fade in and out settings as stimulation to elicit possible sensations on the scalp.

In recent years the field has published open-sourced pipelines named SimNIBS (Guilherme B Saturnino et al., 2019) and ROAST (Huang et al., 2019) to model the EF distribution and strength using finite element modelling for each TES electrode montage. These packages utilise the individual's structural T1 and T2 images to identify their cortical brain anatomy and project defined electrode positions. On a macroscale the EF is influenced by the placement of the electrodes, the interelectrode distance and the current applied (Laakso et al., 2016). On a microscale neuronal modulation produced by the stimulation is influenced by a larger number of factors: (1) neuronal density and geometry, (2) the alignment of dendrites and axons to the EF, (3) the type and distribution of ion channels in the neurons, (4) the degree of myelination and (5) the density of glia in that region (Arlotti et al., 2012; Rahman et al., 2013; Voroslakos et al., 2018). The quantification of the EF is essential to examine individual tDCS effects and to include EF strength and focality as a possible mediator to better evaluate its influence on tDCS neuronal effects. A growing number of studies are publishing their EF calculations for improved reproducibility (Alizadehgoradel et al., 2024; Hauser et al., 2016; Liebrand et al., 2020; Soleimani et al., 2023). Interindividual EF can vary considerably due to cortical gyri and sulci deciding current flow (Datta et al., 2012). Figure 4 shows how thicker gyri, in the case of the Montreal neurological institute (MNI) 152 template, create higher EF values along the frontal lobe. Furthermore, our study aimed to investigate the effects of skull thickness on stimulation-related preSMA brain activation. Voroslakos and colleagues (2018) measured that

58 ±7% of the current applied at the electrodes was diffused through soft tissue surrounding the head and an additional 16 ±8% diffused through the skull, leaving only a remaining fraction to reach the brain tissue and cerebrospinal fluid (CSF). Nevertheless, calculating the exact fraction of current diffusion at the skull varies depending on the subject and point of stimulation as the skull is made up of spongy bone and compact bone which have differing electrical conductivity (McCann et al., 2019). Current diffusion is often labelled the shunting effect, as it occurs due to current spreading through materials of less resistance/ higher electrical conductivity. Estimations of electrical conductivity in different materials are essential to accurately model the shunting effect, however, methods and results vary. One study incorporated magnetic resonance current-density imaging to map current flow in the brain during stimulation, allowing a better assessment of field changes around CSF filled sulci (Goksu et al., 2021). Saturnino and colleagues (2019). utilised a principled approach to estimate conductivity in different tissues and their impact on the EF, which differed depending on whether TMS, high-definition (HD) tDCS (>2 electrodes) or standard tDCS was applied (Saturnino, Thielscher, et al., 2019). Lastly, another meta-analysis makes the recommendation for pipelines to use their weighted average means calculated from 56 papers (McCann et al., 2019). For this reason, absolute EF strength values (v/m^2) are not comparable across platforms, making reproducibility of exact stimulation conditions in literature incredibly difficult. We considered this in the first manuscript of this dissertation and focused on the ratio between EF values rather than the absolute values.

Studies investigating the effects of several sessions (~ 15-25 sessions across several weeks) of tDCS in OCD provide evidence of a clinical efficacy (Brunelin et al., 2018) despite a large diversity of electrode montages i.e., mainly dorsolateral prefrontal cortex, inferior frontal cortex or preSMA. These studies indicate that tDCS appears to be a promising tool to decrease obsessive-compulsive symptoms. However, none of these studies employed fMRI or additional behavioural tasks to find out more about the neurobiological or behavioural mechanisms

underlying the improvement in symptoms. This motivated our study design to include two concurrent behavioural tasks. Upon calculating the EF for several tDCS montages, the anode at the FC1 and cathode at FC2 were chosen as the most optimal distribution of EF strength and focality across the right preSMA. Figure 4 shows the head model on the MNI standard brain and on the default subject in simNIBS, as this had to be done before recruiting OCD patients. In summary, despite EF strength values only being a proxy for stimulation effects on neurons, we have chosen to combine MR and tDCS to more accurately investigate influences on said effects. This includes reconstructing the EF for all patients and a cross over design allowing a paired comparison between the two conditions (figure 3).

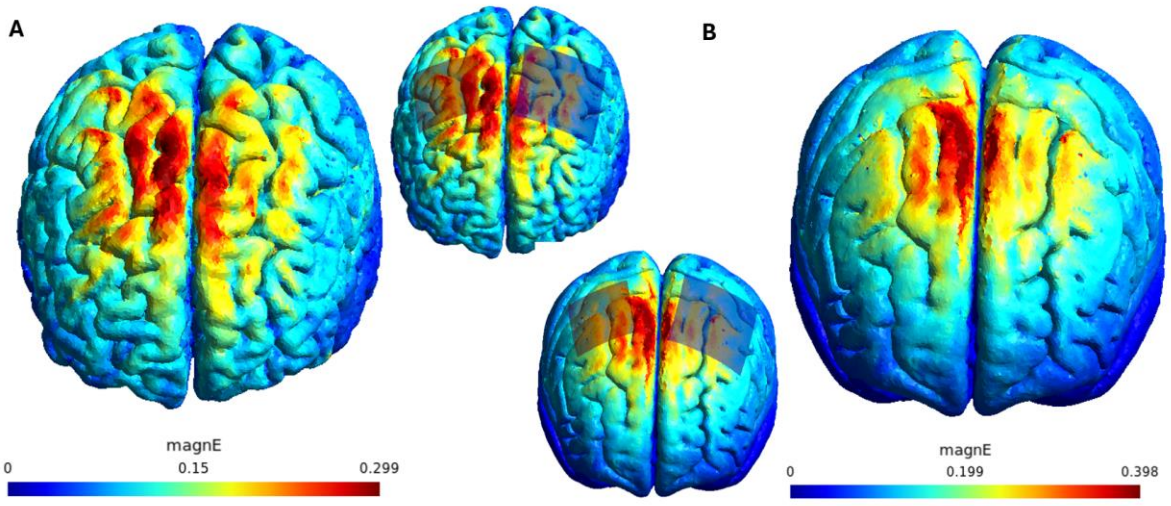


Figure 4: Electric field calculations using SimNIBS for 2mA current with 4x4cm anode at FC1 and 5x5cm cathode at FC2 EEG 10-20 positions. A. shows the EF modelling on the SimNIBS sample subject's T1 and T2 images. B. shows the EF modelling on the MNI152 template. MagnE = Electric field magnitude in V/m.

1.5 Intrinsic Functional Connectivity

Resting-state analyses typically observe either functional connectivity, which usually examines the correlation in the signal between two regions or intrinsic functional connectivity, which examines spontaneous brain activity in the form of low frequency oscillations (LFOs) of the BOLD signal (Fox and Raichle, 2007). The LFOs are within the 0.01-0.08 Hz frequency band and are believed to represent neural excitability. They have additionally demonstrated high replicability (Malinen et al., 2010; Zuo et al., 2010). There is a large amount of evidence showing alterations in LFOs, also when captured through in vivo electrophysiological recordings, and their clinical relevance in OCD, sometimes even predicting treatment efficacy (Welter et al., 2011; Zhang et al., 2023). The second study of this dissertation was designed to contribute to exiting OCD intrinsic functional connectivity literature with a novel measure that had previously not been measured in OCD patients. This measure is comprised of calculating the percentage of BOLD fluctuations relative to the mean signal intensity for that specific voxel (Jia et al., 2020). The BOLD signal is previously filtered to 0.01-0.08 Hz. The measure utilised in our second study is the percentage amplitude of fluctuations (PerAF), calculated as the percentage deviation from the mean signal intensity and then averaged across the whole time series (Jia et al., 2020). We additionally implemented mean PerAF (mPerAF), calculated by dividing the voxel-specific PerAF value by the global mean signal (Jia et al., 2020). There are numerous advantages in comparison to previously employed approaches to capture LFOs, namely amplitude of low frequency fluctuations (ALFF) and fractional ALFF (fALFF). ALFF corresponds to the voxel-specific sum of the power of LFOs. AlFF is thus proportional to the scale of the raw BOLD signal, an improvement which has been implemented in PerAF calculations due to PerAF being a ratio. FALFF is constructed by dividing the sum of the power of LFOs by the sum of power across the entire frequency range and is therefore considered a normalised version of ALFF (Zou et al., 2008). This methodological improvement reduces

fALFF values in areas contaminated with physiological noise, which typically show high power in all frequencies (Kublbock et al., 2014; Meda et al., 2015). However, reproducibility especially regarding sequence acquisition parameters in both ALFF and fALFF is not clear (Huotari et al., 2019; Wu et al., 2011). As mentioned, PerAF has the advantage of being BOLD scale independent. MPerAF additionally is normalised to the subjects' average brain BOLD intensity rather than the average voxel BOLD intensity. This improves group level analysis and reduces false-positive findings which could be related to group acquisition or structural differences.

A large number of studies have reported alterations in spontaneous brain activity in the form of LFOs in patients with OCD. Most of these studies found evidence for alterations within the already discussed CSTS circuitry. The resting state networks most frequently documented to deviate in OCD, are the DMN (Goncalves et al., 2017; Stern et al., 2012), the salience network (Zhu et al., 2016) and the FPN (Stern et al., 2012). This was confirmed in a previous meta-analysis published by my research group, which identified that fronto-striatal deficiencies in OCD lead to impairments in the interaction between the three networks (Gursel et al., 2018). Menon first described the "triple network model" as a way of explaining psychopathology for an array of psychiatric and neurodegenerative disorders (Menon, 2011). The same group had earlier shown the salience network to be responsible for mediating activation between the DMN, crucial for self-referential thoughts and internal processes and the FPN, conversely involved in external goal directed behaviour (Sridharan et al., 2008). As thematised above, OCD patients have a deficiency in switching between internal thoughts and goal-directed behaviour. It is thus congruent that neurobiological pathology of OCD can be described by the triple network model (Bruin et al., 2023). Sridharan and colleagues (2008) found the fronto-insular cortex to be essential for switching in healthy subjects. Therefore, we could expect to see alterations in LFOs in this area during our study comparing OCD patients to HCs.

Gursel et al. (2018) additionally revealed dysconnectivity specifically between frontoparietal regions and the thalamus. Therefore, we could also expect alterations in thalamus intrinsic functional connectivity, also in line with Bruin et al. (2023). They would be in accordance with previously reported structural and functional abnormalities in OCD (Fitzgerald et al., 2000; Perani et al., 1995). Grey matter density alterations have also been found in the thalamus as well as the lenticular nucleus (putamen and GP) of OCD patients (Radua & Mataix-Cols, 2009; Radua et al., 2010; Rotge et al., 2010). This leaves interpretation if structural differences could arise due to underlying changes in neuronal excitability of these areas. Alternatively, they could be a result of OCD-specific altered connectivity within the CSTC circuits, as evidenced by numerous studies (Anticevic et al., 2014; Calza et al., 2019; Harrison et al., 2009). Beucke and colleagues (2013) especially highlight the hyperconnectivity within the OFC and basal ganglia, contrasted to their hypoconnectivity in regards to frontal regions of the CSTC, but with likely compensatory hyperconnectivity to other cortical areas outside of the CSTC circuits. In view of previous findings, differences in neuronal excitability of patients as described by (m)PerAF are expected in areas associated with the salience network and FPN, including the insula, the ACC, the medial frontal cortex but also as mentioned within the OFC and striatum. Given the methodological benefits of this relatively new measure (i.e., perAF and mperAF) the detected differences might even be more distinct than reported in these earlier studies.

Finally, intrinsic functional connectivity has also shown to predict inhibition performance and the ability of tDCS to improve these deficiencies. One study found that an increased functional connectivity between the IFG and the preSMA in OCD was correlated with longer SSRT (Tomiyama et al., 2022). A recent study was able to show that after 20 sessions of tDCS, functional connectivity increased between the sensorimotor network and the DMN after treatment (Echevarria et al., 2024). Additionally, specifically the connectivity between the precuneus and the sensorimotor areas was positively correlated with Y-BOCS score

improvement after tDCS. If our study finds the expected alterations in intrinsic functional connectivity in areas of the sensorimotor network such as the precentral, postcentral gyrus, the SMA, preSMA or the other subcortical structures (putamen, caudate nucleus, thalamus) (van den Heuvel et al., 2016), this would strengthen the usefulness or even necessity for targeting the sensorimotor network with tDCS. This comes in addition to its already evidenced role in habitual behaviours, including compulsions in OCD (Bruin et al., 2023; Shephard et al., 2021; van den Heuvel et al., 2016). Such findings would moreover be an indication to extend the focus that lies currently mainly on the triple network model to focus towards sensorimotor network and DMN interplay in OCD pathology.

1.6 Main Aims And Scope

This dissertation project aims to enhance existing literature on the neuronal correlates of OCD using novel methods and reducing bias through whole-brain analysis. It set out to accomplish this by conducting the first concurrent task fMRI tDCS stimulation study in OCD patients. Additionally, it is the first to utilise (m)PerAF as spontaneous brain activity parameters to distinguish between HC and OCD patients. The results and methods used in this dissertation could provide guidance for future long-term studies looking to validate tDCS therapeutic effects. TES as an effective non-invasive intervention, could drastically improve quality of life for the large percentage of OCD patients that do not respond to first-line treatment options.

Project 1: tDCS induced activation and performance differences during inhibition performance.

The first project aimed to implement a concurrent tDCS-fMRI design where patients would perform two inhibition tasks, each lasting 10 minutes, in the scanner while receiving either 20 minutes of tDCS or only a 30 second stimulation as sham. Patients received both conditions with on average one week apart in a randomized order. The study set out to answer whether tCDS would improve response inhibition of patients in the Stroop and Stop-signal task (results

not part of the current thesis). Furthermore, we tested whether tDCS compared to sham would increase activation during inhibition in the preSMA and vmPFC. Finally, the study also examined if the expected BOLD signal increase would be correlated with an improvement in response inhibition. Instrumental for the implementation of tDCS as an intervention is also categorising whether its efficacy is EF strength dependent so long-term studies can better design their trials.

Project 2: (M)PerAF as a new approach for measuring spontaneous brain activity in OCD.

Given previous studies reporting significant alterations in low frequency oscillations and their association with tDCS effects, the second project aimed to investigate differences in low frequency oscillations between OCD patients and HCs, as measured by percentage amplitude of fluctuation (PerAF) and the further normalised measure (mPerAF). PerAF calculates the percentage of BOLD fluctuations compared to the mean signal and averages this across the whole time series for that voxel. PerAF can additionally be averaged by dividing it by the global mean, i.e. mean PerAF (mPerAF), which has been shown to have better test-retest reliability. PerAF has been proposed as an innovative and scale-independent method for investigating spontaneous brain activity. This is in part as PerAF is not proportional to the scale of the BOLD signal. The data for this study were acquired during a separate PhD project to the one described above, using different fMRI sequences. The whole-brain analysis aimed to test whether expected reduction in spontaneous brain activity in CSTC circuit related areas, including the thalamus, the vmPFC, the ACC and basal ganglia structures were reproducible. In addition we wanted to test for hypothesised compensatory alterations of spontaneous brain activity in the preSMA and IFG.

2.0 Manuscript 1: Investigating the effects of brain stimulation on the neural substrates of inhibition in patients with OCD: A simultaneous tDCS – fMRI study

Daniela Rodriguez Manrique*[1,2,3], Hanyang Ruan [1,2], Chelsea Winkelmann [1,2], Julian Haun [1,2], Götz Berberich[4], Claus Zimmer [1], Kathrin Koch[1,2]

1 Department of Diagnostic and Interventional Neuroradiology, School of Medicine, Technical University of Munich, Munich, Germany

2 Neuroimaging Centre (TUM-NIC), Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

3 Graduate School of Systemic Neurosciences, Ludwig Maximilians University Munich, Martinsried, Germany

4 Windach Institute and Hospital of Neurobehavioural Research and Therapy (WINTR), Windach, Germany

ABSTRACT

Inhibition deficits constitute a core characteristic of obsessive-compulsive disorder (OCD). There is evidence in healthy individuals that transcranial direct current stimulation (tDCS) of the pre-supplementary motor area (preSMA) leads to a significantly improved inhibition performance. Against this background we investigated the effects of preSMA tDCS on inhibition performance and the underlying neural correlates in patients with OCD. Using a double-blind, randomized, sham-controlled, cross-over design (i.e., tDCS sham vs. tDCS stimulation) we investigated the effects of 2mA anodal tDCS stimulation of the right preSMA in a sample of 46 OCD patients. The present study is, to our best knowledge, the first study applying concurrent tDCS-fMRI in patients with OCD. tDCS was applied using the MRI-compatible NeuroConn DC-Stimulator which allowed for a concurrent stimulation, while patients performed an inhibition (i.e., Stroop) task in a 3 T MRI. Imaging data were analysed using a multivariate partial least squares (PLS) approach. tDCS stimulation (vs. sham) was associated with increased activation in a fronto-parieto-cerebellar network comprising, amongst

others, the precentral, middle frontal and inferior frontal gyrus, the anterior cingulate and the superior parietal lobe. On the performance level, tDCS stimulation (vs. sham) was linked to an improved inhibition performance in terms of an increased percentage of correct responses in the Stroop task. Present results indicate that tDCS in patients with OCD goes along with an improved inhibition performance as well as activation increases in regions known to be involved in inhibition, motor, and cognitive control. Thus, our findings suggest that tDCS might be a promising method to improve specific impairments in OCD.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a debilitating psychiatric disorder affecting 1% of the general population (Kessler et al., 2012). It is characterized by time-consuming obsessions (i.e., repetitive intrusive thoughts) and compulsions (i.e., repetitive behaviours that serve to counteract anxiety caused by obsessive thoughts). One major characteristic of OCD is an impaired response inhibition as measured by, for instance, the Stroop or the stop-signal task (SST) (Abramovitch et al., 2013; Lipszyc & Schachar, 2010; Mar et al., 2022). In successful response inhibition one manages to inhibit a specific automatic process (such as, in case of the Stroop task, reading the name of a colour word shown in a colour different from the word or, in case of the SST, performing a motor action in response to the appearance of a stop signal). Problems with inhibition are self-evident in the phenomenology of OCD since patients are obviously unable to properly inhibit their obsessions and compulsions. Accordingly, OCD patients have repeatedly been shown to be impaired in their inhibition performance by demonstrating an increased response time and/or percentage of errors during the Stroop incongruent condition (i.e., when word reading has to be inhibited) (Bannon et al., 2002; Schlosser et al., 2010; Zhang et al., 2015) or an elevated stop-signal reaction time in the SST (Mar et al., 2022; McLaughlin et al., 2016).

In the healthy brain, response inhibition has been linked to increased activation in a network of regions comprising mainly the presupplementary motor area (preSMA), the motor cortex including the precentral gyrus, the dorsolateral prefrontal cortex (DLPFC), the medial prefrontal cortex (mPFC), the subthalamic nucleus, the posterior parietal cortex (PPC) and the right inferior frontal gyrus (IFG) (Li et al., 2006; Sharp et al., 2010; Zandbelt et al., 2013). Previous studies also reported high activation of IFG (Aron et al., 2007) and pre-SMA (Chao et al., 2009) to be related to good performance on the SST in healthy subjects. In addition, a recent activation likelihood estimation meta-analysis investigating brain activation in association with inhibition performance in the Stroop task (Huang et al., 2020) pointed at the involvement of a network containing the right cingulate cortex, the left dorsolateral prefrontal cortex, bilateral inferior frontal gyri, the right superior frontal gyrus and the temporal cortex.

Interestingly, the regions found to be altered in OCD patients in association with inhibition performance are only partly overlapping with those regions found to be relevant for inhibition in healthy subjects. Thus, Norman et al. (2019) who performed a large meta-analysis on the neural substrates of error processing and inhibitory control comprising data from 239 OCD patients and 229 healthy control subjects found inhibition-related hypoactivation in OCD in the rostral and ventral anterior cingulate cortices, the thalamus/caudate, the anterior insula/frontal operculum, the supramarginal gyrus, and the medial orbitofrontal cortex in association with longer inhibitory control reaction times. Single studies, however, provided also some evidence for a decreased inhibition-related activation in, amongst others, the preSMA, the thalamus, the orbitofrontal cortex, the IFG and the striatum in OCD (Page et al., 2009; Roth et al., 2007; van Velzen et al., 2014; Woolley et al., 2008), but also for an increased activation of pre-SMA in association with reduced activation of the IFG (de Wit et al., 2012).

Studies in healthy controls indicate that transcranial direct current stimulation (tDCS), a non-invasive brain stimulation treatment that uses direct electrical currents to stimulate specific

parts of the brain, might be an effective technique to improve specific cognitive processes including inhibition performance (Narmashiri & Akbari, 2023; Yu et al., 2015). In healthy controls, tDCS of the preSMA has been found to increase inhibition performance in terms of an improvement in inhibiting responses when a stop signal was presented in the SST task (Hsu et al., 2011) as well as in terms of an increased stopping speed along with an increased blood-oxygen level dependent (BOLD) response in the preSMA and ventromedial prefrontal cortex (vmPFC) (Yu et al., 2015).

Surprisingly, comparable studies in OCD have – to our best knowledge - not been performed, up to now. Against this background, in the current study we employed an MRI-compatible tDCS device in a sample of patients suffering from OCD to stimulate the brain while patients were performing the Stroop inhibition task in the MRI. Given the relevance of the preSMA for inhibition performance we chose the right preSMA as the main target of anodal stimulation. In addition, given previous studies showing that intensity of the stimulation effects (i.e., electric field strength) and individual brain anatomy are critical determinants of the final stimulation effects (Antonenko et al., 2021; Arlotti et al., 2012; Datta et al., 2012; Opitz et al., 2015; Russell et al., 2013), we investigated potential effects of these parameters in the framework of a mediation analysis (for more details please refer to the methods section).

Imaging data were analysed using an event-related approach with partial least squares (PLS) (McIntosh et al., 1996), a multivariate analysis technique that identifies whole-brain patterns of covariance related to the experimental design. PLS uses singular value decomposition to classify the fMRI data into orthogonal latent variables (LVs) explaining the maximum amount of covariance between the task conditions and the fMRI signal.

In contrast to the classical mass univariate approach which compares activity independently at each voxel, PLS relies on activity patterns from several voxels. Since PLS is sensitive to magnitude of spatial variability in activation and allows for testing how distributed patterns of

BOLD activation across multiple voxels relate to experimental variables, it is often more powerful than the classical univariate approach (Davis et al., 2014; Norman et al., 2006). Moreover, and even more importantly, PLS is insensitive to interindividual variability in mean brain activation (Davis et al., 2014). Given the well-known clinical heterogeneity of OCD and its associated variability in neural activation, there is strong reason to assume the presence of a high interindividual variability in mean brain activation in our patient sample. For the purpose of neutralising the effects of this interindividual variability (which is known to impact detection power also in the context of within-subject designs) we opted for employing the PLS method instead of the classical univariate approach. We expected anodal tDCS over the preSMA to be associated with both a stimulation-related improvement in inhibition performance as well as an increased activation in regions shown to be relevant for inhibition, such as the preSMA and the IFG.

This study set out to study two hypotheses: (1) tDCs as compared to sham stimulation will be associated with a significant improvement in response inhibition and (2) tDCS as compared to sham stimulation will be associated with an increased activation during inhibition in preSMA and vmPFC. The increased activation will be correlated with an improvement in response inhibition.

METHODS

Participants

A total of n = 47 patients with OCD as the primary diagnosis according to DSM-5 criteria were included in the study. Of the 54 patients originally recruited, 7 patients were excluded due to study drop-out (1), major artefacts (2), impedance exceedance (2), button-box malfunction (1) task incompletion (1). Furthermore, one participant was excluded from the field strength analysis, as their T1 hindered the calculations. Adequate power was measured considering

studies measuring tDCS effects on Stroop inhibition performance on healthy participants, as there were no studies in OCD patients with comparable design. The necessary sample size was calculated (based on a paired t-test given medium effect sizes of 0.5 – 0.6). Given a sample size of 39 – 54 participants, medium size effects (0.5 – 0.6) can be detected with a reasonable power of 0.95. Based on these considerations, our sample size of 46 patients seems to be adequate. One patient was excluded from all electric field (EF) and skull thickness related analysis, because he did not have session specific T1 images (there was an export issue with their session two T1). Recruitment took place at several hospitals in and around Munich including the Psychosomatic Clinic in Windach, the Tagesklinik Westend, the Psychiatry at the LMU Clinic and the Schön Klinik Roseneck. All diagnoses were made by an experienced psychiatrist from the respective hospital specialized in the treatment of OCD. Inclusion criteria comprised right-handedness, age 18-65 years, at least a score of 8 in the Y-BOCS scale, willingness, and ability to provide consent and 8 weeks of stable medication/non-medication treatment. Exclusion criteria encompassed neurological disorders (including epilepsy, seizures), psychiatric comorbidities (incl.., schizophrenia, schizo-affective disorder, bipolar disorder, substance abuse, PTSD, and personality disorders), incompatibility with MRI scanners (e.g., intracranial implants, pacemakers, or defibrillators), pregnancy, any additional psychopharmacological medication (e.g. antipsychotic medication) and benzodiazepine intake within 24 hrs of either appointment.

Patients had a mean age of 31.4 (table 1). n = 14 patients were drug-naive or medication-free for at least 8weeks. No patients were excluded due to comorbidities and n = 32 patients had one or more comorbid diagnoses. To assess clinical severity of obsessive-compulsive symptoms, patients filled out the self-rated version of the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989) as well as the Y-BOCS checklist. In addition, the Hamilton Depression Rating Scale (HAMD-D) (Hamilton, 1960) was used to assess depressive and the

Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) was employed to assess anxiety symptoms. Potential tDCS side-effects were assessed by standardized questionnaires immediately after the tDCS-MRI session (table S1). The present study was approved by the Ethics Committee of the Klinikum rechts der Isar in München and it was in accordance with the Declaration of Helsinki and was registered under https://www.isrctn.com/ISRCTN99571476. All participants gave their informed consent to the study.

Image Acquisition

Image acquisition was conducted on a 3 T Philips Ingenia (Philips Healthcare, Best, the Netherlands) using a 32-channel (SENSE) head coil. Imaging consisted of a T1-weighted 3D MPRAGE sequence (230 slices, sagittal orientation, 368 x 317 matrix, 0.7 mm isotropic resolution, TR = 11 ms, TE = 5.2 ms, flip angle = 8°), and a T2*-weighted echo-planar imaging (EPI) imaging sequence (TR = 1000 ms, TE = 30 ms, flip angle = 60°, MB factor = 2, matrix size = 64 x 62, field of view = 192 x 192 x 118.5 mm, 64 transverse slices, 3.0 mm slice thickness, whole brain coverage, 3 x 3 x 3 mm^3 resolution). A series of 660 whole-brain volumes was recorded. In addition, a DTI sequence, another T2* sequence, a resting state fMRI sequence and a FLAIR sequence were acquired in the same imaging session.

Study Design and Paradigm

The study was conducted at the Klinikum rechts der Isar, and had a double-blind, randomized, sham-controlled, cross-over design (tDCS sham vs. tDCS stimulation). Randomisation was performed before study initiation, assigning each participant number its group/condition order. Each patient participated in the study on two distinct days, separated by a 7-day interval to avoid any potential carryover effects. Prior to both tDCS-MRI sessions, patients completed a consent form and a comprehensive questionnaire outlining inclusion/exclusion criteria.

All patients underwent a total of around 50-60 minutes of MRI scanning. The Stroop task was started after the Stop-Signal task, each lasting around 10 minutes, therefore encompassing the entire tDCS stimulation (or tDCS sham stimulation) duration.

The Stroop task was presented in an event-related design and consisted of a congruent and an incongruent condition. In the congruent condition, colour words were presented in the colour denoted by the corresponding word while in the incongruent condition colour words were displayed in one of three colours not denoted by the word. The target stimulus was presented in the centre of the display screen. Two possible answers were presented below, and patients had to indicate the colour by pressing one of two buttons. Stimuli were presented in 48 congruent and 48 incongruent combinations of four colour words ‘‘red,’’ ‘‘green,’’ ‘‘yellow,’’ and ‘‘blue’’ written in the German language and corresponding colours were presented in a pseudorandom sequence. Stimulus presentation time was 1500 ms with a randomised interstimulus interval of between 0.5 s and 4 s with a mean of 1 s. The Stroop task was implemented using Psychopy running on a PC which was connected to a video projector. The stimuli were projected on to a transparent screen inside of the scanner tunnel which could be viewed by the subject through a mirror system mounted on top of the MRI head coil.

tDCS

The tDCS device that we employed in the current study was the MRI-compatible NeuroConn DC-Stimulator (https://www.neurocaregroup.com/de/technologie/dc-stimulator). To ensure both methodological accuracy (e.g., low impedance) and safety of stimulation application, the experimental set-up inside and outside the scanner was tested extensively, examined by our in-house physicist as well as experts from NeuroConn and adhered strictly to the guidelines provided. For electrode placement optimization targeting the preSMA, we employed electrical field calculations using SimNIBS (http://www.simnibs.org). The optimal electrode placement

for stimulating the preSMA was determined using an EEG 10-20 cap. The anodal stimulation site was located over the centre point of the FC1 with a 3x3 rubber electrode; the cathode was placed over the centre 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. The tDCS was configured at a current of 2 mA, with a fade-in and fade-out duration of 15s, and variable stimulation duration of either 30 s (sham condition) or 1200 s (stimulation condition). Impedance was maintained below 15 ohms once the 2mA threshold was reached.

Data analysis

Performance in the Stroop task was analysed using SPSS 28.0.0.1 (https://www.ibm.com/de-de/products/spss-statistics). To investigate potential performance differences between the two conditions (i.e., Stroop inhibition performance during tDCS stimulation vs. Stroop inhibition performance during tDCS sham) we performed two non-parametric paired Wilcoxon tests for percentage of correct responses (incongruent condition – congruent condition) and mean response times (incongruent condition – congruent condition). Non-parametric tests were employed since data were not normally distributed.

fMRI preprocessing and analysis

47 patients with OCD were included in the analysis upon excluding participants whose task performance values were outliers. fMRI data were preprocessed using SPM 12. Realignment of images of a functional time series was completed to account for in-scanner head motion. Data was then normalised to a standard template in Montreal Neurological Institute space. This included coregistration, CAT12 segmentation, creation of a DARTEL template based on tissue probability maps and normalisation by DARTEL. Signal to noise ratio was increased by applying a 6 x 6 x 6 kernel gaussian filter. A band-pass filer 0.01-0.08 (or 0.1 Hz) was also

applied to the data to remove the frequencies which are not of interest such as noise related to scanner drift, coils, cardiac noise etc. Excessive head motion was established with framewise displacement (FD), calculated as the sum of the absolute values of the derivatives of the 6 motion parameters derived from SPM12 (Power et al., 2012).

Partial Least Squares Analysis

The imaging data recorded during the Stroop task were analysed using a non-rotated event-related partial least squares approach (McIntosh et al., 2004). This multivariate analysis technique identifies whole-brain patterns of covariance related to conditions of an experiment. Each brain voxel has a weight, referred to as salience, which specifies how strongly the voxel contributes to the covariance explained by a so-called latent variable (LV). Each LV contains a pair of vectors relating brain activity and experimental design. In the mean-centred event-related PLS, LVs highlight the dominant patterns of cross-covariance between the fMRI data and task conditions within the mean-centred matrix decomposed with singular value decomposition. For the non-rotated version of the PLS, one examines patterns exclusive to a specific contrast of conditions.

The LVs were determined with a permutation test using 2000 permutations, each event had a temporal window size of 14 time-points (i.e., equivalent to 14 seconds) post-stimulus onset, called lags. Permutation tests assesses whether the effect represented in each LV can statistically be differentiated from noise. LVs consist of three components: cross-block variance, singular values describing the proportion of covariance of each LV; design-saliences which display the difference between tasks across groups and time and brain saliences, with weights assigned to each voxel at each lag. PLS additionally calculates temporal brain scores which are subject, design-salience, lag and LV specific. These are calculated as the dot product of design-saliences and the subjects' singular brain activity (Krishnan et al., 2011). To answer our hypothesis on

the effect of tDCS on the inhibition (incongruent) condition, we contrasted between task conditions (i.e., incongruent > congruent) and timepoints (tDCS > sham).

Furthermore, the reliability of each voxel's contribution to a particular LV was tested by submitting all saliences to a bootstrap estimation of the standard errors (SEs), using 2,000 bootstraps. The bootstrap ratio (BSR) is calculated by dividing salience by the SE. Reported are peak voxels with a salience/SE ratio ≥3.0 or ≤-3 for negative correlations ($p < .001$), analogously to z-values ±3, therefore a confidence interval of >99% if the bootstrap distribution is normal (Bellec et al., 2008; Efron, 1981; Krishnan et al., 2011; McIntosh & Misic, 2013; Samson et al., 2023). For the one-sample t-test differentiating between conditions, however, a stricter salience/SE ratio of ≥5.0 or ≤-5 was chosen (Samson et al., 2023). This paper reports the peak coordinates from time lags at which the temporal brains score profiles maximally differentiate (lag 6, see figure 3) (Addis et al., 2004; McIntosh et al., 2004) with a spatial extent threshold of 100 voxels. Of note, lag 6 (i.e., 6 seconds post stimulus) corresponds to the canonical model of the haemodynamic response function resembling a gamma function peaking at 5 to 6 seconds following neuronal activation (see supplementary figure S3) (Bush & Cisler, 2013; Wink et al., 2008). Results based on lags 5, 7 and 8 are reported in the supplementary material. The figures were created using ITK-SNAP and ParaView programs (Madan, 2015; Yushkevich et al., 2006).

Electric Field Modelling

The EF on the grey matter was calculated to quantitively assess the variation in dosage between sessions and subjects. The software SimNIBS was used to calculate the EF induced by individual tDCS set-up (charm — SimNIBS documentation). The exact centre coordinates and orientation of the underlying electrode gel were visible on the T1 images and identified using the regionprops MATLAB function. Individual patient T1 and T2-weighted images were segmented and meshed to create tetrahedral head models using SimNIBS: charm (Puonti et al.,

2020). SimNIBS assigns isotropic conductivity values for the fifteen different head tissues assigned in the head models. The two above mentioned electrode rectangular sizes were simulated, with an electrode thickness of 2mm and a stimulation intensity of -2mA at the anode and 2mA at the cathode. The EF strength and focality were extracted from the individual grey matter region with field strengths higher than the 99.9th percentile (for an illustration of these parameters see supplementary figure S1). MNI coordinates [-6, 11, 60] with a 10mm radius were selected as the ROI for the preSMA, according to the HMAT atlas (Mayka et al., 2006). This allowed the calculation of the mean EF intensity at the ROI with the SimNIBS python package. The mean EF intensity was measured identically for an additional 33 ROIs taken from the Desikan-Killiany-Tourville Atlas (Alexander et al., 2019) (figure 5). Figure 5 was created using python seaborn.clustermap. The cortical surface of each subject was reconstructed using FreeSurfer software with automatic "recon -all" pipeline (version 7.4.0; https://surfer.nmr.mgh.harvard.edu/). This process includes the predefined steps: bias correlation, skull stripping, tissue intensity normalization, Talairach system transformation, and segmentation of grey/white matter. No manual corrections were performed. Subsequently, we extracted the thickness data of the preSMA in both hemispheres, as defined by the HMAT atlas (Mayka et al., 2006).

Mediation analysis

Finally, to investigate the potential influence of the two influencing factors that are known to affect individual tDCS stimulation effects, i.e. EF strength and skull thickness (for details regarding thickness calculation please refer to the supplement), we performed a mediation analysis to assess potential effects of these influencing factors on stimulation-related changes in inhibition performance. Since there were no significant stimulation-related changes in mean response times (see results section), the mediation analysis was performed only for the percentage of correct responses (% correct). Thus, the stimulation-related change in the

percentage of correct responses (i.e., % correct congruent-incongruent for stimulation-sham) constituted the dependent variable, stimulation-related changes in the inhibition-associated brain activation during the Stroop incongruent condition (i.e., PLS brain scores for the incongruent condition for stimulation-sham) the independent variable and EF the mediating variable. Another analogue model was set up with thickness of our anodal stimulation region (i.e., right preSMA) as mediating variable. Using these models, we aimed at investigating both a potential indirect (i.e., mediated via EF strength or right preSMA thickness) effect of stimulation-related brain activation on stimulation-related inhibition performance as well as a potential direct effect of EF strength or right preSMA thickness on stimulation-related inhibition performance. Structural equation modelling was performed using the program Amos 26.0.0 (http://amosdevelopment.com) applying a maximum-likelihood algorithm for estimating path coefficients. We used bootstrapping procedures which make no a priori assumptions about the distribution of the paths. The goodness of fit index (GFI) was used to assess the goodness-of-fit of the two models. Collinearity between brain activation and EF strength (or, respectively, preSMA thickness) was checked using linear regression. This yielded no significant results indicating a statistically negligible collinearity between the two variables.

RESULTS

Category	Description
Sex (male/female)	(32/14)
Age (mean, SD)	(31.4, 11.2)
Duration of illness (mean, SD)	(15.6, 10.5)
Medication (yes/no)	(32/14)
Y-BOCS total (mean, SD)	(20.2, 5.6)
Y-BOCS obsessions (mean, SD)	(10.0, 3.1)
Y-BOCS compulsions (mean, SD)	(10.2, 3.)
Comorbidity (yes/no)	(32/14)

HAM-D (mean, SD)	(19.9, 9.6)
HAM-A (mean, SD)	(19.9, 9.9)
tDCS side effects	See supplementary table S1

Table 1. *Demographic and clinical data of patients (n=46).*

Performance data

The paired Wilcoxon test for the percentage of correct responses (incongruent condition – congruent condition) yielded a significant result (z=2.28, n=46, p=0.02) indicating a significantly larger percentage of correct responses for the stimulation condition. The paired Wilcoxon test for the mean response times (incongruent condition – congruent condition) yielded no significant result (z=1.19, n=46, n.s.).

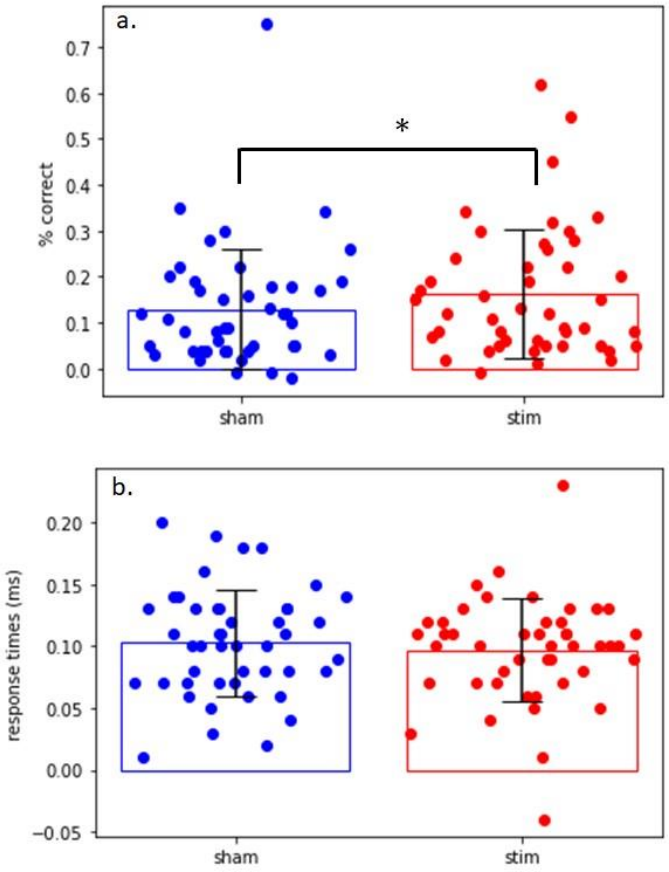


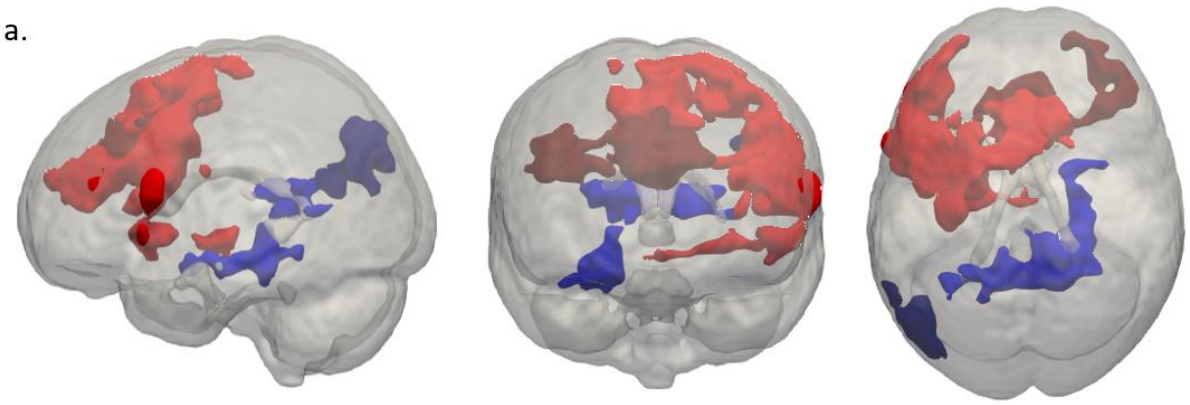
Figure 1*. Inhibition performance outlined as % correct trials and response time in milliseconds. A non-parametric paired Wilcoxon signed-rank test was performed between the two conditions.*

Imaging data

Condition effects. A mean-centred non-rotated PLS was performed to examine, in a first step, the condition effects comparing incongruent vs. congruent trials, independent of timepoint (i.e., stimulation condition). The PLS found a significant condition-LV ($p<0.001$), where the incongruent condition of both timepoints had positive brain scores, indicating a greater activity for the incongruent condition (shown in red in the singular image of lag 6, figure 2). The congruent conditions had negative brain scores, which were significantly different to the incongruent condition ($p<0.05$), thus indicating that for the congruent condition activity was greater in the negative brain salience regions (shown in blue in the singular image of lag 6, figure 2). Figure 2p illustrating activation across the different lags shows, for our condition of interest (i.e., incongruent condition), largest activation for lag 6.

Figure 2. Condition effects, lag 6

a.



x	y	z	BSR	Appro.P	Cluster Size	Location
Positive Salience Regions						
-50	12	26	5.7371	0.0000	6346	inferior frontal gyrus, precentral gyrus
8	22	34	5.2192	0.0000	2628	paracingulate gyrus, cingulate gyrus (anterior)

Negative Salience Regions						
22	-34	-20	-5.9242	0.0000	2281	parahippocampal gyrus (posterior), temporal fusiform cortex (posterior)
-44	-78	34	-5.4345	0.0000	811	middle occipital gyrus

b.

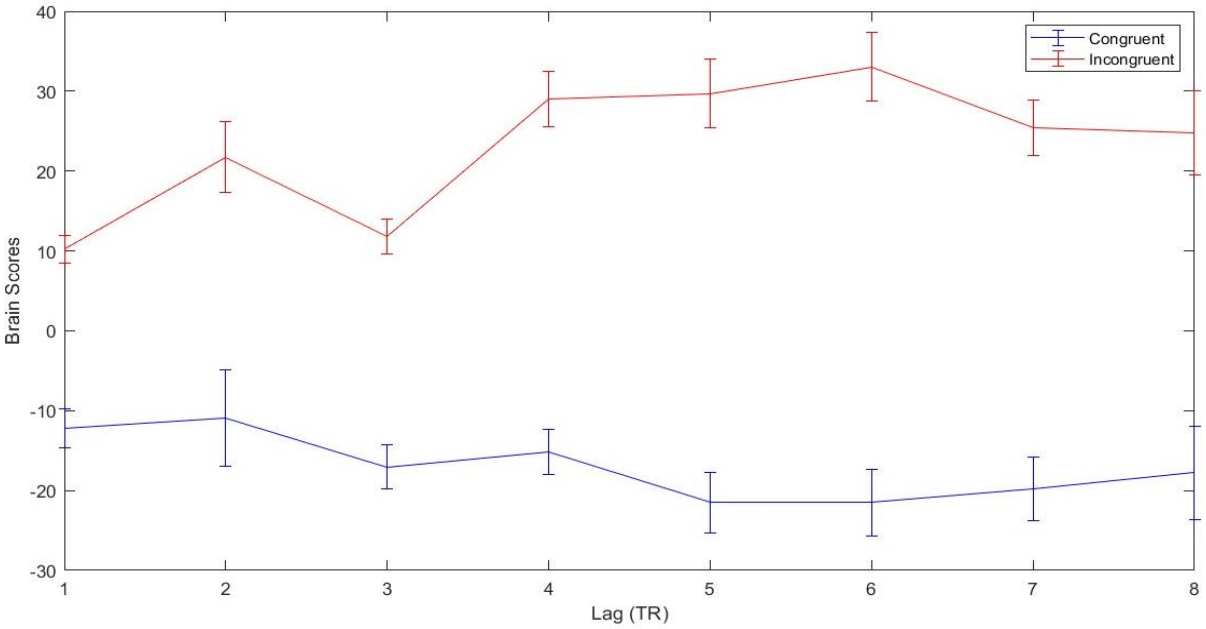
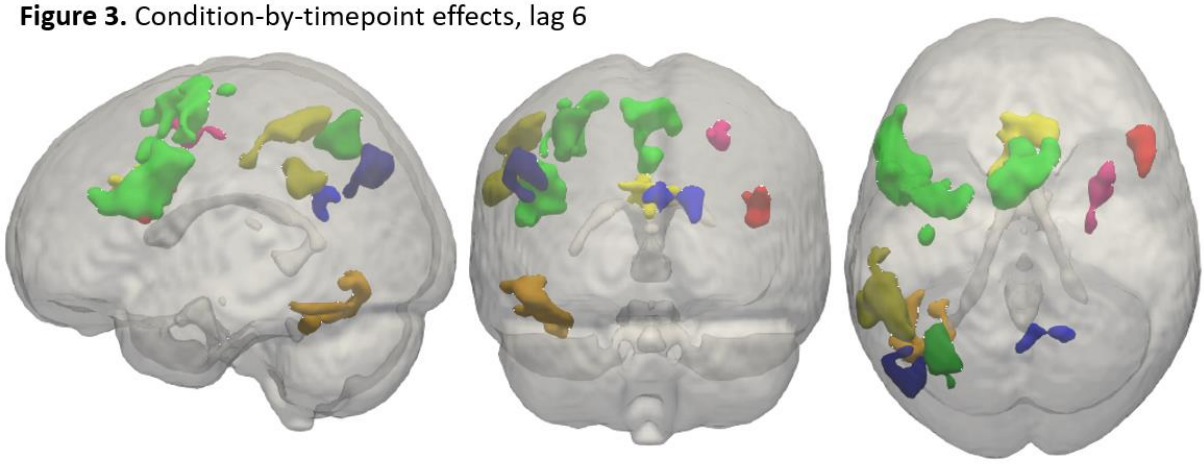


Figure 2. *Condition Effects A. Clusters where peak voxels have a salience/standard error ratio (i.e. Bootstrap ratio; BSR) of ≥5 or ≤-5 for the latent variable (LV) describing 100% of all the variance for our desired contrast comparing incongruent > congruent. Red clusters indicate increased activation for the incongruent condition, blue clusters illustrate increased activation for the congruent condition. Lag 6 represents the brain activity at 6 TRs post stimulus onset (i.e., 6 seconds post stimulus given our sequence with a TR of 1 second). B. Temporal brain scores plot displaying the mean brain scores and standard deviation across all 46 subjects for each condition during the first 8 TRs post stimulus onset. Brain scores are subject, design-salience, lag and LV contrast specific. Note the positive and negative peaks are at around 5-6 seconds after stimulus onset.*

Condition-by-timepoint effects. To answer our main research question (i.e., how tDCS stimulation affects brain activation patterns during inhibition performance), in a second step, the interaction between condition (i.e., incongruent > congruent) and timepoint (i.e., tDCS > sham) was investigated. The PLS found a significant interaction-LV ($p<0.034$) with positive brain scores for stimulation-incongruent and sham-congruent conditions, indicating increased activation during tDCS compared to sham for the incongruent compared to the congruent condition (figure 3). The opposite contrast (i.e., increased activation during sham compared to tDCS) did not display any significant results.

Figure 3. Condition-by-timepoint effects, lag 6



x	y	z	BSR	Appro.P	Cluster Size	Location
Positive Salience Regions						
-32	-2	54	5.911	0.0000	1781	middle frontal gyrus, precentral gyrus
-58	-42	28	5.2458	0.0000	582	supramarginal gyrus (posterior), parietal operculum cortex
-36	-46	-30	5.1341	0.0000	390	cerebellum left VI and left Crus I
48	22	18	4.7996	0.0000	216	inferior frontal gyrus (pars opercularis & pars triangularis)
4	26	26	4.6234	0.0000	409	cingulate gyrus (anterior), parcingulate gyrus
-32	-54	46	4.5217	0.0000	297	superior parietal lobule, angular gyrus

30	0	50	4.1581	0.0000	152	middle frontal gyrus, precentral gyrus
Negative Salience Regions						
-48	-70	38	-4.9701	0.0000	230	angular gyrus
18	-54	18	-3.8626	0.0001	160	precuneous cortex, supracalcarine cortex

Figure 3. *Condition-by-timepoint effects Clusters where peak voxels have a salience/standard error ratio (i.e. Bootstrap ratio; BSR) of ≥3 or ≤-3 ($p<0.001$) for the latent variable (LV) describing 100% of all the variance for our desired contrast comparing conditions and timepoints. Yellow, green, red and pink clusters (i.e., positive salience regions) indicate increased activation during tDCS compared to sham for the incongruent compared to the congruent condition. Blue clusters (i.e., negative salience regions) illustrate increased activation for the opposite contrast (i.e., increased activation during sham compared to tDCS for the incongruent compared to the congruent condition). Lag 6 represents the brain activity at 6 TRs post stimulus onset (this sequence had a TR of 1s). n=47 subjects. Results based on lags 5, 7, and 8 are reported in the supplementary material (figure S2).*

Mediation analysis

Results of the mediation analysis with EF strength as the mediating variable showed no association between stimulation-related changes in brain activation and stimulation-related changes in inhibition performance ($\beta = 0.008$, n.s.), no association between stimulation-related changes in inhibition performance and EF strength ($\beta = -0.05$, n.s.), and no indirect association between stimulation-related changes in brain activation and stimulation-related changes in inhibition performance (i.e., mediated by EF strength) ($\beta = 0.003$, n.s.) (figure 4). The GFI of the mediator ROI model was 0.99, indicating an adequate model fit.

Results of the mediation analysis with right preSMA thickness as the mediating variable showed no association between stimulation-related changes in brain activation and stimulation-related changes in inhibition performance (β = 0.03, n.s.), no association between stimulation-related changes in inhibition performance and thickness (β = -0.11, n.s.), and no indirect association between stimulation-related changes in brain activation and stimulation-related changes in inhibition performance (i.e., mediated by thickness) (β = -0.03, n.s.) (figure 4). The GFI of the mediator ROI model was 0.96, likewise indicating an adequate model fit.

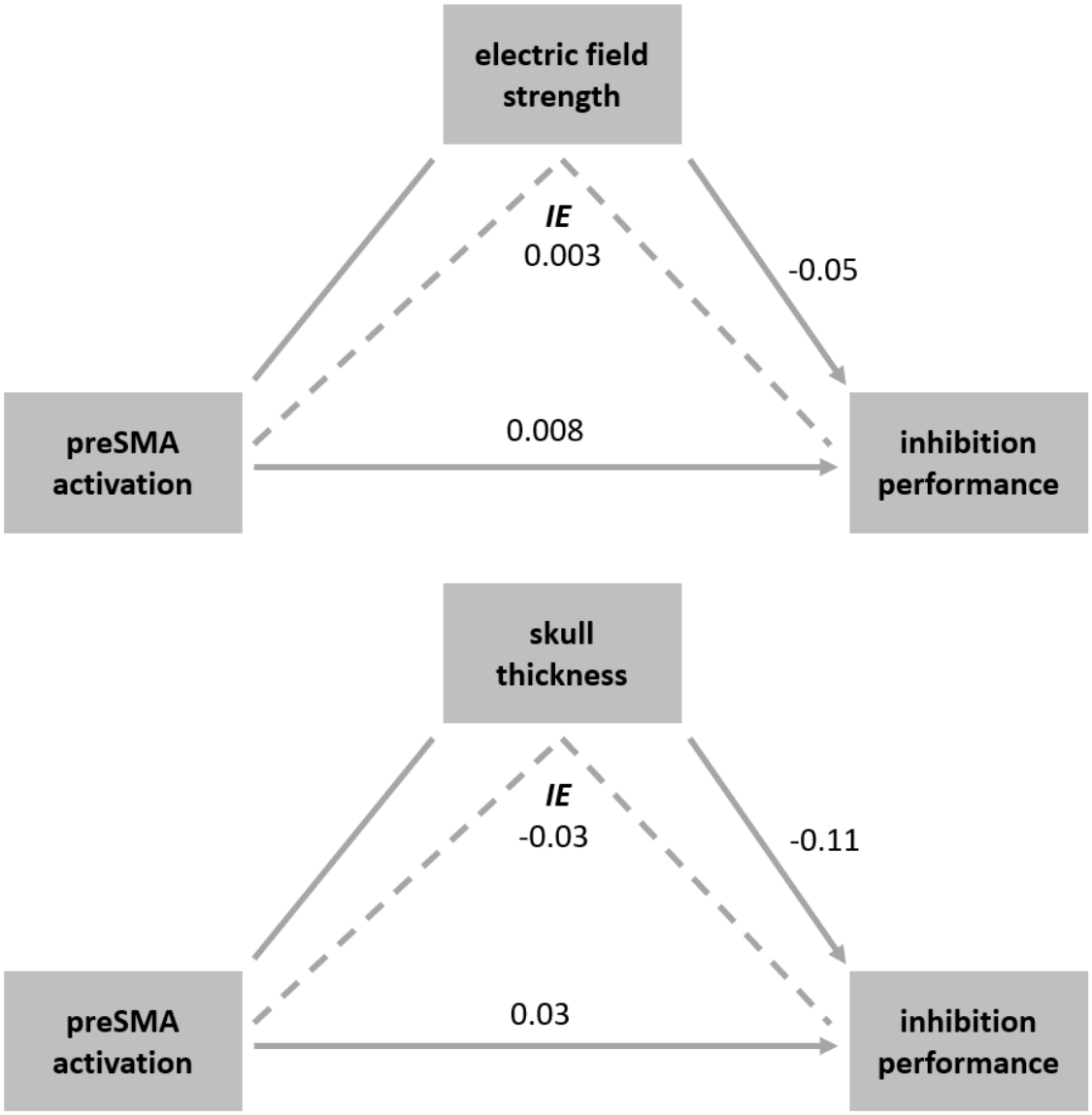


Figure 4. *Mediation Analysis investigating potential effects of electric field strength and skull thickness (n=46). The p-values are depicted on the lines linking the associations and mediations.*

Finally, the assessment of the mean EF intensity for the 33 ROIs taken from the Desikan-Killiany Atlas showed strongest intensities around our target region, the preSMA, as well as moderate to weak intensities in more distant areas (figure 5).

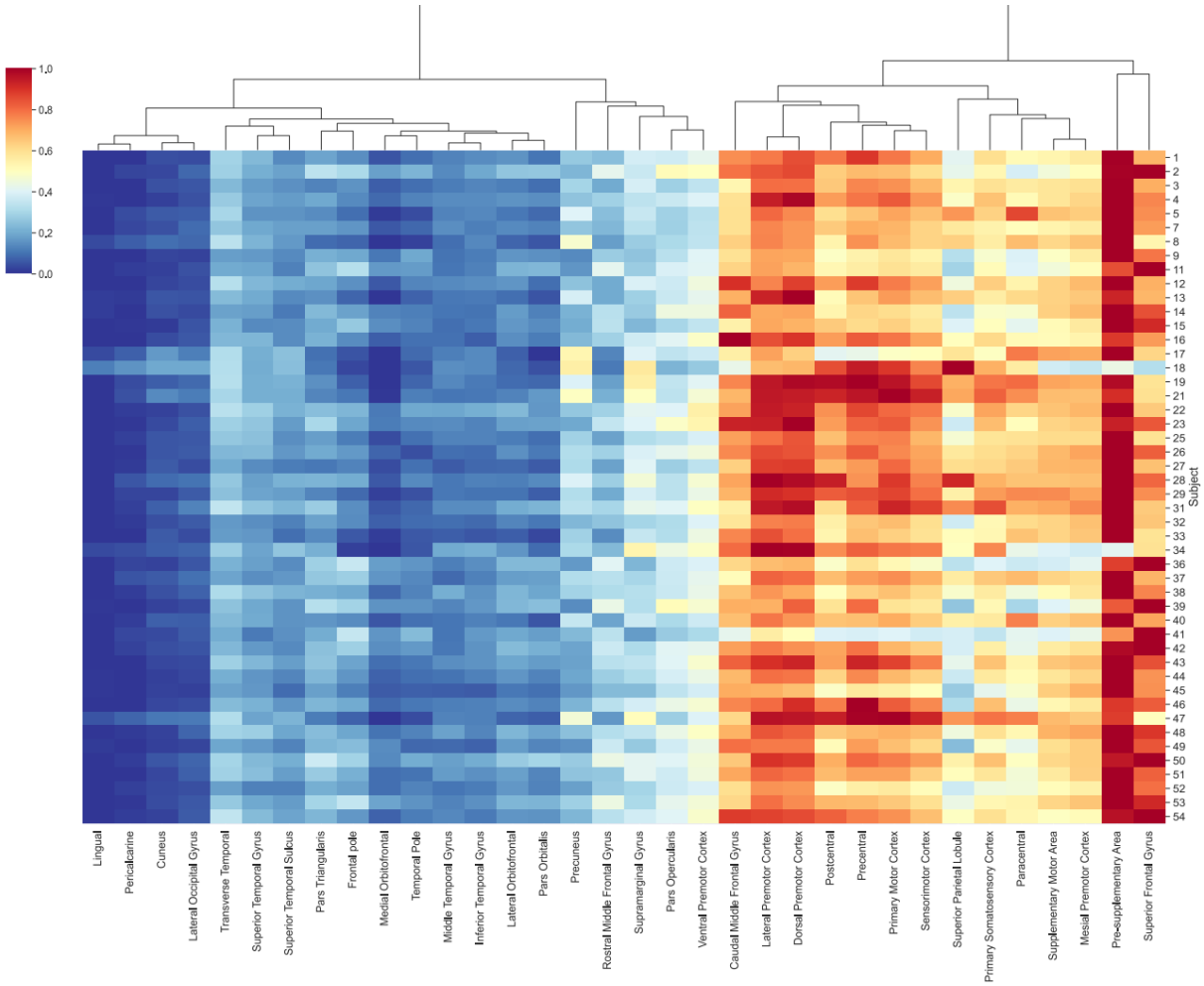


Figure 5. *Mean electric field at 34 different regions of interest, averaged across the two sessions, and normalised across all subjects for comparison (n=46).*

DISCUSSION

Behavioural and brain activity results

In the current study we investigated whether tDCS over the preSMA was able to improve inhibition performance in OCD patients, as had been previously observed in healthy participants (Yu et al., 2015). Irrespective of stimulation timepoint, patients performing the Stroop task displayed a significant increase in percentage of correct responses during stimulation in comparison to sham. On a cerebral level, this improved inhibition performance during tDCS compared to sham was associated with an increased activation in a fronto-parieto-cerebellar network comprising, amongst others, the preSMA, the IFG, the anterior cingulate, the superior parietal lobe and parts of the cerebellum. Hence, present findings indicate tDCS's ability to improve inhibition performance in OCD which has been shown to be impaired in patients (Berlin & Lee, 2018; Snyder et al., 2015; van Velzen et al., 2014). These inhibitory improvements are expected to be sustained after multiple session of stimulation, demonstrated by a recent study also targeting the preSMA (Alizadehgoradel et al., 2024).

There are surprisingly few fMRI-tDCS concurrent studies in OCD patients, despite the field moving towards this format (Brunelin et al., 2018; Ekhtiari et al., 2022; Esmaeilpour et al., 2020). The present study which is, to our best knowledge, the first study applying concurrent tDCS-fMRI in patients with OCD indicates that a 2mA single-session tDCS (compared to sham) over the preSMA induces activation increases in, amongst others, the preSMA and the IFG and thus in areas that have previously been shown to be altered during inhibition tasks in OCD patients (de Wit et al., 2012). In addition, present findings show a tDCS-associated activation increase in several regions that a large meta-analysis (Norman et al., 2019) found to be decreased in OCD patients during inhibition. These regions contain the cingulum, the orbital frontal cortex, the IFG, the cerebellum, and the angular gyrus. Consequently, our findings provide first and, preliminary, evidence that tDCS stimulation of the preSMA and neighbouring regions (Figure 5) can improve inhibition performance and normalize altered neuronal activity in patients with OCD. Two additional aspects should not go unmentioned. First, the opposite

contrast outlining the contrast sham>stimulation for incongruent>congruent was not significant. And, second, our PLS analysis contrasting the incongruent with the congruent condition independent of stimulation condition showed significant activation in several regions (i.e., the cingulum, the inferior/middle/superior frontal gyrus, and the superior parietal gyrus) that have been demonstrated by a recent meta-analysis (Huang et al., 2020) to be involved in inhibition performance in healthy young individuals and which partly showed an additional increase in activation during tDCS. Together, our findings in association with the results of previous studies indicate that 1., in general, patients with OCD seem to employ regions and networks during inhibition that are partly overlapping with those regions found to be activated in healthy young individuals during these processes, 2. activity in some – mainly motor-related - regions (Sallard et al., 2018; Schroeder et al., 2020; Tomiyama et al., 2022), some of which have previously been shown to exhibit a decreased activity in OCD during inhibition, seem to experience an increase in activation during tDCS, and 3. this activation increase might constitute the mechanism enabling a significantly improved behavioural performance.

Skull thickness and electric field

Given previous studies showing that EF strength and individual brain anatomy are critical determinants of the final stimulation effects (Antonenko et al., 2021; Arlotti et al., 2012; Datta et al., 2012; Opitz et al., 2015; Russell et al., 2013) we investigated a potential influence of these parameters by means of a mediation analysis. We found no mediation with EF strength as the mediating variable between preSMA activation and inhibition performance. The same was observed when examining a potential mediating effect of skull thickness. Additionally, the mediation analysis found no direct association between any of the individual factors. One reason for the lack of association might be that tDCS does not exert very focal stimulation effects. As illustrated in Figure 5, although the strongest EF intensities are expectedly detectable around the stimulation target region, i.e., the preSMA, various additional areas present at least

moderate or light EF intensities. Hence, preSMA activation or thickness might not be indicative of overall association between stimulation-driven underlying brain activity and inhibition performance.

Finally, the question of whether stimulation efficacy is driven by brain-state (Batsikadze et al., 2013; Li et al., 2019) or by the angle and intensity (Albizu et al., 2020; Arlotti et al., 2012; Soleimani et al., 2023) at which the current traverses neurons in the grey matter continues to be unresolved. Modelling of the EF field has recently gained a lot of popularity to better account for interindividual changes in brain anatomy. This study shows that modelling alone does not necessarily answer this question. Studies with larger sample sizes and a decreased interindividual variability in brain anatomy might be necessary to further elucidate this.

Inhibition as a measure of stimulation efficacy

tDCS effects are said to last between 20 to 30 min after a single session, dependent on session duration (Hassanzahraee et al., 2020; Nitsche & Paulus, 2001). For sustained OCD symptom alleviation at least 20 repeating sessions are alleged to be necessary (Bation et al., 2019; D'Urso et al., 2016; Narayanaswamy et al., 2015). Therefore, we expected to not find any significant improvement in OCD symptoms. Rather, this study aimed to investigate the underlying neuronal correlates responsible for the plasticity changes during long-term tDCS intervention, by examining short term changes in brain activation or, broadly speaking, the general mechanisms underlying the effects of the stimulation. Given our set-up (i.e., concurrent tDCS-fMRI) we believe that current findings contribute to a better understanding of these mechanisms, predominantly since depolarisation changes in a target region of tDCS can lead to increased activation in an extended network best identified during simultaneous stimulation.

Limitations

The choice of utilising an inhibitory task as an indicator of intervention efficacy was due to inhibition deficits being assumed to constitute a core characteristic, largely independent of clinical profile, within OCD (Snyder et al., 2015). For this reason, the study did not differentiate between symptom profile when including subjects in the study. Nevertheless, symptom heterogeneity in our OCD sample should be mentioned as a limitation since in cannot be excluded that tDCS effects differ depending on the individual symptom profile. Equally, the study recognises that in including both medicated and non-medicated patients it cannot preclude medication effects on tDCS response. Furthermore, a multi-session tDCS study following our parameters would allow us to explore the connectivity and behavioural effects over time, which would be beneficial for investigating future therapeutic application. Another essential exploration would be including a healthy control group in the study to juxtapose the patient findings detailed in this study.

Conclusion

Anodal tDCS in OCD patients can successfully improve inhibition performance in the Stroop task when targeting the preSMA for a 20-minute stimulation duration. In the field's continued effort to establish different types of transcranial electric stimulation (tES) as non-invasive therapeutic interventions, future studies should aim to further investigate the relevance of skull thickness, EF patterns, as well as brain activity and state during stimulation. To the end of increasing knowledge about the mechanisms underlying tES to prospectively establish optimized tES treatment schemes for different psychiatric disorders.

ACKNOWLEDGEMENTS

This study was supported by a DFG grant to KK (KO 3744/11-1). We thank Dr. Christine Preibisch for supporting us with the tDCS implementation in the MRI. We also thank Gülce

Lale and Begüm Sönmez for their efforts in establishing the electric field calculation pipeline during their lab rotations in our lab.

CONFLICT OF INTEREST

The authors have nothing to disclose.

REFERENCES

Abramovitch, A., Abramowitz, J. S., & Mittelman, A. (2013). The neuropsychology of adult obsessive-compulsive disorder: a meta-analysis. *Clin Psychol Rev*, *33*(8), 1163-1171. https://doi.org/10.1016/j.cpr.2013.09.004

Addis, D. R., McIntosh, A. R., Moscovitch, M., Crawley, A. P., & McAndrews, M. P. (2004). Characterizing spatial and temporal features of autobiographical memory retrieval networks: a partial least squares approach. *Neuroimage*, *23*(4), 1460-1471. https://doi.org/10.1016/j.neuroimage.2004.08.007

Albizu, A., Fang, R., Indahlastari, A., O'Shea, A., Stolte, S. E., See, K. B., Boutzoukas, E. M., Kraft, J. N., Nissim, N. R., & Woods, A. J. (2020). Machine learning and individual variability in electric field characteristics predict tDCS treatment response. *Brain Stimul*, *13*(6), 1753-1764. https://doi.org/10.1016/j.brs.2020.10.001

Alexander, B., Loh, W. Y., Matthews, L. G., Murray, A. L., Adamson, C., Beare, R., Chen, J., Kelly, C. E., Anderson, P. J., Doyle, L. W., Spittle, A. J., Cheong, J. L. Y., Seal, M. L., & Thompson, D. K. (2019). Desikan-Killiany-Tourville Atlas Compatible Version of M-CRIB Neonatal Parcellated Whole Brain Atlas: The M-CRIB 2.0. *Front Neurosci*, *13*, 34. https://doi.org/10.3389/fnins.2019.00034

Alizadehgoradel, J., Molaei, B., Barzegar Jalali, K., Pouresmali, A., Sharifi, K., Hallajian, A. H., Nejati, V., Glinski, B., Vicario, C. M., Nitsche, M. A., & Salehinejad, M. A. (2024). Targeting the prefrontal-supplementary motor network in obsessive-compulsive disorder with intensified electrical stimulation in two dosages: a randomized, controlled trial. *Transl Psychiatry*, *14*(1), 78. https://doi.org/10.1038/s41398-024-02736-y

Antonenko, D., Grittner, U., Saturnino, G., Nierhaus, T., Thielscher, A., & Floel, A. (2021). Inter-individual and age-dependent variability in simulated electric fields induced by conventional transcranial electrical stimulation. *Neuroimage*, *224*, 117413. https://doi.org/10.1016/j.neuroimage.2020.117413

Arlotti, M., Rahman, A., Minhas, P., & Bikson, M. (2012). Axon terminal polarization induced by weak uniform DC electric fields: a modeling study. *Annu Int Conf IEEE Eng Med Biol Soc*, *2012*, 4575-4578. https://doi.org/10.1109/EMBC.2012.6346985

Aron, A. R., Behrens, T. E., Smith, S., Frank, M. J., & Poldrack, R. A. (2007). Triangulating a cognitive control network using diffusion-weighted magnetic resonance imaging (MRI) and functional MRI. *J Neurosci*, *27*(14), 3743-3752. https://doi.org/10.1523/JNEUROSCI.0519-07.2007

Bannon, S., Gonsalvez, C. J., Croft, R. J., & Boyce, P. M. (2002). Response inhibition deficits in obsessive-compulsive disorder. *Psychiatry Res*, *110*(2), 165-174. https://doi.org/10.1016/s0165-1781(02)00104-x

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. *Eur Psychiatry*, *62*, 38-44. https://doi.org/10.1016/j.eurpsy.2019.08.011

Batsikadze, G., Moliadze, V., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Partially non-linear stimulation intensity-dependent effects of direct current stimulation on motor cortex excitability in humans. *J Physiol*, *591*(7), 1987-2000. https://doi.org/10.1113/jphysiol.2012.249730

Bellec, P., Marrelec, G., & Benali, H. (2008). A Bootstrap Test to Investigate Changes in Brain Connectivity for Functional MRI. *Statistica Sinica*, *18*(4), 1253-1268. http://www.jstor.org/stable/24308554

Berlin, G. S., & Lee, H. J. (2018). Response inhibition and error-monitoring processes in individuals with obsessive-compulsive disorder. *J Obsessive Compuls Relat Disord*, *16*, 21-27. https://doi.org/10.1016/j.jocrd.2017.11.001

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 Sci*, *8*(2). https://doi.org/10.3390/brainsci8020037

Bush, K., & Cisler, J. (2013). Decoding neural events from fMRI BOLD signal: a comparison of existing approaches and development of a new algorithm. *Magn Reson Imaging*, *31*(6), 976-989. https://doi.org/10.1016/j.mri.2013.03.015

Chao, H. H., Luo, X., Chang, J. L., & Li, C. S. (2009). Activation of the pre-supplementary motor area but not inferior prefrontal cortex in association with short stop signal reaction time--an intra-subject analysis. *BMC Neurosci*, *10*, 75. https://doi.org/10.1186/1471-2202-10-75

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. *Depress Anxiety*, *33*(12), 1132-1140. https://doi.org/10.1002/da.22578

Datta, A., Truong, D., Minhas, P., Parra, L. C., & Bikson, M. (2012). Inter-Individual Variation during Transcranial Direct Current Stimulation and Normalization of Dose Using MRI-Derived Computational Models. *Front Psychiatry*, *3*, 91. https://doi.org/10.3389/fpsyt.2012.00091

Davis, T., LaRocque, K. F., Mumford, J. A., Norman, K. A., Wagner, A. D., & Poldrack, R. A. (2014). What do differences between multi-voxel and univariate analysis mean? How subject-, voxel-, and trial-level variance impact fMRI analysis. *Neuroimage*, *97*, 271-283. https://doi.org/10.1016/j.neuroimage.2014.04.037

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. *Am J Psychiatry*, *169*(10), 1100-1108. https://doi.org/10.1176/appi.ajp.2012.12010073

Efron, B. (1981). Nonparametric estimates of standard error: The jackknife, the bootstrap and other methods. *Biometrika*, *68*(3), 589-599. https://doi.org/10.1093/biomet/68.3.589

Ekhtiari, H., Ghobadi-Azbari, P., Thielscher, A., Antal, A., Li, L. M., Shereen, A. D., Cabral-Calderin, Y., Keeser, D., Bergmann, T. O., Jamil, A., Violante, I. R., Almeida, J., Meinzer, M., Siebner, H. R., Woods, A. J., Stagg, C. J., Abend, R., Antonenko, D., Auer, T., . . . Bikson, M. (2022). A checklist for assessing the methodological quality of concurrent tES-fMRI studies (ContES checklist): a consensus study and statement. *Nat Protoc*, *17*(3), 596-617. https://doi.org/10.1038/s41596-021-00664-5

Esmaeilpour, Z., Shereen, A. D., Ghobadi-Azbari, P., Datta, A., Woods, A. J., Ironside, M., O'Shea, J., Kirk, U., Bikson, M., & Ekhtiari, H. (2020). Methodology for tDCS integration with fMRI. *Hum Brain Mapp*, *41*(7), 1950-1967. https://doi.org/10.1002/hbm.24908

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. *Arch Gen Psychiatry*, *46*(11), 1006-1011. https://doi.org/10.1001/archpsyc.1989.01810110048007

Hamilton, M. (1959). The assessment of anxiety states by rating. *Br J Med Psychol*, *32*(1), 50-55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x

Hamilton, M. (1960). A rating scale for depression. *J Neurol Neurosurg Psychiatry*, *23*(1), 56-62. https://doi.org/10.1136/jnnp.23.1.56

Hassanzahraee, M., Nitsche, M. A., Zoghi, M., & Jaberzadeh, S. (2020). Determination of anodal tDCS duration threshold for reversal of corticospinal excitability: An investigation for induction of counter-regulatory mechanisms. *Brain Stimul*, *13*(3), 832-839. https://doi.org/10.1016/j.brs.2020.02.027

Hsu, T. Y., Tseng, L. Y., Yu, J. X., Kuo, W. J., Hung, D. L., Tzeng, O. J., Walsh, V., Muggleton, N. G., & Juan, C. H. (2011). Modulating inhibitory control with direct current stimulation of the superior medial frontal cortex. *Neuroimage*, *56*(4), 2249-2257. https://doi.org/10.1016/j.neuroimage.2011.03.059

Huang, Y., Su, L., & Ma, Q. (2020). The Stroop effect: An activation likelihood estimation meta-analysis in healthy young adults. *Neurosci Lett*, *716*, 134683. https://doi.org/10.1016/j.neulet.2019.134683

Kessler, R. C., Petukhova, M., Sampson, N. A., Zaslavsky, A. M., & Wittchen, H. U. (2012). Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res*, *21*(3), 169-184. https://doi.org/10.1002/mpr.1359

Krishnan, A., Williams, L. J., McIntosh, A. R., & Abdi, H. (2011). Partial Least Squares (PLS) methods for neuroimaging: a tutorial and review. *Neuroimage*, *56*(2), 455-475. https://doi.org/10.1016/j.neuroimage.2010.07.034

Li, C. S., Huang, C., Constable, R. T., & Sinha, R. (2006). Imaging response inhibition in a stop-signal task: neural correlates independent of signal monitoring and post-response processing. *J Neurosci*, *26*(1), 186-192. https://doi.org/10.1523/JNEUROSCI.3741-05.2006

Li, L. M., Violante, I. R., Leech, R., Ross, E., Hampshire, A., Opitz, A., Rothwell, J. C., Carmichael, D. W., & Sharp, D. J. (2019). Brain state and polarity dependent modulation of brain networks by transcranial direct current stimulation. *Hum Brain Mapp*, *40*(3), 904-915. https://doi.org/10.1002/hbm.24420

Lipszyc, J., & Schachar, R. (2010). Inhibitory control and psychopathology: a meta-analysis of studies using the stop signal task. *J Int Neuropsychol Soc*, *16*(6), 1064-1076. https://doi.org/10.1017/S1355617710000895

Madan, C. R. (2015). Creating 3D visualizations of MRI data: A brief guide. *F1000Res*, *4*, 466. https://doi.org/10.12688/f1000research.6838.1

Mar, K., Townes, P., Pechlivanoglou, P., Arnold, P., & Schachar, R. (2022). Obsessive compulsive disorder and response inhibition: Meta-analysis of the stop-signal task. *J Psychopathol Clin Sci*, *131*(2), 152-161. https://doi.org/10.1037/abn0000732

Mayka, M. A., Corcos, D. M., Leurgans, S. E., & Vaillancourt, D. E. (2006). Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage*, *31*(4), 1453-1474. https://doi.org/10.1016/j.neuroimage.2006.02.004

McIntosh, A. R., Bookstein, F. L., Haxby, J. V., & Grady, C. L. (1996). Spatial pattern analysis of functional brain images using partial least squares. *Neuroimage*, *3*(3 Pt 1), 143-157. https://doi.org/10.1006/nimg.1996.0016

McIntosh, A. R., Chau, W. K., & Protzner, A. B. (2004). Spatiotemporal analysis of event-related fMRI data using partial least squares. *Neuroimage*, *23*(2), 764-775. https://doi.org/10.1016/j.neuroimage.2004.05.018

McIntosh, A. R., & Misic, B. (2013). Multivariate statistical analyses for neuroimaging data. *Annu Rev Psychol*, *64*, 499-525. https://doi.org/10.1146/annurev-psych-113011-143804

McLaughlin, N. C., Kirschner, J., Foster, H., O'Connell, C., Rasmussen, S. A., & Greenberg, B. D. (2016). Stop Signal Reaction Time Deficits in a Lifetime Obsessive-Compulsive Disorder Sample. *J Int Neuropsychol Soc*, *22*(7), 785-789. https://doi.org/10.1017/S1355617716000540

Narayanaswamy, J. C., Jose, D., Chhabra, H., Agarwal, S. M., Shrinivasa, B., Hegde, A., Bose, A., Kalmady, S. V., Venkatasubramanian, G., & Reddy, Y. C. (2015). Successful Application of Add-on Transcranial Direct Current Stimulation (tDCS) for Treatment of SSRI Resistant OCD. *Brain Stimul*, *8*(3), 655-657. https://doi.org/10.1016/j.brs.2014.12.003

Narmashiri, A., & Akbari, F. (2023). The Effects of Transcranial Direct Current Stimulation (tDCS) on the Cognitive Functions: A Systematic Review and Meta-analysis. *Neuropsychol Rev*. https://doi.org/10.1007/s11065-023-09627-x

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology*, *57*(10), 1899-1901. https://doi.org/10.1212/wnl.57.10.1899

Norman, K. A., Polyn, S. M., Detre, G. J., & Haxby, J. V. (2006). Beyond mind-reading: multi-voxel pattern analysis of fMRI data. *Trends Cogn Sci*, *10*(9), 424-430. https://doi.org/10.1016/j.tics.2006.07.005

Norman, L. J., Taylor, S. F., Liu, Y., Radua, J., Chye, Y., De Wit, S. J., Huyser, C., Karahanoglu, F. I., Luks, T., Manoach, D., Mathews, C., Rubia, K., Suo, C., van den Heuvel, O. A., Yucel, M., & Fitzgerald, K. (2019). Error Processing and Inhibitory Control in Obsessive-Compulsive Disorder: A Meta-analysis Using Statistical Parametric Maps. *Biol Psychiatry*, *85*(9), 713-725. https://doi.org/10.1016/j.biopsych.2018.11.010

Opitz, A., Paulus, W., Will, S., Antunes, A., & Thielscher, A. (2015). Determinants of the electric field during transcranial direct current stimulation. *Neuroimage*, *109*, 140-150. https://doi.org/10.1016/j.neuroimage.2015.01.033

Page, L. A., Rubia, K., Deeley, Q., Daly, E., Toal, F., Mataix-Cols, D., Giampietro, V., Schmitz, N., & Murphy, D. G. (2009). A functional magnetic resonance imaging study of inhibitory control in obsessive-compulsive disorder. *Psychiatry Res*, *174*(3), 202-209. https://doi.org/10.1016/j.pscychresns.2009.05.002

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage*, *59*(3), 2142-2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Puonti, O., Van Leemput, K., Saturnino, G. B., Siebner, H. R., Madsen, K. H., & Thielscher, A. (2020). Accurate and robust whole-head segmentation from magnetic resonance images for individualized head modeling. *Neuroimage*, *219*, 117044. https://doi.org/10.1016/j.neuroimage.2020.117044

Roth, R. M., Saykin, A. J., Flashman, L. A., Pixley, H. S., West, J. D., & Mamourian, A. C. (2007). Event-related functional magnetic resonance imaging of response inhibition in obsessive-compulsive disorder. *Biol Psychiatry*, *62*(8), 901-909. https://doi.org/10.1016/j.biopsych.2006.12.007

Russell, M. J., Goodman, T., Pierson, R., Shepherd, S., Wang, Q., Groshong, B., & Wiley, D. F. (2013). Individual differences in transcranial electrical stimulation current density. *J Biomed Res*, *27*(6), 495-508. https://doi.org/10.7555/JBR.27.20130074

Sallard, E., Mouthon, M., De Pretto, M., & Spierer, L. (2018). Modulation of inhibitory control by prefrontal anodal tDCS: A crossover double-blind sham-controlled fMRI study. *PLoS One*, *13*(3), e0194936. https://doi.org/10.1371/journal.pone.0194936

Samson, A. D., Rajagopal, S., Pasvanis, S., Villeneuve, S., Group, P.-A. R., McIntosh, A. R., & Rajah, M. N. (2023). Sex differences in longitudinal changes of episodic memory-related brain activity and cognition in cognitively unimpaired older adults with a family history of Alzheimer's disease. *Neuroimage Clin*, *40*, 103532. https://doi.org/10.1016/j.nicl.2023.103532

Schlosser, R. G., Wagner, G., Schachtzabel, C., Peikert, G., Koch, K., Reichenbach, J. R., & Sauer, H. (2010). Fronto-cingulate effective connectivity in obsessive compulsive disorder: a study with fMRI and dynamic causal modeling. *Hum Brain Mapp*, *31*(12), 1834-1850. https://doi.org/10.1002/hbm.20980

Schroeder, P. A., Schwippel, T., Wolz, I., & Svaldi, J. (2020). Meta-analysis of the effects of transcranial direct current stimulation on inhibitory control. *Brain Stimul*, *13*(5), 1159-1167. https://doi.org/10.1016/j.brs.2020.05.006

Sharp, D. J., Bonnelle, V., De Boissezon, X., Beckmann, C. F., James, S. G., Patel, M. C., & Mehta, M. A. (2010). Distinct frontal systems for response inhibition, attentional capture, and error processing. *Proc Natl Acad Sci U S A*, *107*(13), 6106-6111. https://doi.org/10.1073/pnas.1000175107

Snyder, H. R., Kaiser, R. H., Warren, S. L., & Heller, W. (2015). Obsessive-compulsive disorder is associated with broad impairments in executive function: A meta-analysis. *Clin Psychol Sci*, *3*(2), 301-330. https://doi.org/10.1177/2167702614534210

Soleimani, G., Kupliki, R., Paulus, M., & Ekhtiari, H. (2023). Dose-response in modulating brain function with transcranial direct current stimulation: From local to network levels. *PLoS Comput Biol*, *19*(10), e1011572. https://doi.org/10.1371/journal.pcbi.1011572

Tomiyama, H., Murayama, K., Nemoto, K., Tomita, M., Hasuzawa, S., Mizobe, T., Kato, K., Ohno, A., Tsuruta, S., Togao, O., Hiwatashi, A., & Nakao, T. (2022). Increased functional connectivity between presupplementary motor area and inferior frontal gyrus associated with the ability of motor response inhibition in obsessive-compulsive disorder. *Hum Brain Mapp*, *43*(3), 974-984. https://doi.org/10.1002/hbm.25699

van Velzen, L. S., Vriend, C., de Wit, S. J., & van den Heuvel, O. A. (2014). Response inhibition and interference control in obsessive-compulsive spectrum disorders. *Front Hum Neurosci*, *8*, 419. https://doi.org/10.3389/fnhum.2014.00419

Wink, A. M., Hoogduin, H., & Roerdink, J. B. (2008). Data-driven haemodynamic response function extraction using Fourier-wavelet regularised deconvolution. *BMC Med Imaging*, *8*, 7. https://doi.org/10.1186/1471-2342-8-7

Woolley, J., Heyman, I., Brammer, M., Frampton, I., McGuire, P. K., & Rubia, K. (2008). Brain activation in paediatric obsessive compulsive disorder during tasks of inhibitory control. *Br J Psychiatry*, *192*(1), 25-31. https://doi.org/10.1192/bjp.bp.107.036558

Yu, J., Tseng, P., Hung, D. L., Wu, S. W., & Juan, C. H. (2015). Brain stimulation improves cognitive control by modulating medial-frontal activity and preSMA-vmPFC functional connectivity. *Hum Brain Mapp*, *36*(10), 4004-4015. https://doi.org/10.1002/hbm.22893

Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., & Gerig, G. (2006). User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage*, *31*(3), 1116-1128. https://doi.org/10.1016/j.neuroimage.2006.01.015

Zandbelt, B. B., Bloemendaal, M., Hoogendam, J. M., Kahn, R. S., & Vink, M. (2013). Transcranial magnetic stimulation and functional MRI reveal cortical and subcortical interactions during stop-signal response inhibition. *J Cogn Neurosci*, *25*(2), 157-174. https://doi.org/10.1162/jocn_a_00309

Zhang, J., Yang, X., & Yang, Q. (2015). Neuropsychological dysfunction in adults with early-onset obsessive-compulsive disorder: the search for a cognitive endophenotype. *Braz J Psychiatry*, *37*(2), 126-132. https://doi.org/10.1590/1516-4446-2014-1518

SUPPLEMENTARY FIGURES

side effects tDCS		
	mean	**SD**
headache	0.66	0.74
itch	0.43	0.72
tingling sensation	0.91	0.79
burning sensation	0.72	0.95
neck pain	0.57	0.86
scalp pain	0.57	0.89
fatigue	1.84	1.09
impaired concentration	1.30	0.89
mood change	0.36	0.64
side effects total	7.02	4.35
side effects sham		
	mean	**SD**
headache	0.60	0.85
itch	0.38	0.53
tingling sensation	1.00	0.92
burning sensation	0.79	0.98
neck pain	0.67	0.84
scalp pain	0.52	0.75
fatigue	1.84	1.03
impaired concentration	1.22	0.92
mood change	0.58	0.86
side effects total	7.43	4.56

Table S1. *tDCS side-effects during sham and stimulation*

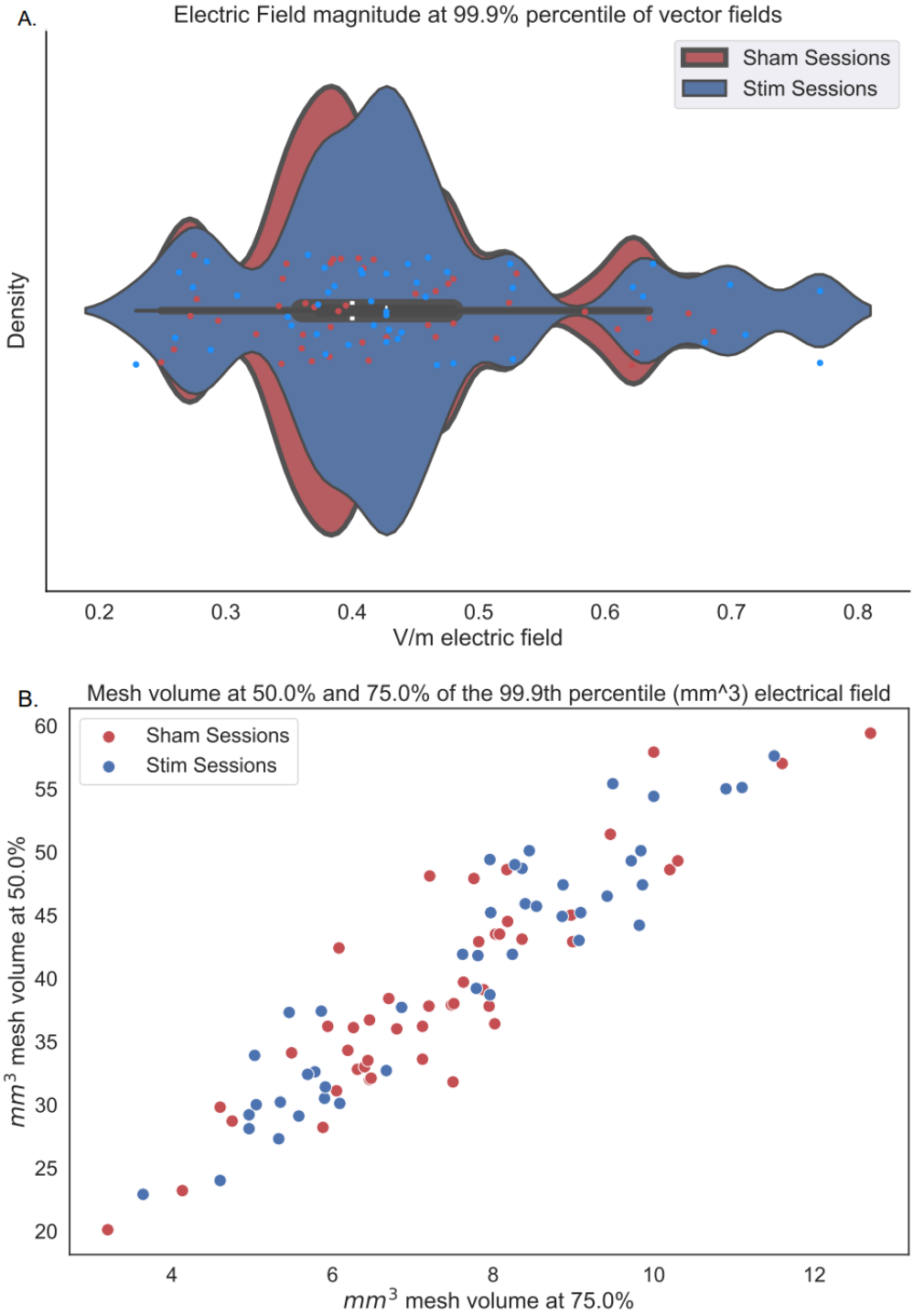
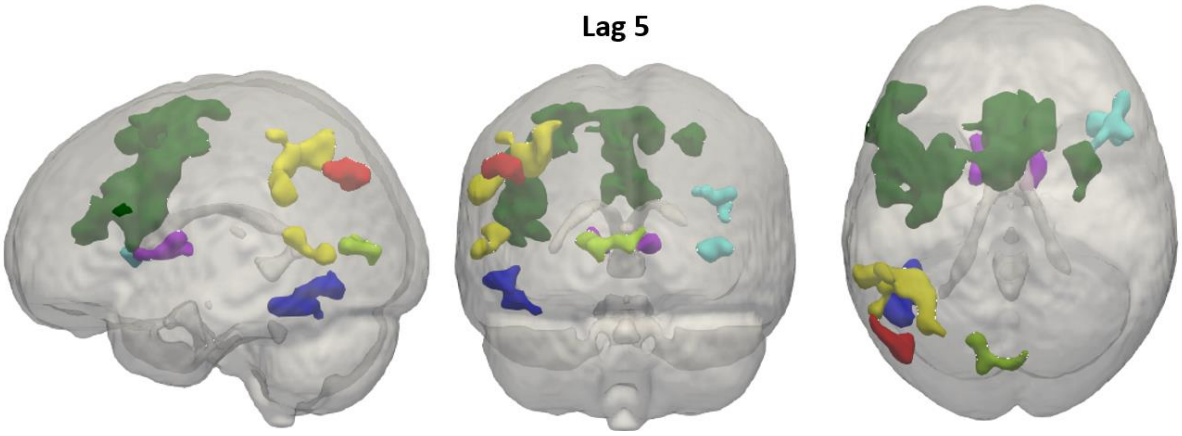
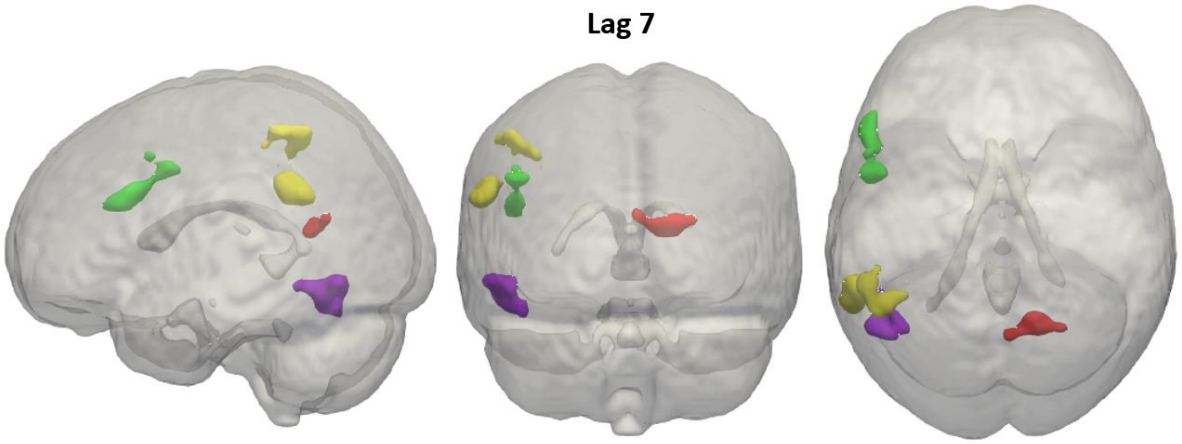


Figure S1. *Focality and top percentile analysis to show variability in the electric field*

Figure S3. Condition-by-timepoint effects at lags 5, 7 and 8

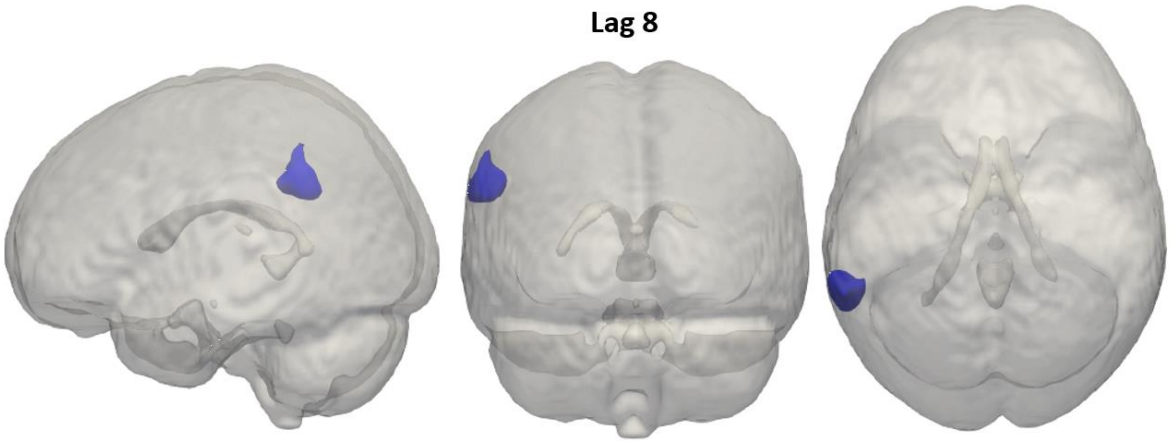


x	y	z	BSR	Appro.P	Cluster Size	Location
Positive Salience Regions						
-32	-2	58	6.6284	0.0000	3911	middle frontal gyrus, precentral gyrus
-60	-42	26	5.1179	0.0000	728	Supramarginal gyrus (posterior), parietal operculum cortex
-10	6	4	4.8881	0.0000	283	Left caudate
40	24	4	4.7682	0.0000	413	Frontal operculum cortex, inferior frontal gyrus (pars triangularis)
-44	-42	-16	4.5949	0.0000	344	Temporal fusiform cortex (posterior), inferior temporal gyrus (posterior)
-14	-72	8	4.1482	0.0000	188	Intracalcarine cortex, precuneous cortex
Negative Salience Regions						
-48	-70	38	-5.1354	0.0000	180	Lateral occipital cortex (superior)



x	y	z	BSR	Appro.P	Cluster Size	Location
Positive Salience Regions						

-58	-44	26	5.2932	0.0000	345	supramarginal gyrus (posterior & anterior), parietal operculum cortex
-50	-50	-10	4.5327	0.0000	237	inferior temporal gyrus (temporoccipital), middle temporal gyrus (temporoccipital)
-54	22	22	4.3491	0.0000	211	inferior frontal gyrus (pars triangularis, pars opercularis)
Negative Salience Regions						
14	-56	12	-4.2739	0.0000	143	precuneous cortex, intracalcarine cortex



x	y	z	BSR	Appro.P	Cluster Size	Location
Positive Salience Regions						
-62	-50	28	4.9131	0.0000	276	supramarginal gyrus (posterior), angular gyrus

Figure S2. *Condition-by-timepoint effects at lags 5, 7 and 8*

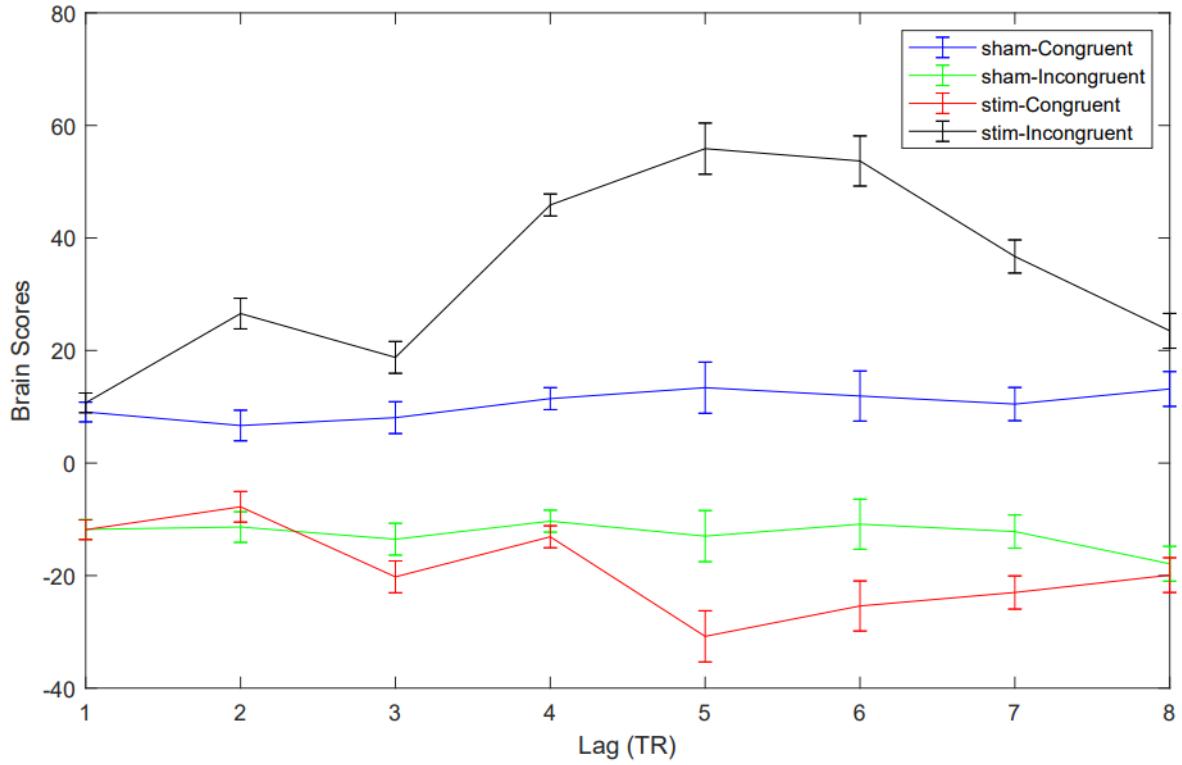


Figure S3. *Temporal brain scores condition-by-timepoint effects*

3.0 Manuscript 2: Percent amplitude of fluctuations demonstrates altered brain activity in patients with Obsessive-Compulsive Disorder

Daniela Rodriguez Manrique*[1,2,3], Benno Bremer [1,2], Deniz A. Gürsel [1], Claus Zimmer [1], Kathrin Koch [1,2,3]

1 Department of Diagnostic and Interventional Neuroradiology, School of Medicine, Technical University of Munich, Munich, Germany

2 Neuroimaging Centre (TUM-NIC), Klinikum rechts der Isar, Technical University of Munich, Munich, Germany

3 Graduate School of Systemic Neurosciences, Ludwig Maximilians University Munich, Martinsried, Germany

ABSTRACT

Resting state fMRI (rs-fMRI) Studies have shown that patients with obsessive-compulsive disorder (OCD) exhibit alterations in cortical excitability and neuronal synchronisation. Amplitude of low frequency fluctuations (ALFF) is a measure used assess the intensity of low frequency oscillations (LFOs) between 0.01-0.1Hz, which are believed to reflect neural activity. Amplitudes of these LFOs are of particular interest as they have shown to range depending on brain area and task. However, ALFF requires standardization and current methods show several shortcomings. To this end, percentage amplitude of fluctuations (PerAF) represents a new approach that has been shown to be valid and more reliable.

To attain an improved understanding of OCD pathophysiology, this study investigated alterations of PerAF in a sample of OCD patients. Rs-fMRI data and Yale-Brown Compulsive Obsessive Scale (Y-BOCS) scores of 47 OCD patients and 36 age- and sex-matched healthy controls were obtained. Using RESTplus, the data were preprocessed and PerAF at each voxel was calculated. Groups were compared using t-tests for independent samples, and results were correlated with Y-BOCS scores.

Compared to controls, OCD patients showed significantly lower PerAF in the bilateral cingulate gyrus and the right temporal gyrus. Additionally, OCD patients also displayed significantly decreased LFOs signal intensity in the bilateral thalamus and the insula. Notably, these

differences showed a trend in correlating with patient-reported compulsion severity and duration of illness.

These results indicate that (m)PerAF identifies differences in spontaneous brain activity between OCD patients and healthy controls. Our study shows alterations in LFOs that seem to be neuropathologically relevant for the disorder of OCD but further studies are certainly needed to assess the reliability of this relatively new analysis approach.

INTRODUCTION

Resting-state functional magnetic resonance imaging (rs-fMRI) relies upon blood-oxygen level dependent (BOLD) signal fluctuations to study the functional architecture of the brain under rest. These BOLD signals are believed to represent neural activity (Biswal et al., 1995; Hillman, 2014), with synchronicity of the BOLD signal between pairs of regions being interpreted as a sign of interaction, i.e., functional connectivity (FC). Observations arising from these synchronous BOLD fluctuations have defined seven networks: the default mode network (DMN), dorsal attention network (DAN), frontoparietal network (FPN), limbic network, visual network, and the salience network, also referred to as the somatosensory and cingulo-opercular network (CON) (Yeo et al., 2011). FC analyses are a common tool to study brain function under rest and have proven particularly valuable in investigating the pathophysiology of psychiatric brain disorders, including obsessive-compulsive disorder (OCD). Various studies have demonstrated disruptions in the cortico-striato-thalamo-cortical (CSTC) circuit in patients with OCD (Calza et al., 2019; Gargano et al., 2023; Posner et al., 2014), thereby providing important information for the development of therapeutic strategies such as deep-brain stimulation (DBS) (Haber et al., 2021). Moreover, synchronized activity can also be detected between sets of regions, referred to as resting-state networks (RSNs). Disruption of network integrity and the interplay between these networks have also been observed in various psychiatric conditions. For example, a meta-analysis demonstrated that OCD patients display hypoconnectivity within and between several RSNs which could contribute to the development of the condition (Gursel et al., 2018).

In addition to FC, rs-fMRI can be used to study spontaneous brain activity (SBA) by examining low frequency oscillations (LFOs) of the BOLD signal. These LFOs are within the 0.01 – 0.08 Hz frequency band and are believed to represent neural excitability, being most prominent in the mid-brain structures associated with the default mode network (DMN) which is generally

known to predominate brain activity in the resting state. Studies conducted in patients with chronic pain have confirmed that LFOs show high replicability, providing evidence for their potential as a biomarker (Malinen et al., 2010; Otti et al., 2013; Zuo et al., 2010).

A popular metric for examining LFOs is the amplitude of low frequency fluctuations (ALFF) which corresponds to the voxel-specific sum of the power of LFOs. ALFF has been shown to be a reliable and sensitive parameter in between-group analyses (Kublbock et al., 2014; Zang et al., 2007; Zuo et al., 2010). However, ALFF depends on the scale of the raw BOLD signal and is therefore measured in arbitrary units. Despite efforts to normalise ALFF, it remains sensitive to various factors, including tissue differences and physiological noise (Zang et al., 2007).

To improve specificity to neural activity, ALFF can be further normalised by dividing the sum of the power of LFOs by the sum of power across the entire frequency range. This reduces the influence of global signal changes and non-neural noise, resulting in a metric called fractional ALFF (fALFF) (Zou et al., 2008). One major asset of this procedure is furthermore that areas contaminated with physiological noise, which typically show high amplitudes in the entire frequency range, would show reduced fALFF values and so selectively targets artifacts. Accordingly, studies confirmed that fALFF shows improved subject specificity and decreased interaction with physiological noise. (Kublbock et al., 2014; Meda et al., 2015; Zuo et al., 2010). Studies additionally were able to improve sensitivity to neural activity in spatial proximity with cisterns, ventricles, and sagittal sinus, all areas with low signal to noise ratio when using fALFF. (Bu et al., 2019; Meda et al., 2015; Zang et al., 2004). Despite these advantages, studies have demonstrated that ALFF has superior replicability and test-retest reliability compared to fALFF (X. Chen et al., 2018; Zuo et al., 2010). It is not clear how the two parameters compete with varying TR and sequence acquisitions. Wu et al. (2011) found ALFF was significantly affected by TR choice and suppressed with smoothing. Meanwhile, Huotari et al. (2019) believed ALFF to show minimal effect on sampling rate yet fALFF values increasing significantly over the TR values of the sequence. Moreover, fALFF is normalised to the average voxel BOLD intensity rather than the average brain BOLD intensity which can create false-positive effects when comparing regions with higher average intensity values.

To address these limitations, Percentage Amplitude of Fluctuations (PerAF) has been proposed as an innovative and scale-independent method for investigating LFOs. PerAF is not proportional to the mean value of the time series, unlike ALFF. This is crucial as BOLD signal intensity has arbitrary units which is not ideal for direct comparison. PerAF calculates the

percentage of BOLD fluctuations compared to the mean signal and averages this across the whole time series (Jia et al., 2020). PerAF can be additionally averaged by dividing it by the global mean, i.e., mean PerAF (mPerAF), which has been shown to have better test-retest reliability (Jia et al., 2020).

Analyses based on the amplitude of low frequency fluctuations have been widely applied to investigate alterations in patients with OCD. It has even been suggested that voxel-wise analyses might be particularly suitable for the investigation of OCD as OCD findings tend to show more alterations in SBA in local regions, compared to findings in disorders such as schizophrenia which tend to demonstrate changes mainly in large-scale FC (Yu et al., 2021). Against this background, the present study investigates potential changes in PerAF in a sample of OCD patients. We hypothesize that PerAF is a suitable metric to differentiate between OCD patients and healthy controls. Furthermore, we believe that the methodological advances of PerAF could contribute to an enhanced understanding of OCD pathophysiology.

METHODS

Participants

Patients were recruited from the Psychosomatic Hospital Windach and diagnosed by an experienced psychiatrist based on the criteria of DSM-5 for OCD. In addition, the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) was used to assess OCD symptoms in patients before the scanning procedure (Goodman et al., 1989). HCs without a history of psychiatric illnesses were recruited through online and newspaper advertisements.

Exclusion criteria for both groups were: a history of clinically relevant head injuries, seizures, neurological disorders, schizophrenia, autism, substance and alcohol abuse, mental retardation, pregnancy, and any severe medical condition, as well as general MRI exclusion criteria. Other co-morbidities were not an exclusion criterion. Differences in age and sex between the two groups (HC vs. OCD) were analysed using a two-sample t-tests and a chi-square test respectively. The present study was approved by the Ethics Committee of the Klinikum rechts der Isar and was in accordance with the Declaration of Helsinki. All participants gave their informed consent to the study prior to participation.

Image Acquisition

Imaging data were obtained using a 3T Philips Ingenia MRI Scanner with a 32-channel head coil at Klinikum Rechts der Isar, München.

High-resolution anatomical T1-weighted images were acquired using a magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: TR of 11.08 ms, echo time (TE) of 5.1 ms, flip angle of 8°, matrix size of 368 x 318 and 230 slices with a resolution of 0.7 x 0.7 x 0.7 mm^3. The scan duration was 299 seconds.

T2*-weighted rs-fMRI data were obtained using echo-planar imaging (EPI) with the following parameters: TR of 2.7 s, TE of 33 ms, flip angle of 90°, matrix size of 96 x 94 and a field of view of 192 x 192 x 141 mm. 64 transverse slices with 2.0 mm thickness, covering the entire brain with a resolution of 2 x 2 x 2 mm^3 were acquired in ascending slice order. The scanning protocol incorporated a multiband factor of two, allowing for the simultaneous recording of two slices (starting with slice 1 and 33). A series of 200 whole-brain volumes was recorded. This equated to all subjects being scanned for 9 minutes during which they were instructed to keep the eyes closed, relax, and avoid falling asleep.

A subset of 10 controls had resting-state data which was acquired in a previous study using a T2*-weighted EPI sequence with a resolution of 1.7 x 1.7 x 2 mm. We corrected for the difference in voxel size by including it as a covariate in the two-sample t-test.

Preprocessing

Functional and structural MRI data were preprocessed using the RESTplus v1.21 toolbox (Huang et al., 2020), which incorporates tools from REST (Song et al., 2011), DPARSF (Yan & Zang, 2010) and SPM 12 (The Wellcome Centre for Human Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). The data were slice-time corrected, realigned, and normalised to a standard Montreal Neurological Institute template. This process included co-registration, segmentation, creation of a DARTEL template based on tissue probability maps, and normalisation by DARTEL. Preprocessing steps for images with different voxel sizes were performed separately until normalization, after which all data processing steps were conducted on the combined dataset. To increase signal to noise ratio, the data were smoothed with a 6 x 6 x 6 mm^3 full-width at half maximum gaussian filter, following previous studies including those by the developers of the PerAF method (Jia et al., 2020; Zhao et al., 2018). The data were detrended, and nuisance covariates regression was performed, including head-motion regression with a Friston 24-parameter model, as previous research indicated this increases test-retest reliability for PerAF. A band-pass filter 0.01-0.1 Hz) was applied to the data to remove

unwanted frequencies. Excessive head motion was calculated with the framewise displacement (FD) method integrated into RESTplus , calculated as the sum of the absolute values of the derivatives of the 6 motion parameters derived from SPM12 (Power at al., 2012). 9 subjects were removed due to a mean FD of larger than 0.2. A two-sided independent samples t-test revealed no significant differences in mean FD between OCD patients and HC ($t(81.0) = 0.85$, $p = 0.40$).

First-level Analysis

The RESTplus postprocessing toolkit was used to calculate PerAF and mPerAF. For each voxel, the percentage deviation from the mean signal intensity is calculated and then averaged across the whole time series, resulting in voxel-wise PerAF values (Jia et al., 2020). Additionally, PerAF was standardized by dividing it by the global mean signal, resulting in mPerAF (Jia et al., 2020). Confounding white matter and cerebrospinal fluid components, as well as the six head motion parameters generated during realignment, were added as nuisance covariates to the first level analyses.

Second-level Analysis

PerAF and mPerAF maps for each participant were z-transformed and entered into a second-level analysis using SPM 12. A two-sided independent samples t-test was performed to investigate group differences in PerAF and mPerAF between HC and OCD patients. During the second-level analysis, differences in voxel size were included as a covariate. A whole-brain grey matter mask was applied, and all results were based on an FDR-corrected threshold of $p < 0.05$ and an extent threshold of $k < 5$ voxels. To ensure correctness of methods, the analyses were independently verified by two researchers.

Correlation with Clinical Characteristics

Average PerAF and mPerAF values were extracted from clusters showing significant group differences. These values were then correlated with clinical scores (i.e., obsession and compulsion Y-BOCS scores as well as duration of illness) using Pearson correlation. To account for multiple testing, significance levels were adjusted to the number of significant clusters for each parameter according to the Bonferroni method, resulting in $p\ (0.05 / 3) = 0.017$ for PerAF, and $p\ (0.05 / 6) = 0.008$ for mPerAF. Additionally, the effect of medication on PerAF and mPerAF values was tested with a Welch's t-test if the populations passed the Shapiro-Wilk normality test or a Mann-Whitney test (also referred to as non-paired Wilcoxon test) in the case the data was not normally distributed.

RESULTS

Participants

Initially, 83 (47 OCD, 36 HC) participants were recruited. HC (M_{age} = 34.4, *SD* = 11.0) and OCD patients (M_{age} = 32.9, *SD* = 11.7) did not significantly differ in age (t (82.0) = 0.64, p = 0.54) or gender (χ^2 =0.26, p = 0.61). The demographic and clinical characteristics of the subjects are shown in table 1. 18 patients had co-morbidities. At the time of scanning, 34 patients were receiving medication, 16 were medication-naïve or stopped medication at least 1 week before scanning (table 1). Five controls and four patients were excluded due to head movement. In total, data of 51 patients with OCD (30 female) and 41 HC (22 female) matched for age and gender were included in the study.

Table 1: Demographic and Clinical Characteristics for Healthy Controls and OCD patients

	Healthy Controls (n=36)	OCD Patients (n=47)	p-value
Demographics			
Age, Mean (SD)	34.44 (11.03)	32.85 (11.70)	0.54
Gender, Males (%)	16 (44%)	19 (40%)	0.61
Clinical Characteristics			
Medication (Yes/No)	-	31/ 16	-
Age of Onset (Mean/ Min/ Max)	-	17.36/ 5 /57	-
Y-BOCS Total, Mean (SD)	-	20.55 (6.04)	-
Y-BOCS Obsessions, Mean (SD)	-	10.40 (3.27)	-
Y-BOCS Compulsions Mean (SD)	-	10.15 (3.95)	-
SD = standard deviation, Y-BOCS = Yale-Brown Obsessive-Compulsive Scale			

Imaging Group Differences

Compared to HC, OCD patients displayed significantly decreased PerAF and mPerAF values in the bilateral cingulate gyrus, as well as the right temporal gyrus (figure 1, table 2). Additionally, significantly decreased mPerAF values were observed in the right insula, as well as in the bilateral thalamus in the control group (figure 2, table 3). The opposite contrast (OCD > HC) yielded no significant results at $p < 0.05$ FDR-corrected.

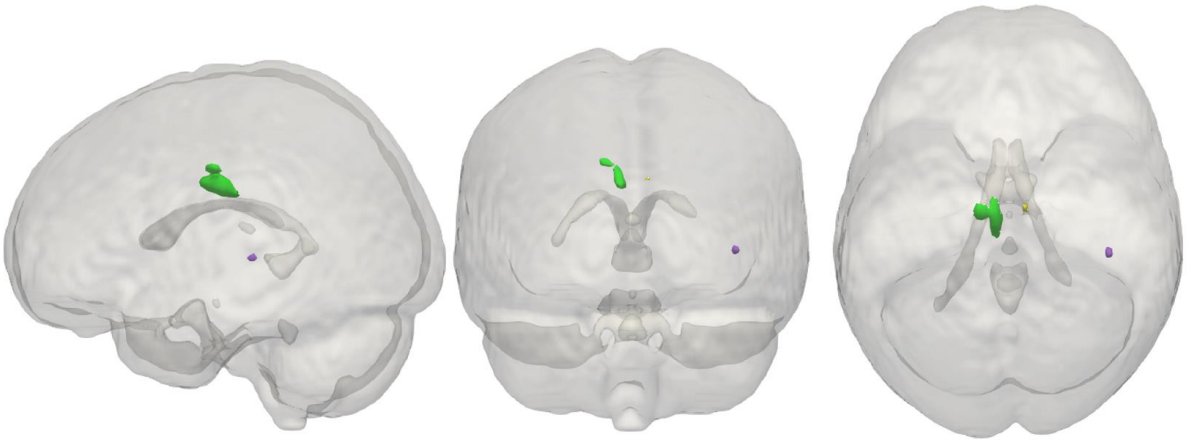


Figure 1: Independent t-test showing clusters at p = 0.05 FDR-corrected, and k > 5. Results show significant increases in percent amplitude fluctuations (PerAF) in the bilateral cingulate gyrus and right temporal gyrus of healthy controls compared to OCD patients.

PerAF t-test, HC > OCD							
x	**y**	**z**	**P-value**	**T-value**	**Cluster Size**	**Location**	**Cluster #**
-6	-12	32	0.022	5.05	97	Cingulate Gyrus Left	1
42	-28	0	0.023	4.76	16	Temporal Gyrus Right	2
8	-14	28	0.031	4.39	19	Cingulate Gyrus Right	3

Table 2: Summary of group level PerAF results.

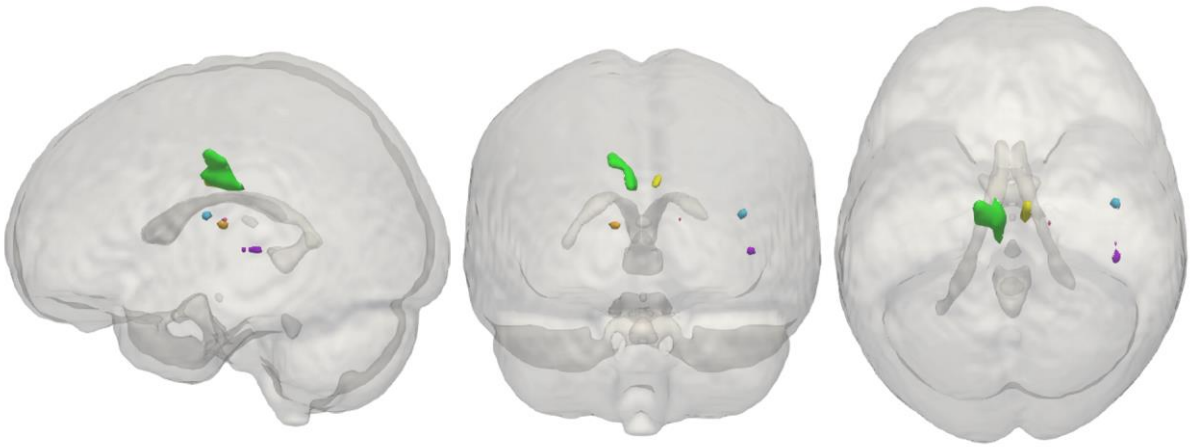


Figure 2: Independent t-test showing clusters found at p = 0.05 FDR-corrected, and k > 5. Results show significant increases in mean percent amplitude fluctuations (mPerAF) in the bilateral cingulate gyrus, the bilateral thalamus, the right temporal gyrus, and right insula of healthy controls compared to OCD patients.

mPerAF t-test, HC > OCD							
					Cluster		
x	**y**	**z**	**P-value**	**T-value**	**Size**	**Location**	**Cluster #**
-6	-14	28	0.015	5.06	131	Cingulate Gyrus Left	1
16	-14	14	0.015	4.98	15	Thalamus Right	2
44	-28	0	0.018	4.60	26	Temporal Gyrus Right	3
8	-8	30	0.018	4.57	31	Cingulate Gyrus Right	4
42	-6	16	0.020	4.42	28	Right Insula	5
-12	-14	12	0.022	4.33	19	Thalamus Left	6

Table 3: Summary of group level mPerAF results.

Correlations between (m)PerAF values and clinical characteristics

No correlations were significant after multi-comparison corrections. All our findings demonstrate trends toward correlations. For PerAF, negative correlations could be observed

between patient-reported compulsion and both clusters within the cingulate gyri, as well as between duration of illness and the cluster within the right temporal gyrus (see figure 3 and table 4). However, these results did not withstand correction for multiple testing. Correlation analyses conducted with mPerAF did not yield any significant or trending results (see table 4). However, medicated patients showed higher mPerAF in the right temporal gyrus, compared to unmedicated patients, although this did also not survive the Bonferroni-corrected threshold (see table 5 and supplementary material). Notably, medicated and non-medicated groups did not differ significantly in symptom severity ($D = 0.17$, $p = 0.88$).

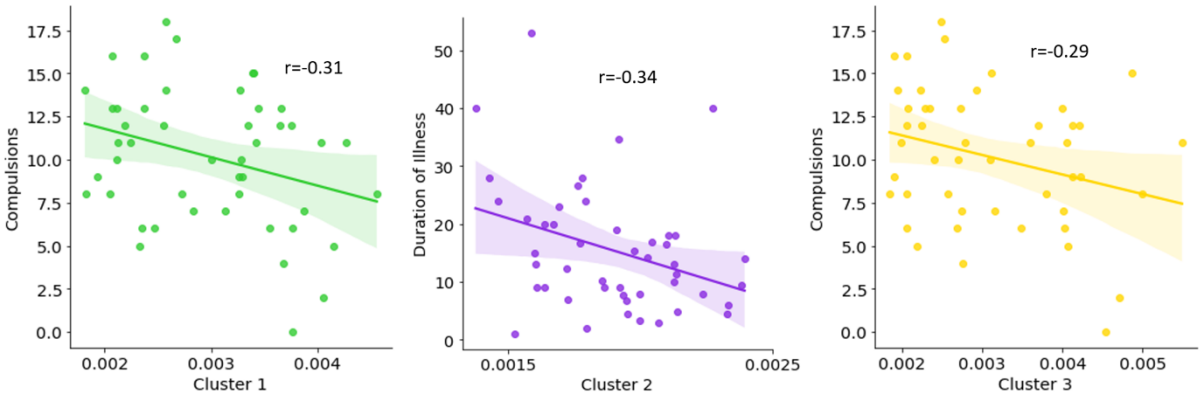


Figure 3: Correlation between PerAF within significant clusters and patient-reported compulsion and duration of illness. The shaded area on the graph indicates the confidence interval for the Pearson correlation.

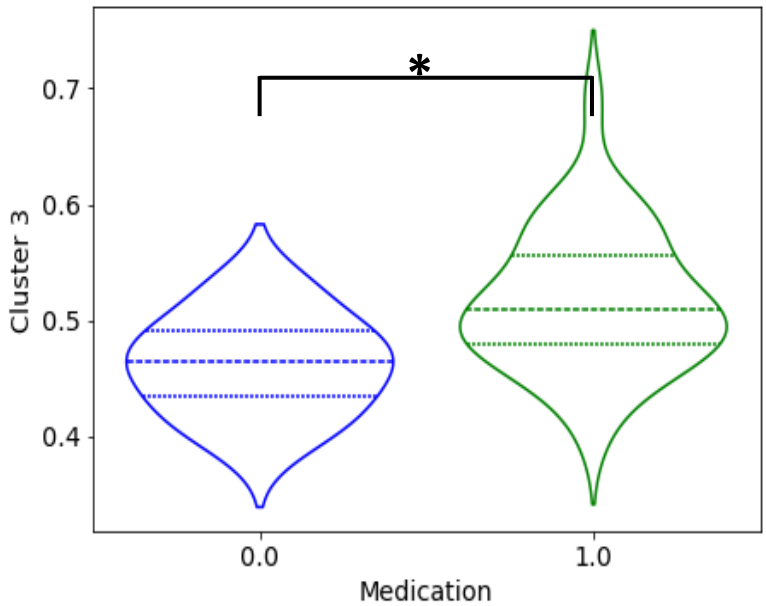
Table 4: Correlation between PerAF values and clinical characteristics

		Cluster 1	Cluster 2	Cluster 3
Obsessions	p-value	0.91	0.97	0.72
	r-coefficient	-0.02	-0.01	-0.05
Compulsions	p-value	**0.03**	0.72	**0.05**
	r-coefficient	-0.31	-0.05	-0.29
Y-BOCS total score	p-value	0.15	0.79	0.14
	r-coefficient	-0.21	-0.04	-0.21
Duration of illness	p-value	0.16	**0.02**	0.22
	r-coefficient	-0.21	-0.34	-0.18
Medication	p-value	0.92	0.11	0.73
	test	MW (243)	MW (319)	W (0.35)

Table 4: Effect of obsessions, compulsions, and medication on cluster-wise PerAF of OCD patients. (MW = results from Mann-Whitney tests; W = results from Welch's t-test)

Table 5: The effect of clinical characteristics on their mPerAF values							
		Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6
Obsessions	p-value	0.51	0.53	0.38	0.96	0.17	0.87
	r-coefficient	0.1	0.09	0.13	-0.01	0.21	-0.02
Compulsions	p-value	0.21	0.85	0.33	0.17	0.87	0.89
	r-coefficient	-0.19	0.03	0.15	-0.2	0.03	0.02
Y-BOCS total score	p-value	0.64	0.64	0.26	0.36	0.39	0.99
	r-coefficient	-0.07	0.07	0.17	-0.14	0.13	0.00
Duration of illness	p-value	0.75	0.34	0.38	0.80	0.26	0.30
	r-coefficient	-0.05	-0.14	-0.13	-0.04	-0.17	-0.16
Medication	p-value	0.66	0.67	**0.00**	0.52	0.66	0.83
	test	W (0.45)	W (0.43)	MW (386)	W (0.65)	MW (268)	MW (238)

Table 5: Effect of obsessions, compulsions, and medication on cluster-wise mPerAF of OCD patients. (MW = results from Mann-Whitney tests; W = results from Welch's t-test)



Supplementary Figure 1: A violin plot shows the difference in cluster 3 mPerAF values between medicated (n = 31) and unmedicated (n = 16) patients as assessed by a Mann-Whitney test. The medicated group had significantly higher beta values (Mann-Whitney U statistic = 386.0, p = 0.002)

DISCUSSION

(m)PerAF

In this study, we investigated differences in LFOs between OCD patients and HCs using PerAF and mPerAF. As hypothesized, PerAF and mPerAF successfully differentiated between OCD patients and HCs, providing new insights into spontaneous fluctuations at rest in OCD patients and contributing to an improved understanding of the underlying pathophysiology.

Notably, the group comparison revealed decreased spontaneous fluctuations in OCD patients, compared to HCs. No increases in spontaneous fluctuations were detectable in any region. Using both metrics, decreased LFOs were observed in the bilateral cingulate gyrus and right temporal gyrus. Additional decreases were detected with mPerAF, including the bilateral thalamus and right insula. Interestingly, decreased PerAF in the bilateral cingulate was associated with increased patient-reported compulsions, indicating that less spontaneous fluctuations in these regions are related to stronger compulsions. Additionally, PerAF in the temporal gyrus decreased with duration of illness, suggesting that the longer patients have been diagnosed with OCD, the less activity they display in the temporal gyrus. However, LFOs in the temporal gyrus were stronger in medicated compared to unmedicated patients, indicating a potential therapeutic effect.

The cingulate cortex is known to be critically involved in cognitive control processes (Hoffstaedter et al., 2014; Schulz et al., 2011), as well as in OCD pathophysiology (van de Veerdonk et al., 2023). Hence, decreased intrinsic activity in this part of the brain might be related to patients´ impaired ability to objectively evaluate the outcomes of their actions and, consequently, control specific behaviour. Compulsions, such as compulsive checking, might be the behavioural response to decreased activity in this region. This corresponds well to the findings from the correlational analysis, indicating a trend in compulsions increase with decreased LFOs of bilateral cingulate gyri; notably, a relationship was observed for both clusters independently.

The literature on the relationship between LFOs of the cingulate gyrus with OCD is inconsistent. A recent meta-analysis reported increased fALFF within the left medial cingulate gyrus (Li et al., 2023) suggesting increased spontaneous fluctuations in this region, which somewhat opposes the findings made in the present study. However, fALFF has several methodological limitations and, therefore, cannot be directly compared with (m)PerAF. To recapitulate: ALFF is calculated as the average square root across each frequency between 0.01-

0.08 Hz of that voxel (Zang et al., 2007). Normalising each timepoint signal intensity to the mean value of the time series, is a methodological improvement which made PerAF no longer proportional to the mean intensity of the timeseries (unlike ALFF). Furthermore, to enhance group comparison, the PerAF of each voxel is divided by the global mean PerAF of each participant to create mPerAF. This makes mPerAF also mathematically distinct from fALFF, as fALFF is a ratio of power of all frequencies to power of lower frequencies. This makes a direct comparison with the results of the mentioned meta-analysis challenging.

Other studies have provided indirect evidence for increased activity of the anterior cingulate gyrus (ACC), showing that regions associated with the CSTC loop are increasingly modulated by the ACC in OCD patients (Diwadkar et al., 2015) or that metabolic activity decreased in OCD patients after therapeutic capsulotomy which correlated with clinical improvement (Zuo et al., 2013). On the other hand, some studies indicate that the function of the cingulate gyrus might be reduced in patients with OCD. Data derived from a large sample of almost 300 children demonstrated that heightened performance monitoring, a risk factor for OCD, is associated with decreased volume in the ACC, suggesting less structural integrity of the cingulate gyrus in youth at risk for OCD (Gilbert et al., 2018). Another study reported that the longer the illness persists, the less activity of the ACC can be found (Medvedeva et al., 2020). Nevertheless, there is a lack of direct evidence for altered SBA in the cingulate gyrus in patients with OCD. This might be due to different implications of the methods used in these studies, specific involvement of anatomic subdivisions of the cingulate gyrus, or heterogeneities in the underlying samples. Future research should address these issues when investigating SBA in OCD patients. However, the bilateral affection of the cingulate gyrus as well as the independently observed correlation with compulsion severity provides strong evidence for the relevance of decreased SBA in the cingulate gyrus for OCD pathophysiology.

Furthermore, we found decreased PerAF and mPerAF in the right temporal gyrus. A previous study observed decreased ALFF in the temporal gyrus and attributed this to pathophysiologically relevant OCD-specific (DMN and FPN) network dysconnectivity (Yu et al., 2021). Interestingly, this study also reported that spontaneous fluctuations in the temporal gyrus decrease with the duration of OCD illness, similar to our observations. Moreover, previous research has linked poor disease insight, a recognized subtype of OCD as well as a disease reinforcing mechanism, with less ALFF within the temporal gyrus (Fan et al., 2017). However, insight is not rated in the Y-BOCS. Thus, decreased SBA in the right temporal gyrus might indicate the presence of patients of the poor insight subtype within our sample who were

not identified with our behavioural assessment. Such classification of OCD subtypes should be addressed by future studies, since it may provide important insights into neuropathological heterogeneities within OCD.

The significantly lower mPerAF that we observed in the bilateral thalamus may be linked to OCD-specific alterations in neural circuitry including a potential impact on thalamo-striatal connectivity (Mennes et al., 2011; Zuo et al., 2010). Accordingly, two recent meta-analyses have reported hypoconnectivity between the thalamus and the striatum within the CSTC circuit (Gursel et al., 2018; Liu et al., 2022). This is not surprising as thalamus-striatum connectivity is involved in cognitive control and hypofunction of this network is found already at illness onset (Fitzgerald et al., 2011; Posner et al., 2014). Moreover, studies have demonstrated that OCD patients display less structural integrity within the thalamus, specifically a reduction in thalamus size along with deficits in the connecting fibre tracts (Piras et al., 2021; Weeland et al., 2022). Hence, reduced thalamic spontaneous fluctuations integrate well into the literature and could contribute to dysfunction of OCD-specific neural circuitry.

In addition, our study demonstrated decreased mPerAF in the right insular cortex. This finding is consistent with previous research reporting decreased LFOs in the insula (Li et al., 2023), as well as reduced structural integrity of the insula in OCD patients (Rus et al., 2017; Stevens et al., 2022), indicating functional and structural deficits. Another study showed decreased insular ALFF values to be correlated to Y-BOCS compulsion scores in non-medicated OCD patients (Zhu et al., 2016). However, no assessment of insight was done here to explore whether symptom type skewed the observation, as it has been shown that insula task activation and dysconnectivity to the medial orbital frontal cortex plays a key role in poor insight in OCD (Broekhuizen et al., 2023; Koch & Rodriguez-Manrique, 2023). The anterior insula is furthermore an important component of the resting state salience network (Cauda et al., 2011), which has proven critical in OCD pathology (Y. H. Chen et al., 2018; Fan et al., 2017; Gursel et al., 2020; Hu et al., 2019; Zhu et al., 2016). The salience network as well as the insula per se are generally associated with interoception and the integration of bodily and emotional perceptions into awareness (Craig, 2003). Aberrant insula activity in OCD patients might be linked to abnormalities in subjective perception, resulting in an increased urge to engage in behavioural reactions (Eng et al., 2022). Other studies associated dysfunction of the insula with depressive symptoms in OCD patients and altered risk processing (Luigjes et al., 2016; Zhou et al., 2022). These studies suggest that the insula plays an important role in various symptoms associated with OCD, although the exact function remains to be fully identified. Again, a

differential involvement of its anatomical subdivisions, as well as interdependence with OCD subtypes, seems plausible and requires further investigation.

PerAF and mPerAF group differences show a large overlap, with both metrics indicating decreased values in the bilateral cingulate gyrus, as well as the right temporal gyrus. However, the mPerAF differences between the control and OCD patients were more extensive, including significant alterations in the bilateral thalamus and right insula. The temporal gyrus is in the sylvian fissure, the insula is located in the sylvian cistern and the thalamus next to the quadrigeminal cistern (Kucukyuruk et al., 2012; Liliequist, 1956). Since mPerAF normalises individual PerAF values with their global mean, it is plausible that subject-specific variations in tissue vascularisation and heart rate, amplified in signal near the cisterns have been accounted for with mPerAF. Thus, this normalization potentially enhances the group-level contrast (Kalcher et al., 2013). Future studies should particularly address which of the two parameters, PerAF or mPerAF, is more reliable.

Limitations

The findings of the study presented here must be considered under some limitations. Results of the correlational analyses did not surpass corrections for multiple testing, although the Bonferroni method is quite conservative and carries the risk of inflating false negatives. Moreover, we observed increased compulsion scores associated with bilateral decreases in cingulate LFOs and a correlation between duration of illness and temporal gyrus LFOs that has been reported before. Despite not surviving multiple correction, these consistencies render the findings of the correlational analysis plausible.

Finally, our sample was quite heterogeneous, lacking documentation of poor insight, anxiety and depression levels. This could also partially explain why only a trend in the correlations was observed. In addition, not all patients were unmedicated, and when examining medication, the study only considers the current 8-week period before data acquisition according to previous research (Shin et al., 2014). Lifetime medication would be a more indicative measure to consider. Symptom heterogeneity could additionally contribute to disparities between (f)ALFF and (m)PerAF results, as patients differed in their individual symptom profiles albeit this makes results more representative of the general OCD population. Future studies may nevertheless want to account for such symptom profiles and subtypes to attain a more differentiated understanding of the clinical landscape of OCD.

Conclusion

To the authors' knowledge, this is the first study to analyse (m)PerAF in OCD patients. The results indicated reduced SBA in the bilateral cingulate gyrus which was associated with a trend in increased compulsions in OCD patients, as well as reduced spontaneous fluctuations in the temporal gyrus that decreased with the duration of illness. Moreover, we found reductions in thalamic spontaneous fluctuations, which may be linked to altered CSTC circuitry, and reduced spontaneous fluctuations in the insula, potentially related to alterations in interoception. (M)PerAF showed potential in enhanced affinity in regions proximal to cisterns. Additionally, if proven to have improved re-test reliability and reproducibility compared to (f)ALFF, (m)PerAF could become an instrumental metric in studying OCD. We believe that further studies should employ this approach to further investigate differences between PerAF and mPerAF and further contextualise present findings. Overall, our findings demonstrate that (m)PerAF successfully differentiates between OCD patients and HCs and is a promising biomarker for future investigations of neuropsychiatric pathophysiology.

REFERENCES

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med*, *34*(4), 537-541. https://doi.org/10.1002/mrm.1910340409

Broekhuizen, A., Vriend, C., Wolf, N., Koenen, E. H., van Oppen, P., van Balkom, A., Visser, H. A. D., & van den Heuvel, O. A. (2023). Poor Insight in Obsessive-Compulsive Disorder as a Multifaceted Phenomenon: Evidence From Brain Activation During Symptom Provocation. *Biol Psychiatry Cogn Neurosci Neuroimaging*, *8*(11), 1135-1144. https://doi.org/10.1016/j.bpsc.2023.04.006

Bu, X., Hu, X., Zhang, L., Li, B., Zhou, M., Lu, L., Hu, X., Li, H., Yang, Y., Tang, W., Gong, Q., & Huang, X. (2019). Investigating the predictive value of different resting-state functional MRI parameters in obsessive-compulsive disorder. *Transl Psychiatry*, *9*(1), 17. https://doi.org/10.1038/s41398-018-0362-9

Calza, J., Gursel, D. A., Schmitz-Koep, B., Bremer, B., Reinholz, L., Berberich, G., & Koch, K. (2019). Altered Cortico-Striatal Functional Connectivity During Resting State in Obsessive-Compulsive Disorder. *Front Psychiatry*, *10*, 319. https://doi.org/10.3389/fpsyt.2019.00319

Cauda, F., D'Agata, F., Sacco, K., Duca, S., Geminiani, G., & Vercelli, A. (2011). Functional connectivity of the insula in the resting brain. *Neuroimage*, *55*(1), 8-23. https://doi.org/10.1016/j.neuroimage.2010.11.049

Chen, X., Lu, B., & Yan, C. G. (2018). Reproducibility of R-fMRI metrics on the impact of different strategies for multiple comparison correction and sample sizes. *Hum Brain Mapp*, *39*(1), 300-318. https://doi.org/10.1002/hbm.23843

Chen, Y. H., Li, S. F., Lv, D., Zhu, G. D., Wang, Y. H., Meng, X., Hu, Q., Li, C. C., Zhang, L. T., Chu, X. P., Wang, X. P., & Li, P. (2018). Decreased Intrinsic Functional Connectivity of the Salience Network in Drug-Naive Patients With Obsessive-Compulsive Disorder. *Front Neurosci*, *12*, 889. https://doi.org/10.3389/fnins.2018.00889

Craig, A. D. (2003). Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol*, *13*(4), 500-505. https://doi.org/10.1016/s0959-4388(03)00090-4

Diwadkar, V. A., Burgess, A., Hong, E., Rix, C., Arnold, P. D., Hanna, G. L., & Rosenberg, D. R. (2015). Dysfunctional Activation and Brain Network Profiles in Youth with Obsessive-Compulsive Disorder: A Focus on the Dorsal Anterior Cingulate during Working Memory. *Front Hum Neurosci*, *9*, 149. https://doi.org/10.3389/fnhum.2015.00149

Eng, G. K., Collins, K. A., Brown, C., Ludlow, M., Tobe, R. H., Iosifescu, D. V., & Stern, E. R. (2022). Relationships between interoceptive sensibility and resting-state functional connectivity of the insula in obsessive-compulsive disorder. *Cereb Cortex*, *32*(23), 5285-5300. https://doi.org/10.1093/cercor/bhac014

Fan, J., Zhong, M., Gan, J., Liu, W., Niu, C., Liao, H., Zhang, H., Yi, J., Chan, R. C. K., Tan, C., & Zhu, X. (2017). Altered connectivity within and between the default mode, central executive, and salience networks in obsessive-compulsive disorder. *J Affect Disord*, *223*, 106-114. https://doi.org/10.1016/j.jad.2017.07.041

Fitzgerald, K. D., Welsh, R. C., Stern, E. R., Angstadt, M., Hanna, G. L., Abelson, J. L., & Taylor, S. F. (2011). Developmental Alterations of Frontal-Striatal-Thalamic Connectivity in Obsessive-Compulsive Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *50*(9), 938-948.e933. https://doi.org/https://doi.org/10.1016/j.jaac.2011.06.011

Gargano, S. P., Santos, M. G., Taylor, S. M., & Pastis, I. (2023). A closer look to neural pathways and psychopharmacology of obsessive compulsive disorder. *Front Behav Neurosci*, *17*, 1282246. https://doi.org/10.3389/fnbeh.2023.1282246

Gilbert, K. E., Barclay, M. E., Tillman, R., Barch, D. M., & Luby, J. L. (2018). Associations of Observed Performance Monitoring During Preschool With Obsessive-Compulsive Disorder and Anterior Cingulate Cortex Volume Over 12 Years. *JAMA Psychiatry*, *75*(9), 940-948. https://doi.org/10.1001/jamapsychiatry.2018.1805

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. *Arch Gen Psychiatry*, *46*(11), 1006-1011. https://doi.org/10.1001/archpsyc.1989.01810110048007

Gursel, D. A., Avram, M., Sorg, C., Brandl, F., & Koch, K. (2018). Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. *Neurosci Biobehav Rev*, *87*, 151-160. https://doi.org/10.1016/j.neubiorev.2018.01.016

Gursel, D. A., Reinholz, L., Bremer, B., Schmitz-Koep, B., Franzmeier, N., Avram, M., & Koch, K. (2020). Frontoparietal and salience network alterations in obsessive-compulsive disorder: insights from independent component and sliding time window analyses. *J Psychiatry Neurosci*, *45*(3), 214-221. https://doi.org/10.1503/jpn.190038

Haber, S. N., Yendiki, A., & Jbabdi, S. (2021). Four Deep Brain Stimulation Targets for Obsessive-Compulsive Disorder: Are They Different? *Biol Psychiatry*, *90*(10), 667-677. https://doi.org/10.1016/j.biopsych.2020.06.031

Hillman, E. M. (2014). Coupling mechanism and significance of the BOLD signal: a status report. *Annu Rev Neurosci*, *37*, 161-181. https://doi.org/10.1146/annurev-neuro-071013-014111

Hoffstaedter, F., Grefkes, C., Caspers, S., Roski, C., Palomero-Gallagher, N., Laird, A. R., Fox, P. T., & Eickhoff, S. B. (2014). The role of anterior midcingulate cortex in cognitive motor control: evidence from functional connectivity analyses. *Hum Brain Mapp*, *35*(6), 2741-2753. https://doi.org/10.1002/hbm.22363

Hu, X., Zhang, L., Bu, X., Li, H., Li, B., Tang, W., Lu, L., Hu, X., Tang, S., Gao, Y., Yang, Y., Roberts, N., Gong, Q., & Huang, X. (2019). Localized Connectivity in Obsessive-

Compulsive Disorder: An Investigation Combining Univariate and Multivariate Pattern Analyses. *Front Behav Neurosci*, *13*, 122. https://doi.org/10.3389/fnbeh.2019.00122

Huang, Y., Su, L., & Ma, Q. (2020). The Stroop effect: An activation likelihood estimation meta-analysis in healthy young adults. *Neurosci Lett*, *716*, 134683. https://doi.org/10.1016/j.neulet.2019.134683

Huotari, N., Raitamaa, L., Helakari, H., Kananen, J., Raatikainen, V., Rasila, A., Tuovinen, T., Kantola, J., Borchardt, V., Kiviniemi, V. J., & Korhonen, V. O. (2019). Sampling Rate Effects on Resting State fMRI Metrics. *Front Neurosci*, *13*, 279. https://doi.org/10.3389/fnins.2019.00279

Jia, X. Z., Sun, J. W., Ji, G. J., Liao, W., Lv, Y. T., Wang, J., Wang, Z., Zhang, H., Liu, D. Q., & Zang, Y. F. (2020). Percent amplitude of fluctuation: A simple measure for resting-state fMRI signal at single voxel level. *PLoS One*, *15*(1), e0227021. https://doi.org/10.1371/journal.pone.0227021

Kalcher, K., Boubela, R. N., Huf, W., Biswal, B. B., Baldinger, P., Sailer, U., Filzmoser, P., Kasper, S., Lamm, C., Lanzenberger, R., Moser, E., & Windischberger, C. (2013). RESCALE: Voxel-specific task-fMRI scaling using resting state fluctuation amplitude. *Neuroimage*, *70*, 80-88. https://doi.org/10.1016/j.neuroimage.2012.12.019

Koch, K., & Rodriguez-Manrique, D. (2023). Unraveling the Neural Substrates of Insight in Obsessive-Compulsive Disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *8*(11), 1070-1071.

Kublbock, M., Woletz, M., Hoflich, A., Sladky, R., Kranz, G. S., Hoffmann, A., Lanzenberger, R., & Windischberger, C. (2014). Stability of low-frequency fluctuation amplitudes in prolonged resting-state fMRI. *Neuroimage*, *103*, 249-257. https://doi.org/10.1016/j.neuroimage.2014.09.038

Kucukyuruk, B., Richardson, R. M., Wen, H. T., Fernandez-Miranda, J. C., & Rhoton, A. L., Jr. (2012). Microsurgical anatomy of the temporal lobe and its implications on temporal lobe epilepsy surgery. *Epilepsy Res Treat*, *2012*, 769825. https://doi.org/10.1155/2012/769825

Li, H., Wang, Y., Xi, H., Zhang, J., Zhao, M., & Jia, X. (2023). Alterations of regional spontaneous brain activity in obsessive-compulsive disorders: A meta-analysis. *J Psychiatr Res*, *165*, 325-335. https://doi.org/10.1016/j.jpsychires.2023.07.036

Liliequist, B. (1956). The anatomy of the subarachnoid cisterns. *Acta radiol*, *46*(1-2), 61-71. https://doi.org/10.3109/00016925609170813

Liu, J., Cao, L., Li, H., Gao, Y., Bu, X., Liang, K., Bao, W., Zhang, S., Qiu, H., Li, X., Hu, X., Lu, L., Zhang, L., Hu, X., Huang, X., & Gong, Q. (2022). Abnormal resting-state functional connectivity in patients with obsessive-compulsive disorder: A systematic review and meta-analysis. *Neurosci Biobehav Rev*, *135*, 104574. https://doi.org/10.1016/j.neubiorev.2022.104574

Luigjes, J., Figee, M., Tobler, P. N., van den Brink, W., de Kwaasteniet, B., van Wingen, G., & Denys, D. (2016). Doubt in the Insula: Risk Processing in Obsessive-Compulsive Disorder. *Front Hum Neurosci*, *10*, 283. https://doi.org/10.3389/fnhum.2016.00283

Malinen, S., Vartiainen, N., Hlushchuk, Y., Koskinen, M., Ramkumar, P., Forss, N., Kalso, E., & Hari, R. (2010). Aberrant temporal and spatial brain activity during rest in patients with chronic pain. *Proc Natl Acad Sci U S A*, *107*(14), 6493-6497. https://doi.org/10.1073/pnas.1001504107

Meda, S. A., Wang, Z., Ivleva, E. I., Poudyal, G., Keshavan, M. S., Tamminga, C. A., Sweeney, J. A., Clementz, B. A., Schretlen, D. J., Calhoun, V. D., Lui, S., Damaraju, E., & Pearlson, G. D. (2015). Frequency-Specific Neural Signatures of Spontaneous Low-Frequency Resting State Fluctuations in Psychosis: Evidence From Bipolar-

Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Consortium. *Schizophr Bull*, *41*(6), 1336-1348. https://doi.org/10.1093/schbul/sbv064

Medvedeva, N. S., Masharipov, R. S., Korotkov, A. D., Kireev, M. V., & Medvedev, S. V. (2020). Dynamics of Activity in the Anterior Cingulate Cortex on Development of Obsessive-Compulsive Disorder: a Combined PET and FMRI Study. *Neuroscience and Behavioral Physiology*, *50*(3), 298-305. https://doi.org/10.1007/s11055-020-00901-6

Mennes, M., Zuo, X. N., Kelly, C., Di Martino, A., Zang, Y. F., Biswal, B., Castellanos, F. X., & Milham, M. P. (2011). Linking inter-individual differences in neural activation and behavior to intrinsic brain dynamics. *Neuroimage*, *54*(4), 2950-2959. https://doi.org/10.1016/j.neuroimage.2010.10.046

Otti, A., Guendel, H., Wohlschläger, A., Zimmer, C., & Noll-Hussong, M. (2013). Frequency shifts in the anterior default mode network and the salience network in chronic pain disorder. *BMC Psychiatry*, *13*(1), 84. https://doi.org/10.1186/1471-244X-13-84

Piras, F., Piras, F., Abe, Y., Agarwal, S. M., Anticevic, A., Ameis, S., Arnold, P., Banaj, N., Bargallo, N., Batistuzzo, M. C., Benedetti, F., Beucke, J. C., Boedhoe, P. S. W., Bollettini, I., Brem, S., Calvo, A., Cho, K. I. K., Ciullo, V., Dallaspezia, S., . . . Spalletta, G. (2021). White matter microstructure and its relation to clinical features of obsessive-compulsive disorder: findings from the ENIGMA OCD Working Group. *Transl Psychiatry*, *11*(1), 173. https://doi.org/10.1038/s41398-021-01276-z

Posner, J., Marsh, R., Maia, T. V., Peterson, B. S., Gruber, A., & Simpson, H. B. (2014). Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with obsessive-compulsive disorder. *Hum Brain Mapp*, *35*(6), 2852-2860. https://doi.org/10.1002/hbm.22371

Rus, O. G., Reess, T. J., Wagner, G., Zaudig, M., Zimmer, C., & Koch, K. (2017). Hypogyrification in obsessive-compulsive disorder. *Psychol Med*, *47*(6), 1053-1061. https://doi.org/10.1017/S0033291716003202

Schulz, K. P., Bedard, A. V., Czarnecki, R., & Fan, J. (2011). Preparatory activity and connectivity in dorsal anterior cingulate cortex for cognitive control. *Neuroimage*, *57*(1), 242-250. https://doi.org/10.1016/j.neuroimage.2011.04.023

Shin, D. J., Jung, W. H., He, Y., Wang, J., Shim, G., Byun, M. S., Jang, J. H., Kim, S. N., Lee, T. Y., Park, H. Y., & Kwon, J. S. (2014). The effects of pharmacological treatment on functional brain connectome in obsessive-compulsive disorder. *Biol Psychiatry*, *75*(8), 606-614. https://doi.org/10.1016/j.biopsych.2013.09.002

Song, X.-W., Dong, Z.-Y., Long, X.-Y., Li, S.-F., Zuo, X.-N., Zhu, C.-Z., He, Y., Yan, C.-G., & Zang, Y.-F. (2011). REST: a toolkit for resting-state functional magnetic resonance imaging data processing. *PLoS One*, *6*(9), e25031.

Stevens, B. W., Morris, J. K., Diazgranados, N., & Ramchandani, V. A. (2022). Common Gray Matter Reductions in Alcohol Use and Obsessive-Compulsive Disorders: A Meta-analysis. *Biol Psychiatry Glob Open Sci*, *2*(4), 421-431. https://doi.org/10.1016/j.bpsgos.2021.11.010

van de Veerdonk, M. M. G. H., Bouwens van der Vlis, T. A. M., Ackermans, L., Schruers, K. R. J., Temel, Y., & Leentjens, A. F. G. (2023). The role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder. *Deep Brain Stimulation*, *3*, 1-7. https://doi.org/10.1016/j.jdbs.2023.07.001

Weeland, C. J., Kasprzak, S., de Joode, N. T., Abe, Y., Alonso, P., Ameis, S. H., Anticevic, A., Arnold, P. D., Balachander, S., & Banaj, N. (2022). The thalamus and its subnuclei—a gateway to obsessive-compulsive disorder. *Translational psychiatry*, *12*(1), 70.

Wu, C. W., Chen, C. L., Liu, P. Y., Chao, Y. P., Biswal, B. B., & Lin, C. P. (2011). Empirical evaluations of slice-timing, smoothing, and normalization effects in seed-based,

resting-state functional magnetic resonance imaging analyses. *Brain Connect*, *1*(5), 401-410. https://doi.org/10.1089/brain.2011.0018

Yan, C., & Zang, Y. (2010). DPARSF: a MATLAB toolbox for" pipeline" data analysis of resting-state fMRI. *Frontiers in systems neuroscience*, *4*, 1377.

Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zollei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*, *106*(3), 1125-1165. https://doi.org/10.1152/jn.00338.2011

Yu, X. M., Qiu, L. L., Huang, H. X., Zuo, X., Zhou, Z. H., Wang, S., Liu, H. S., & Tian, L. (2021). Comparison of resting-state spontaneous brain activity between treatment-naive schizophrenia and obsessive-compulsive disorder. *BMC Psychiatry*, *21*(1), 544. https://doi.org/10.1186/s12888-021-03554-y

Zang, Y., Jiang, T., Lu, Y., He, Y., & Tian, L. (2004). Regional homogeneity approach to fMRI data analysis. *Neuroimage*, *22*(1), 394-400. https://doi.org/10.1016/j.neuroimage.2003.12.030

Zang, Y. F., He, Y., Zhu, C. Z., Cao, Q. J., Sui, M. Q., Liang, M., Tian, L. X., Jiang, T. Z., & Wang, Y. F. (2007). Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain Dev*, *29*(2), 83-91. https://doi.org/10.1016/j.braindev.2006.07.002

Zhou, Z., Li, B., Jiang, J., Li, H., Cao, L., Zhang, S., Gao, Y., Zhang, L., Qiu, C., Huang, X., & Gong, Q. (2022). Abnormal resting-state functional connectivity of the insula in medication-free patients with obsessive-compulsive disorder. *BMC Psychiatry*, *22*(1), 742. https://doi.org/10.1186/s12888-022-04341-z

Zhu, Y., Fan, Q., Zhang, H., Qiu, J., Tan, L., Xiao, Z., Tong, S., Chen, J., & Li, Y. (2016). Altered intrinsic insular activity predicts symptom severity in unmedicated obsessive-compulsive disorder patients: a resting state functional magnetic resonance imaging study. *BMC Psychiatry*, *16*, 104. https://doi.org/10.1186/s12888-016-0806-9

Zou, Q. H., Zhu, C. Z., Yang, Y., Zuo, X. N., Long, X. Y., Cao, Q. J., Wang, Y. F., & Zang, Y. F. (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J Neurosci Methods*, *172*(1), 137-141. https://doi.org/10.1016/j.jneumeth.2008.04.012

Zuo, C., Ma, Y., Sun, B., Peng, S., Zhang, H., Eidelberg, D., & Guan, Y. (2013). Metabolic imaging of bilateral anterior capsulotomy in refractory obsessive compulsive disorder: an FDG PET study. *J Cereb Blood Flow Metab*, *33*(6), 880-887. https://doi.org/10.1038/jcbfm.2013.23

Zuo, X. N., Di Martino, A., Kelly, C., Shehzad, Z. E., Gee, D. G., Klein, D. F., Castellanos, F. X., Biswal, B. B., & Milham, M. P. (2010). The oscillating brain: complex and reliable. *Neuroimage*, *49*(2), 1432-1445. https://doi.org/10.1016/j.neuroimage.2009.09.037

4.0 General Discussion

4.1 Using tDCS To Modulate Inhibition In Patients

The present dissertation has successfully captured novel methods with which to quantify brain activity in OCD patients. We were able to successfully record BOLD measurements during inhibition task completion and non-invasive brain stimulation in OCD patients. Irrespective of the sequence order in which the stimulation was received, patients displayed a significant increase in the percentage of correct responses in the Stroop task during the stimulation condition in comparison to sham. Alongside this improvement in inhibition there were alterations in the fronto-parieto-cerebellar network, which included increased activation in the preSMA, the IFG, the ACC, the superior parietal lobe and parts of the cerebellum and thus in regions known to be highly relevant for inhibition and cognitive control. Hence, this dissertation indicates tDCS can improve inhibition in OCD, which is a ubiquitous deficit in OCD patients (Berlin & Lee, 2018; Snyder et al., 2015; van Velzen et al., 2014). We expect such inhibitory improvements to be sustained and, most probably, even stronger after multiple sessions of stimulation. A study recently demonstrated that with 10 repeating sessions of 2mA tDCS to the preSMA, albeit with a different electrode montage, it was able to show improved inhibition performance, in the form of significantly higher accuracy and reduced response times (RTs) in the inhibition trials up to a month post-intervention (Alizadehgoradel et al., 2024). There were unfortunately no fMRI recordings, making the comparison between underlying brain activation changes in our study and theirs difficult.

There have been additional studies investigating 10-20 multi-session tDCS effects in OCD, as summarised by this meta-analysis (Brunelin et al., 2018). The largest limitation facing such studies are their small power, as most only have a sample of around 10 participants. Narayanaswamy and colleagues (2015) showed anodal left preSMA tDCS successfully

increased preSMA activation during inhibition trials in their single case study, restoring OCD-typical preSMA hypoactivity during inhibition. This was additionally paired with symptom improvement following the 10 sessions (Narayanaswamy et al., 2015). PreSMA reduced activity during inhibition trials relative to HCs has generously been reported (Fitzgerald et al., 2005; Page et al., 2009; Roth et al., 2007; Rubia et al., 2010; Rubia et al., 2011; Woolley et al., 2008). 10 sessions of cathodal preSMA stimulation equally resulted in Y-BCOS score improvement in a different study, while opposite anodal stimulation worsened symptoms for most patients (D'Urso et al., 2016). Both these studies placed their other electrode outside of the 10-20 EEG coordinate system. We, however placed the anode lateral to the right preSMA and the cathode lateral to the left preSMA. It is likely that the direction of current has little influence on symptom and brain activity changes, so long as the EF reaches the preSMA bilaterally. The same was observed with the anodal left dorsolateral PFC and cathodal preSMA electrode montage of Alizadehgoradel et al. (2024). Meanwhile, Bation and colleagues (2019) did not find a larger improvement in Y-BOCS scores in the stimulation group compared to sham when applying tDCS to the OFC. Further studies are needed that incorporate fMRI recordings to better understand the underlying mechanisms associated with Y-BOCS score and inhibition performance improvement. This would allow enhanced insights into why Alizadehgoradel and colleagues (2024) found long-term improvements in only one of two inhibition tasks, despite both measuring response inhibition.

Our study set out to explore whether BOLD activation observations are in concert with measurable task performance improvement. This could then allude to BOLD activation changes being necessary for behavioural changes or vice versa no BOLD activation changes during stimulation being indicative of an accompanying lack of inhibition performance differences. We found that observed inhibition performance improvement in the Stroop task did occur in concert with increased BOLD activation in the ACC, the bilateral middle frontal gyrus, IFG,

supramarginal gyrus and cerebellum during stimulation. These observed BOLD activation alterations however did not correspond to a stimulation-induced decrease in reaction time in incongruent Stroop task trials. Hereby, our study adds to the evidence that increased activation in the preSMA, IFG, ACC, and other regions in the superior parietal lobe could be imperative for inhibition performance improvement. Additionally, momentarily reversing deficiencies found in OCD patients in the preSMA (de Wit et al., 2012; Nachev et al., 2007), the ACC (Norman et al., 2019)(see results in manuscript 2) and IFG (van Velzen et al., 2014).

4.1.1 Limitations Of FMRI

FMRI limitations encompass primarily the design of the study and this, in turn, can pertain to data acquisition considerations or data analysis interpretations. Limitations include signal to noise ratio alterations of specific sequences due to introducing tES cables into the scanner and headcoil. Additionally, head motion in patient populations and during task completion are to be considered, paired with the varying efficacy of head motion correction approaches (Goto et al., 2016). When examining the neuronal correlates of inhibition, the literature primarily reports concurrence of activation to be observed in a predominantly right-lateralized network involving the right preSMA, right middle/inferior frontal gyrus, bilateral inferior parietal regions, occipital regions and putamen (Nachev et al., 2007; Simmonds et al., 2008; Verbruggen & Logan, 2008). Even in a task with a relatively low complexity, such as inhibition tasks, findings between different studies are often relatively inconsistent. Tasks are chosen to adhere to either block or event-related fMRI task design. These have varying advantages and disadvantages which influence the BOLD activation contrasts between task conditions and baseline. Block designs are preferential for tasks which do not fit a trial-by-trial framework such as continuous exercises. Additionally, they optimise signal-to-noise ratio, as task conditions are clearly differentiated from baseline by forming blocks of identical trial types (Petersen & Dubis, 2012). Block designs, however, do not distinguish between correct and incorrect trials within a block,

instead averaging the two responses. They therefore do not represent the complexity and magnitude of the neural processes involved (Meltzer et al., 2008). In our case distinguishing between successful and unsuccessful inhibition trials was inherently crucial, therefore steering us towards an event-related design. The event-related design looks to extract neuronal activity from evoked haemodynamic responses and improves temporal resolution of fMRI analyses. Unfortunately, the signal-to-noise ratio is lower compared to block designs. Inclusion of jittered fixation frames in between trials allowed the haemodynamic response to return to baseline while still successfully describing a trial-type specific time course (Miezin et al., 2000).

Discrepancies in experimental observations described in the literature are because fMRI is only a proxy for neuronal activity. These recordings can also be influenced by acquisition sequences and environmental factors such as cardiovascular signals (Turner, 2016). The BOLD signal records the ratio between the strongly paramagnetic deoxygenated and non-magnetic oxygenated haemoglobin. Oxygen binds to the iron ion at the centre of each of the four heme groups, hence in deoxygenated haemoglobin there are unpaired electrons at each iron centre, which causes its strong paramagnetic characteristics (Marengo-Rowe, 2006; Zborowski et al., 2003). Increases in blood flow result in an increase in oxygenated haemoglobin and decrease in deoxygenated haemoglobin at the site of brain activation. The BOLD signal captured with EPI sequences thus simply represents changes in magnetic susceptibility of that voxel. Through neurovascular coupling, neuron and astrocyte activity elicits subsequent regional cerebral blood flow changes to restore oxygen levels. This cause a net decrease in deoxygenated haemoglobin concentration, which leads to an increase in the MR T2* signal (Turner, 2016). For this reason, the magnetic susceptibility changes due to increased oxygenated haemoglobin have a delay of 6 seconds from neuronal excitation (Bush & Cisler, 2013; Wink et al., 2008). This delay can additionally vary slightly depending on tissue perfusion and more largely due to pathological conditions such as ischemic stroke and hypertension (Girouard & Iadecola, 2006). During either

study, we unfortunately did not inquire about hypertension in participants. Furthermore, MR T2* signal is not always correlated to neuronal activity in the healthy brain. Specifically, a reduction in neuronal activity does not necessarily result in a decrease in BOLD signal (Schridde et al., 2008). Additionally, distinguishing the signal from neuronal activity to oxygen absorption rate at these voxels is incredibly challenging. These metabolic changes could be intrinsic to that area or being observed as a result of metabolic changes in other connected areas.

FMRI has gained a lot of popularity in the last two decades due to its high spatial resolution, with fMRI voxel sizes typically ranging between 2-3 mm^2. Advances in MR sequence design have allowed the implementation of slice acceleration using multiband echo planar imaging (EPI) at 3T (Xu et al., 2013). Nonetheless, multiband sequences also employed in the current study bring their own additional risk of other artefact formations, which is why slice acquisition acceleration and acquisition of too many slices at once should be avoided (Wall, 2023). Using a multiband factor of 2 in data acquisition of the first study described in this dissertation, allowed us to cut down repetition time to 1 second. Meaning we were able to acquire an entire 3D volume of the whole brain every second. Since we were scanning patients, who are already prone to more movement, while additionally receiving stimulation and performing button presses, we wanted to account for as much movement as possible to reduce movement-related false positive findings (Maknojia et al., 2019). Accounting for head motion during acquisition is not sufficient, as studies have found that even with nuisance regression and band pass filtering head motion can still influence connectivity outcomes (Hallquist et al., 2013). Hallquist and colleagues (2013) recommend a simultaneous filtering approach. For our rs-fMRI study we did successfully apply band pass filtering following nuisance regression, which performs better than the opposite. There was however no option to complete this simultaneously for the RESTplus toolbox utilised.

Finally, the context of an MR scan can be incredibly challenging for patients. In part due to being exposed to a hospital environment which sometimes triggered symptoms, but also due to being exposed to constant noise and distractions within the scanner.

4.1.2 Limitations Of TDCS

Variations in EF strength and focality are to be expected between patients and sessions. The individual brain anatomy varies depending on age and other environmental factors. Replicating exact electrode placement between the two sessions was impossible in our study, as we did not have access to expensive neurosurgery Neuronavigation systems and were therefore limited to EEG 10-20 placement. When electrode location was assessed via the T1 and T2 images of each session, we found electrode position and orientation to have slightly shifted between the sessions, in some participants more than others. Therefore, the need to quantify altering EFs post-hoc per subject and session was instrumental. The section below will highlight why despite having included these calculations in our manuscript, some considerations are essential to evaluating their validity.

Saturnino and colleagues (2019) investigated the effect of modelling EF using different tissue conductivities found in the literature for different types of tES montages. They found that in the case of two-electrode tDCS the grey matter conductivity uncertainty, in comparison to other tissues, was most relevant for EF calculations (Saturnino, Thielscher, et al., 2019). EF modelling for each individual participant's cortical gyrification and volume was therefore imperative. Especially as variability in cortical gyrification in disorder-relevant regions is more likely in patients (Fan et al., 2013; Park et al., 2023). Against this background, in the current study the potential influence of subject-specific EF strength values at the preSMA were therefore investigated using a mediation analysis. The analysis found no direct or indirect mediation effect of preSMA EF on the influence of stimulation-related preSMA brain activation on the stimulation-related inhibition. It neither found any association between the individual

measures. The investigation was aimed to additionally gain insight on whether tDCS has activity-selectivity: the assumption that tDCS will preferentially modulate specific forms of ongoing activity. A previous study with a bihemispheric tDCS montage targeting sensorimotor regions through tDCS stimulation during an online motor task showed dose dependent regional cerebral blood flow (CBF) recruitment and motor task improvement (Shinde et al., 2021). Only the highest dosage of 4 mA was able to additionally show indirect regional CBF effects in functionally connected regions for this set-up. While this is only a surrogate measure for neuronal depolarisation effects of tDCS, it demonstrates why accounting for dosage is vital. EF strength at sensorimotor or inhibition related areas could explain recruitment of other areas during either Stop-signal or Stroop inhibition task. Extending the mediation analysis to other functionally connected ROIs could have resulted in other findings, which were not originally envisioned when only the preSMA was included.

A second mediation analysis in our study examined whether skull thickness above the preSMA mediated preSMA activation or inhibition performance. Our analysis found that skull thickness did not mediate preSMA activation or inhibition performance nor inhibition performance through preSMA BOLD activation. This could be as target accuracy and focality with tES is limited, due to the afore mentioned low conductivity of the skull coupled with the comparatively high conductivity of CSF. This combination causes the EF to spatially disperse intrinsically and to hereby limit the achievable spatial resolution (Dmochowski et al., 2012). When only quantifying skull thickness, the relatively large volume of CSF surrounding the preSMA is ignored. Close to the CSF the EFs have the tendency to point in the lateral direction (towards CSF) enforcing a field direction normal to the cortical sheet, compromising targeting accuracy (Saturnino, Siebner, et al., 2019). Another limitation of the second mediation analysis is that it lacks information on the proportion of spongy and compact bone observed at the skull above the preSMA. The different bone types have differing conductivity values, thus deeming

skull thickness an incomplete measure. These results paired with investigations showing a wide variety in spatial distributions of axonal and dendritic terminal polarisation, suggest tDCS specific effects could arise from selective modulation of active circuits or biasing of different synaptic inputs instead (Bikson et al., 2013).

Studies have reported that EF spatial focality is strongly dependent on electrode position (Klaus & Schutter, 2021; Videira et al., 2022). Evaluating differences in EF location and strength between multiple timepoints is essential to better understand varying tDCS effects (Klaus & Schutter, 2021). There has been growing evidence on how relatively minor anatomical differences such as skull thickness (Antonenko et al., 2021; Opitz et al., 2015), CSF thickness (Mosayebi-Samani et al., 2021; Opitz et al., 2015), local tissue variability (Russell et al., 2013), general subcutaneous fat (Truong et al., 2013), neuron orientation to the field (Arlotti et al., 2012) and gyrification (Datta et al., 2012; Opitz et al., 2015) can alter tDCS neuromodulatory effects. These characteristics not only range per individual but also vary depending on the electrode position and orientation of that session, which once more highlights the importance of EF modelling (Foerster et al., 2019; Klaus & Schutter, 2021; Saturnino et al., 2015; Videira et al., 2022).

Commonplace EF modelling software only allows studies to investigate the uniform direct current EF. With this model, distant current sources on the head create an EF in the brain where stimulation establishes a gradient of polarization across a neuron's morphology. Depolarisation happens at the anode, hyperpolarization at the cathode and virtually no change near the centre (Akiyama et al., 2011; Bikson et al., 2004). Conclusions of Akiyama et al. (2011) and Bikson et al. (2004) were based on in vitro recording of rat hippocampal slices. Conversely, when consulting human cortex modelling, cortical gyrification leads to both directions of current flow in neighbouring neurons, complicating the overall polarisation effects. Aberra et al. (2023) more recently investigated neuronal polarisation in a morphologically realistic human cortical neuron

model. They found that the polarisation of soma, axon and dendrites across EF varied by cell type, albeit axonal and dendritic terminals being overall more polarised than the soma in all neuron types. Polarisation of any neurons, including even interneurons was not correlated with the tangential current of the electrodes. Pyramidal cell somatic polarisation was strongly correlated with the normal component of the EF but had weaker correlations with the axonal and dendritic polarisation, more important for overall excitatory effect (Aberra et al., 2023). The normal component has previously been given a lot of importance in EF modelling, due to its comparative strength to the weaker tangential component (Miranda et al., 2013). Generally, both the high-definition (HD) set-up, which uses four circular cathodes and one anode, as well as the regular tDCS, showed depolarisation and hyperpolarisation beneath the anode, with bimodal distributions of peak polarisation in the dendrite and axon (Aberra et al., 2023). This could explain why, rather than EF distribution, the area covered by the electrode over the M1 was indicative to whether cortical excitability/inhibition was observed in another study (Foerster et al., 2019).

In summary, complexities of EF projection to the pyramidal neuros in the cortex result in tES montages stimulating large areas, which make it difficult to attribute an experimental outcome to the stimulation of a particular brain region. Our design aims to circumvent this by identifying the brain activity changes between the sham and stimulation timepoints of the same participant. This way we could identify areas attributed to behavioural improvements and other experimental outcomes. To better outline this causality, concurrent tES-fMRI or tES-EEG studies are needed. Another recent trend in tES is the designing of so called closed-loop studies, which record brain activity before, throughout and after the stimulation to better understand effects derived from it (Ekhtiari et al., 2022; Stecher et al., 2021).

4.1.3 Task Limitations

One of the aims of the first study was to assess whether tCDS targeting the right preSMA of OCD patients was able to improve inhibition performance of these patients. Previous tDCS studies had indicated these effects to be measurable using both Stroop and Stop-signal tasks in healthy and ADHD patients (Cai et al., 2016; Narmashiri & Akbari, 2023; Schroeder et al., 2020; Tomiyama et al., 2022; Yu et al., 2015). Some of these studies performed the task following tDCS application (Cai et al., 2016; Tomiyama et al., 2022; Yu et al., 2015), while others reported both online and offline task effects (Narmashiri & Akbari, 2023; Schroeder et al., 2020). Our study was able to demonstrate a tDCS-induced improvement in inhibition performance in the Stroop task and an associated increase in inhibition-relevant brain activity. The improvement in inhibition performance was detectable in terms of an increased response velocity, yet we did not observe a significant improvement in inhibition accuracy. Null findings following a single session of tDCS are common in the literature. One meta-analysis examined single session tDCS effect on working memory and language production tasks and found it had no reliable influence on either (Horvath et al., 2015). Schroeder and colleagues (2020) examined 45 tDCS studies on HCs and concluded that Stop-signal task performance modulation from a single session of tDCS was quite unlikely. Furthermore, the task variation in this meta-analysis significantly shaped behavioural outcomes at least as much as technical tDCS parameters, which could explain significant findings of some studies in HCs. These observations are also in line with the aforementioned proposal of functional specificity and non-focal nature of tDCS (Bikson et al., 2013). Nonetheless, the study was not able to do an extensive variable moderation analysis, leaving us to speculate (Schroeder et al., 2020). Poor effect sizes on modulation of inhibitory performance after a single session tDCS in HCs are not necessarily directly applicable to OCD patient studies. OCD-specific deficiencies in inhibition tasks have a multitude of underlying mechanisms that contribute to performance effects

differently depending on the task design. This makes their sensitivity to being altered by tDCS not comparable to HCs. Studies have shown that OCD patients have greater avoidance habits and hyperactive neural error-signals (Gillan et al., 2014; Riesel, 2019; Riesel et al., 2019). These differences depend on the type of task being performed and are exacerbated when speed is prioritised, while not being significant between OCD and HCs when accuracy is encouraged (Riesel, 2019; Riesel et al., 2019). Another key component for activity specificity is taking into consideration online vs offline effects. Narmashiri and Akbari (2023) investigated the effect online tDCS had on cognitive task performance in 69 studies. Online task design compared to offline task completion showed significantly larger effect size in inhibition RT. It curiously showed a significantly larger effect size in working memory accuracy but a significantly lower effect size in flexibility accuracy in online studies (Narmashiri & Akbari, 2023).

Finally, yet another aspect to highlight is the variability of cognitive mechanisms that different tasks target. Sebastian et al. (2013) differentiates between inference inhibition, action withholding and action cancellation, listed in order of complexity of demands. The study set out to build a task which incorporated all subprocesses, showing that depending on task parameters they can capture different behaviours. When comparing action cancellation with action withholding they found increased activation in the bilateral IFC, preSMA, right striatum and left inferior parietal lobule (Sebastian et al., 2013). Deficits observed in OCD patients differ, for example Chamberlain and colleagues (2006) found action cancellation, assessed with the stop-signal task, correlated with OCD disease severity, while cognitive flexibility deficits were not found to be correlated in both Chamberlain et al. (2006) and Britton et al. (2010). However, Bohne and colleagues (2008) found action restrain impairments to be inconsistent and only observed in patients with an early onset of the disorder. The relevance of these different inhibitory sub-processes might explain why studies using different inhibition tasks reported partly inconsistent results. The Stroop task is more challenging to categorise.

Participants must refrain from reading the word and simply focus on the colour it is printed in. However, since these are the colours red, blue, green and yellow, our brain would read them in milliseconds speed. Therefore, it could be argued the participant is withholding the action of responding to the meaning of the word, forcing themselves to refocus on the colour it is printed in. There is a lot of disparity on the definition between these subprocesses, making it hard to directly compare previous findings.

4.2 Altered Intrinsic Functional Connectivity in OCD

The present dissertation successfully executed the calculation of the novel methods PerAF and mPerAF in resting-state fMRI (rs-fMRI). The results presented indicate that (m)perAF identifies differences in LFOs between OCD patients and HCs, providing new insights into spontaneous brain activity in OCD patients and contributing to an improved understanding of the underlying pathophysiology.

We expected to find alterations in LFOs in areas related to the CSTC loop, as well as in those areas involved in inhibition performance, as underlined in the previous study. Markedly, the group comparison revealed decreased LFOs in OCD patients, compared to HCs. Both metrics found decreased LFOs in the bilateral cingulate gyrus and right temporal gyrus. Additionally, mPerAF detected decreases in the bilateral thalamus and right insula. There were some trends in correlations, but none were significant after multiple comparisons. Decreased PerAF in the bilateral cingulate was associated with increased Y-BOCS compulsion scores. Lower LFOs in the cingulate gyrus were found in patients with higher compulsions, thus emphasizing the clinical relevance of these LFO alterations. PerAF additionally decreased in the temporal gyrus with duration of illness whereas mPerAF in the temporal gyrus was significantly higher in medicated patients. This suggests that the longer patients have been diagnosed with OCD, the less activity they display in the temporal gyrus, whereas medication seems to rather have a therapeutic effect in this case on LFOs irregularities.

Bruin et al. (2023) published the largest resting state connectivity analysis in OCD conducted to date, which found no differences in fronto-striatal connectivity between OCD patients and HCs. The only alteration in functional differences within the basal ganglia were found between the thalamus and the caudate. This is in line with (m)PerAF also only observing significant changes in LFOs in the thalamus and no other stratal regions in our study. Despite our rs-fMRI study finding altered LFOs in parts of the CSTC circuit (e.g., the thalamus) in the present OCD sample, our hypothesis to detect the "classical" CSTC changes could not be corroborated by the present findings. A possible reason for discrepancies with other studies which found other alterations in the basal ganglia could be their use of pre-determined seeds, which has previously featured heavily in rs-fMRI analyses.

Switching or mediating activation between DMN, involved in self-referential thoughts and internal processes, and FPN, involved in external goal directed behaviour, is assumed to constitute the underlying neurobiological function of the salience network (Menon, 2011). This notion of the salience network switching between DMN and frontoparietal network has been conceptualized in the "triple network model" (Gursel et al., 2018; Menon, 2011; Stern et al., 2012). OCD patients' inability to switch attention between internal thoughts and goal-directed behaviour may thus constitute a central mechanism underlying obsessive-compulsive behavioural patterns. Sridharan and colleagues (2008) have found the ACC and right insula to be critical in switching between the DMN and executive networks in HCs. In line with this Stern et al. (2012) investigated connectivity between the FPN and the DMN in OCD patients and found altered connectivity between the anterior insula and the DMN. Another functional connectivity study highlighted the importance of cortical networks, particularly involving the insula and cingulate cortex in the pathophysiology of OCD (Cocchi et al., 2012). Our study's bilateral cingulate gyrus alterations in PerAF and mPerAF, as well as PerAF differences in the

right insula between the groups might likewise be an indicator of these deficiencies in network switching.

The bilateral thalamus has been widely implicated in the pathophysiology of OCD, especially in the framework of an alteration within the CSTC circuit. Studies reporting on thalamic volume alterations have seen contrasting results, with some reporting increases (Atmaca et al., 2019; Atmaca et al., 2007) in volume and others reporting decreases in volume (Jurng et al., 2021; Weeland et al., 2022). Weeland and colleagues (2022) conducted a large multi-cite study and showed larger thalamic volumes in children with OCD yet smaller thalamic volumes in adults with OCD. Additionally, only symptom severity in adults was negatively associated with volume. Our (m)PerAf findings showing decreased spontaneous brain activity in the bilateral thalamus might be related to these grey matter alterations, albeit the extent of these structural alterations is certainly much lower than the observed LFO changes.

The alterations found in the second study are in concordance with previous literature, contributing evidence to specific regions which should be revised further. It should also be noted that there were no significant LFO increases in patients compared to healthy individuals. This is partly in line with previous, albeit methodologically different, studies. Thus, the present study differs not only with regards to the analysis parameter (i.e., (m)perAF), but also stands out through its comparatively large study size and its unbiased design, not including any pre-determined seeds or ROIs. It further has implemented multiple comparison thresholds, which previous studies variably do (Bennett et al., 2009). Nonetheless, a limitation of applying a new intrinsic functional connectivity method, is that there is a lack of studies testing its reliability using different statistical methods. Therefore, we have no evidence for an improvement or lack thereof of (m)PerAF's test-retest reliability and replicability albeit previous findings suggest an improved test-retest reliability predominantly for the mPerAF parameter. Nevertheless,

additional studies are certainly needed to assess the reliability and replicability of this relatively new resting state measure.

5.0 Conclusions & Outlook

Implementation of tCDS as a potential therapeutic agent has so far seen poor study design, including open label studies (Bation et al., 2016; Dinn et al., 2016; Najafi et al., 2017), low number of subjects and no EEG or MRI biomarker measurements (Brunelin et al., 2018; D'Urso et al., 2016). tDCS as an alternative therapeutic has wide-reaching implications, as it is mobile and relatively easy for patients to implement with non-specialised personnel at the clinic or alternatively on their own. Not only for these reasons, tDCS is increasingly being applied as an add-on therapy in hospital care for several different disorders or mental states. With causal modulation of cerebral excitability with tDCS, we expected to momentarily restore functional abnormalities in the OCD-relevant brain circuity. In principal accordance, we expected the intervention to be associated with behavioural and clinical improvement in our study. Clinical improvement was not achieved from a single session of tDCS. At first sight, this seems somewhat surprising considering that we assume a close association between inhibition capacities and compulsions as well as, albeit to a lesser degree, obsessions. Our findings however suggest that single session tDCS has the capacity to, potentially transiently, improve behavioural inhibition without leading to a perceived amelioration of compulsions or obsessions. This, in turn, may have various reasons including heterogeneity of clinical characteristics, limited self-awareness (which is necessary for a patient to realize a potential, even transient, symptom relief) or study-design related aspects (i.e., inhibition performance was recorded during tDCS whereas assessment of clinical symptoms could only be performed about an hour after tDCS. Alternatively, it is also conceivable that the relationship between inhibition capacities and clinical symptoms is not as close as assumed and single session tDCS simply does not have a significant effect on symptomatology. Despite this limitation, the changes in inhibition-related BOLD activations and the improvement in inhibition performance indicate that it might be worthwhile to apply this study design in the context of a multi-session study.

Future studies could make use of HD tDCS montages, which consist of usually 4 circular cathode electrodes surrounding one circular anode. They are designed to produce more focal polarisation, reducing current in off-target structures. One study comparing the HD montage to the standard tDCS montage found stronger, longer-lasting motor cortex excitability enhancements, as measured by TMS, with the HD montage (Kuo et al., 2013), In concordance, Aberra and colleagues' (2023) morphologically realistic cortical neuron models showed that HD montages also produced higher maximum neuronal polarisation in the gyral crown. We were unable to implement an HD montage, as the tDCS-MRI compatible device and cables we had access to limited its configuration to a single anode and cathode. The manufacturer, Neurocare, has only recently released MR compatible components allowing for more electrodes.

The areas showing significant (m)PerAF differences were neuropathologically relevant and plausible, thereby providing valuable insights into the underlying pathophysiology. LFOs in patients were all weaker compared to those in healthy individuals thus suggesting a lack of spontaneous brain activity in these networks known to be relevant for diverse processes as discussed above. The second study presented suggests multiple avenues for future research. Particularly, a methodological (m)PerAF study is necessary, where with a larger OCD sample, the effect of different preprocessing parameters on PerAF and mPerAF are reported. This would aid in reconfirming the preprocessing choices that were made, following Jia et al. (2020). Additionally, the field requires investigation of these parameters on different rs-fMRI acquisition sequences, necessary to elucidate reproducibility of these metrics.

In conclusion, the two projects included in this dissertation reaffirmed key neuronal correlates of OCD. They additionally provide future studies with well documented metrics to replicate these studies in larger samples and/or less heterogenic samples.

6.0 References

Aberra, A. S., Wang, R., Grill, W. M., & Peterchev, A. V. (2023). Multi-scale model of axonal and dendritic polarization by transcranial direct current stimulation in realistic head geometry. *Brain Stimul*, *16*(6), 1776-1791. https://doi.org/10.1016/j.brs.2023.11.018

Akiyama, H., Shimizu, Y., Miyakawa, H., & Inoue, M. (2011). Extracellular DC electric fields induce nonuniform membrane polarization in rat hippocampal CA1 pyramidal neurons. *Brain Res*, *1383*, 22-35. https://doi.org/10.1016/j.brainres.2011.01.097

Alizadehgoradel, J., Molaei, B., Barzegar Jalali, K., Pouresmali, A., Sharifi, K., Hallajian, A. H., Nejati, V., Glinski, B., Vicario, C. M., Nitsche, M. A., & Salehinejad, M. A. (2024). Targeting the prefrontal-supplementary motor network in obsessive-compulsive disorder with intensified electrical stimulation in two dosages: a randomized, controlled trial. *Transl Psychiatry*, *14*(1), 78. https://doi.org/10.1038/s41398-024-02736-y

American Psychiatric Association, D., & Association, A. P. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (Vol. 5). American psychiatric association Washington, DC.

Anticevic, A., Hu, S., Zhang, S., Savic, A., Billingslea, E., Wasylink, S., Repovs, G., Cole, M. W., Bednarski, S., Krystal, J. H., Bloch, M. H., Li, C. S., & Pittenger, C. (2014). Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. *Biol Psychiatry*, *75*(8), 595-605. https://doi.org/10.1016/j.biopsych.2013.10.021

Antonenko, D., Grittner, U., Saturnino, G., Nierhaus, T., Thielscher, A., & Floel, A. (2021). Inter-individual and age-dependent variability in simulated electric fields induced by conventional transcranial electrical stimulation. *Neuroimage*, *224*, 117413. https://doi.org/10.1016/j.neuroimage.2020.117413

Arlotti, M., Rahman, A., Minhas, P., & Bikson, M. (2012). Axon terminal polarization induced by weak uniform DC electric fields: a modeling study. *Annu Int Conf IEEE Eng Med Biol Soc*, *2012*, 4575-4578. https://doi.org/10.1109/EMBC.2012.6346985

Atmaca, M., Korucu, T., Tabara, M. F., Yildirim, H., & Kilic, M. C. (2019). Volumetric MRI study of orbito-frontal cortex and thalamus in obsessive-compulsive personality disorder. *J Clin Neurosci*, *64*, 89-93. https://doi.org/10.1016/j.jocn.2019.03.062

Atmaca, M., Yildirim, H., Ozdemir, H., Tezcan, E., & Poyraz, A. K. (2007). Volumetric MRI study of key brain regions implicated in obsessive-compulsive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*, *31*(1), 46-52. https://doi.org/10.1016/j.pnpbp.2006.06.008

Balasubramani, P. P., Pesce, M. C., & Hayden, B. Y. (2020). Activity in orbitofrontal neuronal ensembles reflects inhibitory control. *Eur J Neurosci*, *51*(10), 2033-2051. https://doi.org/10.1111/ejn.14638

Banca, P., Voon, V., Vestergaard, M. D., Philipiak, G., Almeida, I., Pocinho, F., Relvas, J., & Castelo-Branco, M. (2015). Imbalance in habitual versus goal directed neural systems during symptom provocation in obsessive-compulsive disorder. *Brain*, *138*(Pt 3), 798-811. https://doi.org/10.1093/brain/awu379

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. *Eur 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. *Prog Neuropsychopharmacol Biol Psychiatry*, *65*, 153-157. https://doi.org/10.1016/j.pnpbp.2015.10.001

Baup, N., Grabli, D., Karachi, C., Mounayar, S., Francois, C., Yelnik, J., Feger, J., & Tremblay, L. (2008). High-frequency stimulation of the anterior subthalamic nucleus reduces stereotyped behaviors in primates. *J Neurosci*, *28*(35), 8785-8788. https://doi.org/10.1523/JNEUROSCI.2384-08.2008

Baxter Jr, L., Schwartz, J., Mazziotta, J., Phelps, M., Pahl, J., Guze, B., & Fairbanks, L. (1988). Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *The American journal of psychiatry*, *145*(12), 1560-1563.

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.

Bennett, C. M., Wolford, G. L., & Miller, M. B. (2009). The principled control of false positives in neuroimaging. *Soc Cogn Affect Neurosci*, *4*(4), 417-422. https://doi.org/10.1093/scan/nsp053

Berlin, G. S., & Lee, H. J. (2018). Response inhibition and error-monitoring processes in individuals with obsessive-compulsive disorder. *J Obsessive Compuls Relat Disord*, *16*, 21-27. https://doi.org/10.1016/j.jocrd.2017.11.001

Beucke, J. C., Sepulcre, J., Talukdar, T., Linnman, C., Zschenderlein, K., Endrass, T., Kaufmann, C., & Kathmann, N. (2013). Abnormally high degree connectivity of the orbitofrontal cortex in obsessive-compulsive disorder. *JAMA Psychiatry*, *70*(6), 619-629. https://doi.org/10.1001/jamapsychiatry.2013.173

Bikson, M., Inoue, M., Akiyama, H., Deans, J. K., Fox, J. E., Miyakawa, H., & Jefferys, J. G. (2004). Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices in vitro. *J Physiol*, *557*(Pt 1), 175-190. https://doi.org/10.1113/jphysiol.2003.055772

Bikson, M., Name, A., & Rahman, A. (2013). Origins of specificity during tDCS: anatomical, activity-selective, and input-bias mechanisms. *Front Hum Neurosci*, *7*, 688. https://doi.org/10.3389/fnhum.2013.00688

Bloch, M. H., Green, C., Kichuk, S. A., Dombrowski, P. A., Wasylink, S., Billingslea, E., Landeros-Weisenberger, A., Kelmendi, B., Goodman, W. K., Leckman, J. F., Coric, V., & Pittenger, C. (2013). Long-term outcome in adults with obsessive-compulsive disorder. *Depress Anxiety*, *30*(8), 716-722. https://doi.org/10.1002/da.22103

Bohne, A., Savage, C. R., Deckersbach, T., Keuthen, N. J., & Wilhelm, S. (2008). Motor inhibition in trichotillomania and obsessive-compulsive disorder. *J Psychiatr Res*, *42*(2), 141-150. https://doi.org/10.1016/j.jpsychires.2006.11.008

Britton, J. C., Rauch, S. L., Rosso, I. M., Killgore, W. D., Price, L. M., Ragan, J., Chosak, A., Hezel, D. M., Pine, D. S., & Leibenluft, E. (2010). Cognitive inflexibility and frontal-cortical activation in pediatric obsessive-compulsive disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*(9), 944-953.

Broekhuizen, A., Vriend, C., Wolf, N., Koenen, E. H., van Oppen, P., van Balkom, A., Visser, H. A. D., & van den Heuvel, O. A. (2023). Poor Insight in Obsessive-Compulsive Disorder as a Multifaceted Phenomenon: Evidence From Brain Activation During Symptom Provocation. *Biol Psychiatry Cogn Neurosci Neuroimaging*, *8*(11), 1135-1144. https://doi.org/10.1016/j.bpsc.2023.04.006

Bruin, W. B., Abe, Y., Alonso, P., Anticevic, A., Backhausen, L. L., Balachander, S., Bargallo, N., Batistuzzo, M. C., Benedetti, F., & Bertolin Triquell, S. (2023). The functional connectome in obsessive-compulsive disorder: resting-state mega-analysis and machine learning classification for the ENIGMA-OCD consortium. *Molecular Psychiatry*, 1-13.

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 Sci*, *8*(2). https://doi.org/10.3390/brainsci8020037

Bush, K., & Cisler, J. (2013). Decoding neural events from fMRI BOLD signal: a comparison of existing approaches and development of a new algorithm. *Magn Reson Imaging*, *31*(6), 976-989. https://doi.org/10.1016/j.mri.2013.03.015

Cai, Y., Li, S., Liu, J., Li, D., Feng, Z., Wang, Q., Chen, C., & Xue, G. (2016). The Role of the Frontal and Parietal Cortex in Proactive and Reactive Inhibitory Control: A Transcranial Direct Current Stimulation Study. *Journal of Cognitive Neuroscience*, *28*(1), 177-186. https://doi.org/10.1162/jocn_a_00888

Calza, J., Gursel, D. A., Schmitz-Koep, B., Bremer, B., Reinholz, L., Berberich, G., & Koch, K. (2019). Altered Cortico-Striatal Functional Connectivity During Resting State in Obsessive-Compulsive Disorder. *Front Psychiatry*, *10*, 319. https://doi.org/10.3389/fpsyt.2019.00319

Catapano, F., Perris, F., Fabrazzo, M., Cioffi, V., Giacco, D., De Santis, V., & Maj, M. (2010). Obsessive-compulsive disorder with poor insight: a three-year prospective study. *Prog Neuropsychopharmacol Biol Psychiatry*, *34*(2), 323-330. https://doi.org/10.1016/j.pnpbp.2009.12.007

Chamberlain, S. R., Fineberg, N. A., Blackwell, A. D., Robbins, T. W., & Sahakian, B. J. (2006). Motor inhibition and cognitive flexibility in obsessive-compulsive disorder and trichotillomania. *American Journal of Psychiatry*, *163*(7), 1282-1284.

Chambers, C. D., Bellgrove, M. A., Gould, I. C., English, T., Garavan, H., McNaught, E., Kamke, M., & Mattingley, J. B. (2007). Dissociable mechanisms of cognitive control in prefrontal and premotor cortex. *J Neurophysiol*, *98*(6), 3638-3647. https://doi.org/10.1152/jn.00685.2007

Chambers, C. D., Garavan, H., & Bellgrove, M. A. (2009). Insights into the neural basis of response inhibition from cognitive and clinical neuroscience. *Neurosci Biobehav Rev*, *33*(5), 631-646. https://doi.org/10.1016/j.neubiorev.2008.08.016

Chen, C. Y., Muggleton, N. G., Tzeng, O. J., Hung, D. L., & Juan, C. H. (2009). Control of prepotent responses by the superior medial frontal cortex. *Neuroimage*, *44*(2), 537-545. https://doi.org/10.1016/j.neuroimage.2008.09.005

Cocchi, L., Harrison, B. J., Pujol, J., Harding, I. H., Fornito, A., Pantelis, C., & Yucel, M. (2012). Functional alterations of large-scale brain networks related to cognitive control in obsessive-compulsive disorder. *Hum Brain Mapp*, *33*(5), 1089-1106. https://doi.org/10.1002/hbm.21270

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

Datta, A., Truong, D., Minhas, P., Parra, L. C., & Bikson, M. (2012). Inter-Individual Variation during Transcranial Direct Current Stimulation and Normalization of Dose Using MRI-Derived Computational Models. *Front Psychiatry*, *3*, 91. https://doi.org/10.3389/fpsyt.2012.00091

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. *Am J Psychiatry*, *169*(10), 1100-1108. https://doi.org/10.1176/appi.ajp.2012.12010073

Del Casale, A., Sorice, S., Padovano, A., Simmaco, M., Ferracuti, S., Lamis, D. A., Rapinesi, C., Sani, G., Girardi, P., Kotzalidis, G. D., & Pompili, M. (2019). Psychopharmacological Treatment of Obsessive-Compulsive Disorder (OCD). *Curr*

Neuropharmacol, *17*(8), 710-736. https://doi.org/10.2174/1570159X16666180813155017

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. https://doi.org/10.1016/j.npbr.2016.08.003

Dmochowski, J. P., Bikson, M., & Parra, L. C. (2012). The point spread function of the human head and its implications for transcranial current stimulation. *Phys Med Biol*, *57*(20), 6459-6477. https://doi.org/10.1088/0031-9155/57/20/6459

Echevarria, M. A. N., Batistuzzo, M. C., Silva, R. M. F., Brunoni, A. R., Sato, J. R., Miguel, E. C., Hoexter, M. Q., & Shavitt, R. G. (2024). Increases in functional connectivity between the default mode network and sensorimotor network correlate with symptomatic improvement after transcranial direct current stimulation for obsessive-compulsive disorder. *J Affect Disord*, *355*, 175-183. https://doi.org/10.1016/j.jad.2024.03.141

Ekhtiari, H., Ghobadi-Azbari, P., Thielscher, A., Antal, A., Li, L. M., Shereen, A. D., Cabral-Calderin, Y., Keeser, D., Bergmann, T. O., Jamil, A., Violante, I. R., Almeida, J., Meinzer, M., Siebner, H. R., Woods, A. J., Stagg, C. J., Abend, R., Antonenko, D., Auer, T., . . . Bikson, M. (2022). A checklist for assessing the methodological quality of concurrent tES-fMRI studies (ContES checklist): a consensus study and statement. *Nat Protoc*, *17*(3), 596-617. https://doi.org/10.1038/s41596-021-00664-5

Elliott, R., & Deakin, B. (2005). Role of the orbitofrontal cortex in reinforcement processing and inhibitory control: evidence from functional magnetic resonance imaging studies in healthy human subjects. *International review of neurobiology*, *65*, 89-116.

Fan, Q., Palaniyappan, L., Tan, L., Wang, J., Wang, X., Li, C., Zhang, T., Jiang, K., Xiao, Z., & Liddle, P. F. (2013). Surface anatomical profile of the cerebral cortex in obsessive-compulsive disorder: a study of cortical thickness, folding and surface area. *Psychol Med*, *43*(5), 1081-1091. https://doi.org/10.1017/S0033291712001845

Fettes, P., Schulze, L., & Downar, J. (2017). Cortico-Striatal-Thalamic Loop Circuits of the Orbitofrontal Cortex: Promising Therapeutic Targets in Psychiatric Illness. *Front Syst Neurosci*, *11*, 25. https://doi.org/10.3389/fnsys.2017.00025

Fineberg, N. A., Tonnoir, B., Lemming, O., & Stein, D. J. (2007). Escitalopram prevents relapse of obsessive-compulsive disorder. *Eur Neuropsychopharmacol*, *17*(6-7), 430-439. https://doi.org/10.1016/j.euroneuro.2006.11.005

Fitzgerald, K. D., Moore, G. J., Paulson, L. A., Stewart, C. M., & Rosenberg, D. R. (2000). Proton spectroscopic imaging of the thalamus in treatment-naive pediatric obsessive–compulsive disorder∗. *Biological Psychiatry*, *47*(3), 174-182.

Fitzgerald, K. D., Welsh, R. C., Gehring, W. J., Abelson, J. L., Himle, J. A., Liberzon, I., & Taylor, S. F. (2005). Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biol Psychiatry*, *57*(3), 287-294. https://doi.org/10.1016/j.biopsych.2004.10.038

Floden, D., & Stuss, D. T. (2006). Inhibitory Control is Slowed in Patients with Right Superior Medial Frontal Damage. *Journal of Cognitive Neuroscience*, *18*(11), 1843-1849. https://doi.org/10.1162/jocn.2006.18.11.1843

Foerster, A., Yavari, F., Farnad, L., Jamil, A., Paulus, W., Nitsche, M. A., & Kuo, M. F. (2019). Effects of electrode angle-orientation on the impact of transcranial direct current stimulation on motor cortex excitability. *Brain Stimul*, *12*(2), 263-266. https://doi.org/10.1016/j.brs.2018.10.014

Gargano, S. P., Santos, M. G., Taylor, S. M., & Pastis, I. (2023). A closer look to neural pathways and psychopharmacology of obsessive compulsive disorder. *Front Behav Neurosci*, *17*, 1282246. https://doi.org/10.3389/fnbeh.2023.1282246

Gillan, C. M., Morein-Zamir, S., Urcelay, G. P., Sule, A., Voon, V., Apergis-Schoute, A. M., Fineberg, N. A., Sahakian, B. J., & Robbins, T. W. (2014). Enhanced avoidance habits in obsessive-compulsive disorder. *Biol Psychiatry*, *75*(8), 631-638. https://doi.org/10.1016/j.biopsych.2013.02.002

Gillan, C. M., Papmeyer, M., Morein-Zamir, S., Sahakian, B. J., Fineberg, N. A., Robbins, T. W., & de Wit, S. (2011). Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *American Journal of Psychiatry*, *168*(7), 718-726.

Girouard, H., & Iadecola, C. (2006). Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. *J Appl Physiol (1985)*, *100*(1), 328-335. https://doi.org/10.1152/japplphysiol.00966.2005

Goddard, A. W., Shekhar, A., Whiteman, A. F., & McDougle, C. J. (2008). Serotoninergic mechanisms in the treatment of obsessive-compulsive disorder. *Drug Discov Today*, *13*(7-8), 325-332. https://doi.org/10.1016/j.drudis.2007.12.009

Goksu, C., Scheffler, K., Gregersen, F., Eroglu, H. H., Heule, R., Siebner, H. R., Hanson, L. G., & Thielscher, A. (2021). Sensitivity and resolution improvement for in vivo magnetic resonance current-density imaging of the human brain. *Magn Reson Med*, *86*(6), 3131-3146. https://doi.org/10.1002/mrm.28944

Goncalves, O. F., Soares, J. M., Carvalho, S., Leite, J., Ganho-Avila, A., Fernandes-Goncalves, A., Pocinho, F., Carracedo, A., & Sampaio, A. (2017). Patterns of Default Mode Network Deactivation in Obsessive Compulsive Disorder. *Sci Rep*, *7*, 44468. https://doi.org/10.1038/srep44468

Goto, M., Abe, O., Miyati, T., Yamasue, H., Gomi, T., & Takeda, T. (2016). Head Motion and Correction Methods in Resting-state Functional MRI. *Magn Reson Med Sci*, *15*(2), 178-186. https://doi.org/10.2463/mrms.rev.2015-0060

Gray, N. A., Milak, M. S., DeLorenzo, C., Ogden, R. T., Huang, Y. Y., Mann, J. J., & Parsey, R. V. (2013). Antidepressant treatment reduces serotonin-1A autoreceptor binding in major depressive disorder. *Biol Psychiatry*, *74*(1), 26-31. https://doi.org/10.1016/j.biopsych.2012.11.012

Gremel, C. M., & Costa, R. M. (2013). Orbitofrontal and striatal circuits dynamically encode the shift between goal-directed and habitual actions. *Nat Commun*, *4*, 2264. https://doi.org/10.1038/ncomms3264

Guehl, D., Benazzouz, A., Aouizerate, B., Cuny, E., Rotge, J. Y., Rougier, A., Tignol, J., Bioulac, B., & Burbaud, P. (2008). Neuronal correlates of obsessions in the caudate nucleus. *Biol Psychiatry*, *63*(6), 557-562. https://doi.org/10.1016/j.biopsych.2007.06.023

Gursel, D. A., Avram, M., Sorg, C., Brandl, F., & Koch, K. (2018). Frontoparietal areas link impairments of large-scale intrinsic brain networks with aberrant fronto-striatal interactions in OCD: a meta-analysis of resting-state functional connectivity. *Neurosci Biobehav Rev*, *87*, 151-160. https://doi.org/10.1016/j.neubiorev.2018.01.016

Haber, S. N., Yendiki, A., & Jbabdi, S. (2021). Four Deep Brain Stimulation Targets for Obsessive-Compulsive Disorder: Are They Different? *Biol Psychiatry*, *90*(10), 667-677. https://doi.org/10.1016/j.biopsych.2020.06.031

Hallquist, M. N., Hwang, K., & Luna, B. (2013). The nuisance of nuisance regression: spectral misspecification in a common approach to resting-state fMRI preprocessing reintroduces noise and obscures functional connectivity. *Neuroimage*, *82*, 208-225. https://doi.org/10.1016/j.neuroimage.2013.05.116

Harrison, B. J., Soriano-Mas, C., Pujol, J., Ortiz, H., López-Solà, M., Hernández-Ribas, R., Deus, J., Alonso, P., Yücel, M., Pantelis, C., Menchon, J. M., & Cardoner, N. (2009). Altered Corticostriatal Functional Connectivity in Obsessive-compulsive Disorder. *Archives of General Psychiatry*, *66*(11), 1189-1200. https://doi.org/10.1001/archgenpsychiatry.2009.152

Hassanzahraee, M., Nitsche, M. A., Zoghi, M., & Jaberzadeh, S. (2020). Determination of anodal tDCS duration threshold for reversal of corticospinal excitability: An investigation for induction of counter-regulatory mechanisms. *Brain Stimul*, *13*(3), 832-839. https://doi.org/10.1016/j.brs.2020.02.027

Hauser, T. U., Rutsche, B., Wurmitzer, K., Brem, S., Ruff, C. C., & Grabner, R. H. (2016). Neurocognitive Effects of Transcranial Direct Current Stimulation in Arithmetic Learning and Performance: A Simultaneous tDCS-fMRI Study. *Brain Stimul*, *9*(6), 850-858. https://doi.org/10.1016/j.brs.2016.07.007

Hikosaka, K., & Watanabe, M. (2004). Long- and short-range reward expectancy in the primate orbitofrontal cortex. *Eur J Neurosci*, *19*(4), 1046-1054. https://doi.org/10.1111/j.0953-816x.2004.03120.x

Hollander, E., Bienstock, C. A., Koran, L. M., Pallanti, S., Marazziti, D., Rasmussen, S. A., Ravizza, L., Benkelfat, C., Saxena, S., & Greenberg, B. D. (2002). Refractory obsessive-compulsive disorder: state-of-the-art treatment. *Journal of Clinical Psychiatry*, *63*, 20-29.

Horvath, J. C., Forte, J. D., & Carter, O. (2015). Quantitative Review Finds No Evidence of Cognitive Effects in Healthy Populations From Single-session Transcranial Direct Current Stimulation (tDCS). *Brain Stimul*, *8*(3), 535-550. https://doi.org/10.1016/j.brs.2015.01.400

Huang, Y., Datta, A., Bikson, M., & Parra, L. C. (2019). Realistic volumetric-approach to simulate transcranial electric stimulation—ROAST—a fully automated open-source pipeline. *Journal of neural engineering*, *16*(5), 056006.

Huotari, N., Raitamaa, L., Helakari, H., Kananen, J., Raatikainen, V., Rasila, A., Tuovinen, T., Kantola, J., Borchardt, V., Kiviniemi, V. J., & Korhonen, V. O. (2019). Sampling Rate Effects on Resting State fMRI Metrics. *Front Neurosci*, *13*, 279. https://doi.org/10.3389/fnins.2019.00279

Jacobson, L., Koslowsky, M., & Lavidor, M. (2012). tDCS polarity effects in motor and cognitive domains: a meta-analytical review. *Exp Brain Res*, *216*(1), 1-10. https://doi.org/10.1007/s00221-011-2891-9

Jahfari, S., Waldorp, L., van den Wildenberg, W. P., Scholte, H. S., Ridderinkhof, K. R., & Forstmann, B. U. (2011). Effective connectivity reveals important roles for both the hyperdirect (fronto-subthalamic) and the indirect (fronto-striatal-pallidal) fronto-basal ganglia pathways during response inhibition. *J Neurosci*, *31*(18), 6891-6899. https://doi.org/10.1523/JNEUROSCI.5253-10.2011

Jia, X. Z., Sun, J. W., Ji, G. J., Liao, W., Lv, Y. T., Wang, J., Wang, Z., Zhang, H., Liu, D. Q., & Zang, Y. F. (2020). Percent amplitude of fluctuation: A simple measure for resting-state fMRI signal at single voxel level. *PLoS One*, *15*(1), e0227021. https://doi.org/10.1371/journal.pone.0227021

Jurng, J., Park, H., Kim, T., Park, I., Moon, S. Y., Lho, S. K., Kim, M., & Kwon, J. S. (2021). Smaller volume of posterior thalamic nuclei in patients with obsessive-compulsive disorder. *Neuroimage Clin*, *30*, 102686. https://doi.org/10.1016/j.nicl.2021.102686

Klaus, J., & Schutter, D. (2021). Electrode montage-dependent intracranial variability in electric fields induced by cerebellar transcranial direct current stimulation. *Sci Rep*, *11*(1), 22183. https://doi.org/10.1038/s41598-021-01755-9

Klomjai, W., Katz, R., & Lackmy-Vallee, A. (2015). Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). *Ann Phys Rehabil Med*, *58*(4), 208-213. https://doi.org/10.1016/j.rehab.2015.05.005

Koch, K., & Rodriguez-Manrique, D. (2023). Unraveling the Neural Substrates of Insight in Obsessive-Compulsive Disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *8*(11), 1070-1071.

Koran, L. M., Hanna, G. L., Hollander, E., Nestadt, G., Simpson, H. B., & Association, A. P. (2007). Practice guideline for the treatment of patients with obsessive-compulsive disorder. *The American journal of psychiatry*, *164*(7 Suppl), 5-53.

Kricheldorff, J., Goke, K., Kiebs, M., Kasten, F. H., Herrmann, C. S., Witt, K., & Hurlemann, R. (2022). Evidence of Neuroplastic Changes after Transcranial Magnetic, Electric, and Deep Brain Stimulation. *Brain Sci*, *12*(7). https://doi.org/10.3390/brainsci12070929

Kublbock, M., Woletz, M., Hoflich, A., Sladky, R., Kranz, G. S., Hoffmann, A., Lanzenberger, R., & Windischberger, C. (2014). Stability of low-frequency fluctuation amplitudes in prolonged resting-state fMRI. *Neuroimage*, *103*, 249-257. https://doi.org/10.1016/j.neuroimage.2014.09.038

Kuo, H. I., Bikson, M., Datta, A., Minhas, P., Paulus, W., Kuo, M. F., & Nitsche, M. A. (2013). Comparing cortical plasticity induced by conventional and high-definition 4 x 1 ring tDCS: a neurophysiological study. *Brain Stimul*, *6*(4), 644-648. https://doi.org/10.1016/j.brs.2012.09.010

Laakso, I., Tanaka, S., Mikkonen, M., Koyama, S., Sadato, N., & Hirata, A. (2016). Electric fields of motor and frontal tDCS in a standard brain space: A computer simulation study. *Neuroimage*, *137*, 140-151. https://doi.org/10.1016/j.neuroimage.2016.05.032

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional neuroanatomy of the basal ganglia. *Cold Spring Harb Perspect Med*, *2*(12), a009621. https://doi.org/10.1101/cshperspect.a009621

Leksell, L., Backlund, E.-O., Hitchcock, E., Ballantine, H., & Meyerson, B. (1979). Stereotactic gamma capsulotomy. *Modern concepts in psychiatric surgery. Amsterdam: Elsevier*, 213-216.

Liebrand, M., Karabanov, A., Antonenko, D., Floel, A., Siebner, H. R., Classen, J., Kramer, U. M., & Tzvi, E. (2020). Beneficial effects of cerebellar tDCS on motor learning are associated with altered putamen-cerebellar connectivity: A simultaneous tDCS-fMRI study. *Neuroimage*, *223*, 117363. https://doi.org/10.1016/j.neuroimage.2020.117363

Lippitz, B. E., Mindus, P., Meyerson, B. A., Kihlström, L., & Lindquist, C. (1999). Lesion topography and outcome after thermocapsulotomy or gamma knife capsulotomy for obsessive-compulsive disorder: relevance of the right hemisphere. *Neurosurgery*, *44*(3), 452-458.

Maknojia, S., Churchill, N. W., Schweizer, T. A., & Graham, S. J. (2019). Resting State fMRI: Going Through the Motions. *Front Neurosci*, *13*, 825. https://doi.org/10.3389/fnins.2019.00825

Malinen, S., Vartiainen, N., Hlushchuk, Y., Koskinen, M., Ramkumar, P., Forss, N., Kalso, E., & Hari, R. (2010). Aberrant temporal and spatial brain activity during rest in patients with chronic pain. *Proc Natl Acad Sci U S A*, *107*(14), 6493-6497. https://doi.org/10.1073/pnas.1001504107

Maltby, N., Tolin, D. F., Worhunsky, P., O'Keefe, T. M., & Kiehl, K. A. (2005). Dysfunctional action monitoring hyperactivates frontal-striatal circuits in obsessive-compulsive disorder: an event-related fMRI study. *Neuroimage*, *24*(2), 495-503. https://doi.org/10.1016/j.neuroimage.2004.08.041

Mancebo, M. C., Greenberg, B., Grant, J. E., Pinto, A., Eisen, J. L., Dyck, I., & Rasmussen, S. A. (2008). Correlates of occupational disability in a clinical sample of obsessive-

compulsive disorder. *Compr Psychiatry*, *49*(1), 43-50. https://doi.org/10.1016/j.comppsych.2007.05.016
Mar, K., Townes, P., Pechlivanoglou, P., Arnold, P., & Schachar, R. (2022). Obsessive compulsive disorder and response inhibition: Meta-analysis of the stop-signal task. *J Psychopathol Clin Sci*, *131*(2), 152-161. https://doi.org/10.1037/abn0000732
Marengo-Rowe, A. J. (2006). Structure-function relations of human hemoglobins. Baylor University Medical Center Proceedings,
McCann, H., Pisano, G., & Beltrachini, L. (2019). Variation in Reported Human Head Tissue Electrical Conductivity Values. *Brain Topogr*, *32*(5), 825-858. https://doi.org/10.1007/s10548-019-00710-2
Meda, S. A., Wang, Z., Ivleva, E. I., Poudyal, G., Keshavan, M. S., Tamminga, C. A., Sweeney, J. A., Clementz, B. A., Schretlen, D. J., Calhoun, V. D., Lui, S., Damaraju, E., & Pearlson, G. D. (2015). Frequency-Specific Neural Signatures of Spontaneous Low-Frequency Resting State Fluctuations in Psychosis: Evidence From Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) Consortium. *Schizophr Bull*, *41*(6), 1336-1348. https://doi.org/10.1093/schbul/sbv064
Meltzer, J. A., Negishi, M., & Constable, R. T. (2008). Biphasic hemodynamic responses influence deactivation and may mask activation in block-design fMRI paradigms. *Hum Brain Mapp*, *29*(4), 385-399. https://doi.org/10.1002/hbm.20391
Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*, *15*(10), 483-506. https://doi.org/10.1016/j.tics.2011.08.003
Menzies, L., Chamberlain, S. R., Laird, A. R., Thelen, S. M., Sahakian, B. J., & Bullmore, E. T. (2008). Integrating evidence from neuroimaging and neuropsychological studies of obsessive-compulsive disorder: the orbitofronto-striatal model revisited. *Neurosci Biobehav Rev*, *32*(3), 525-549. https://doi.org/10.1016/j.neubiorev.2007.09.005
Mergenthaler, P., Lindauer, U., Dienel, G. A., & Meisel, A. (2013). Sugar for the brain: the role of glucose in physiological and pathological brain function. *Trends Neurosci*, *36*(10), 587-597. https://doi.org/10.1016/j.tins.2013.07.001
Miezin, F. M., Maccotta, L., Ollinger, J. M., Petersen, S. E., & Buckner, R. L. (2000). Characterizing the hemodynamic response: effects of presentation rate, sampling procedure, and the possibility of ordering brain activity based on relative timing. *Neuroimage*, *11*(6 Pt 1), 735-759. https://doi.org/10.1006/nimg.2000.0568
Miranda, P. C., Mekonnen, A., Salvador, R., & Ruffini, G. (2013). The electric field in the cortex during transcranial current stimulation. *Neuroimage*, *70*, 48-58. https://doi.org/10.1016/j.neuroimage.2012.12.034
Modell, J. G., Mountz, J. M., Curtis, G. C., & Greden, J. F. (1989). Neurophysiologic dysfunction in basal ganglia/limbic striatal and thalamocortical circuits as a pathogenetic mechanism of obsessive-compulsive disorder. *The Journal of Neuropsychiatry and Clinical Neurosciences*.
Mosayebi-Samani, M., Jamil, A., Salvador, R., Ruffini, G., Haueisen, J., & Nitsche, M. A. (2021). The impact of individual electrical fields and anatomical factors on the neurophysiological outcomes of tDCS: A TMS-MEP and MRI study. *Brain Stimul*, *14*(2), 316-326. https://doi.org/10.1016/j.brs.2021.01.016
Mostofsky, S. H., Schafer, J. G., Abrams, M. T., Goldberg, M. C., Flower, A. A., Boyce, A., Courtney, S. M., Calhoun, V. D., Kraut, M. A., Denckla, M. B., & Pekar, J. J. (2003). fMRI evidence that the neural basis of response inhibition is task-dependent. *Brain Res Cogn Brain Res*, *17*(2), 419-430. https://doi.org/10.1016/s0926-6410(03)00144-7
Nachev, P., Wydell, H., O'Neill, K., Husain, M., & Kennard, C. (2007). The role of the pre-supplementary motor area in the control of action. *Neuroimage*, *36 Suppl 2*(3-3), T155-163. https://doi.org/10.1016/j.neuroimage.2007.03.034

Najafi, K., Fakour, Y., Zarrabi, H., Heidarzadeh, A., Khalkhali, M., Yeganeh, T., Farahi, H., Rostamkhani, M., Najafi, T., Shabafroz, S., & Pakdaman, M. (2017). Efficacy of Transcranial Direct Current Stimulation in the Treatment: Resistant Patients who Suffer from Severe Obsessive-compulsive Disorder. *Indian J Psychol Med*, *39*(5), 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. (2015). Successful Application of Add-on Transcranial Direct Current Stimulation (tDCS) for Treatment of SSRI Resistant OCD. *Brain Stimul*, *8*(3), 655-657. https://doi.org/10.1016/j.brs.2014.12.003

Narmashiri, A., & Akbari, F. (2023). The Effects of Transcranial Direct Current Stimulation (tDCS) on the Cognitive Functions: A Systematic Review and Meta-analysis. *Neuropsychol Rev*. https://doi.org/10.1007/s11065-023-09627-x

Nordahl, T. E., Benkelfat, C., Semple, W. E., Gross, M., King, A., & Cohen, R. (1989). Cerebral glucose metabolic rates in obsessive compulsive disorder. *Neuropsychopharmacology*.

Norman, L. J., Taylor, S. F., Liu, Y., Radua, J., Chye, Y., De Wit, S. J., Huyser, C., Karahanoglu, F. I., Luks, T., Manoach, D., Mathews, C., Rubia, K., Suo, C., van den Heuvel, O. A., Yucel, M., & Fitzgerald, K. (2019). Error Processing and Inhibitory Control in Obsessive-Compulsive Disorder: A Meta-analysis Using Statistical Parametric Maps. *Biol Psychiatry*, *85*(9), 713-725. https://doi.org/10.1016/j.biopsych.2018.11.010

Opitz, A., Paulus, W., Will, S., Antunes, A., & Thielscher, A. (2015). Determinants of the electric field during transcranial direct current stimulation. *Neuroimage*, *109*, 140-150. https://doi.org/10.1016/j.neuroimage.2015.01.033

Ost, 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. *Clin Psychol Rev*, *40*, 156-169. https://doi.org/10.1016/j.cpr.2015.06.003

Page, L. A., Rubia, K., Deeley, Q., Daly, E., Toal, F., Mataix-Cols, D., Giampietro, V., Schmitz, N., & Murphy, D. G. (2009). A functional magnetic resonance imaging study of inhibitory control in obsessive-compulsive disorder. *Psychiatry Res*, *174*(3), 202-209. https://doi.org/10.1016/j.pscychresns.2009.05.002

Pallanti, S., Grassi, G., Sarrecchia, E. D., Cantisani, A., & Pellegrini, M. (2011). Obsessive-compulsive disorder comorbidity: clinical assessment and therapeutic implications. *Front Psychiatry*, *2*, 70. https://doi.org/10.3389/fpsyt.2011.00070

Paneri, B., Adair, D., Thomas, C., Khadka, N., Patel, V., Tyler, W. J., Parra, L., & Bikson, M. (2016). Tolerability of Repeated Application of Transcranial Electrical Stimulation with Limited Outputs to Healthy Subjects. *Brain Stimul*, *9*(5), 740-754. https://doi.org/10.1016/j.brs.2016.05.008

Park, I., Ha, M., Kim, T., Lho, S. K., Moon, S. Y., Kim, M., & Kwon, J. S. (2023). Cortical gyrification differences between early- and late-onset obsessive-compulsive disorder: neurobiological evidence for neurodevelopmentally distinct subtypes. *Psychol Med*, *53*(13), 5976-5985. https://doi.org/10.1017/S0033291722003129

Perani, D., Colombo, C., Bressi, S., Bonfanti, A., Grassi, F., Scarone, S., Bellodi, L., Smeraldi, E., & Fazio, F. (1995). [18F]FDG PET study in obsessive-compulsive disorder. A clinical/metabolic correlation study after treatment. *Br J Psychiatry*, *166*(2), 244-250. https://doi.org/10.1192/bjp.166.2.244

Perris, F., Fabrazzo, M., De Santis, V., Luciano, M., Sampogna, G., Fiorillo, A., & Catapano, F. (2019). Comorbidity of Obsessive-Compulsive Disorder and Schizotypal Personality Disorder: Clinical Response and Treatment Resistance to

Pharmacotherapy in a 3-Year Follow-Up Naturalistic Study. *Front Psychiatry*, *10*, 386. https://doi.org/10.3389/fpsyt.2019.00386
Petersen, S. E., & Dubis, J. W. (2012). The mixed block/event-related design. *Neuroimage*, *62*(2), 1177-1184. https://doi.org/10.1016/j.neuroimage.2011.09.084
Radua, J., & Mataix-Cols, D. (2009). Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *Br J Psychiatry*, *195*(5), 393-402. https://doi.org/10.1192/bjp.bp.108.055046
Radua, J., van den Heuvel, O. A., Surguladze, S., & Mataix-Cols, D. (2010). Meta-analytical Comparison of Voxel-Based Morphometry Studies in Obsessive-Compulsive Disorder vs Other Anxiety Disorders. *Archives of General Psychiatry*, *67*(7), 701-711. https://doi.org/10.1001/archgenpsychiatry.2010.70
Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L. C., & Bikson, M. (2013). Cellular effects of acute direct current stimulation: somatic and synaptic terminal effects. *J Physiol*, *591*(10), 2563-2578. https://doi.org/10.1113/jphysiol.2012.247171
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/10.1111/psyp.13348
Riesel, A., Kathmann, N., & Klawohn, J. (2019). Flexibility of error-monitoring in obsessive-compulsive disorder under speed and accuracy instructions. *J Abnorm Psychol*, *128*(7), 671-677. https://doi.org/10.1037/abn0000463
Rotge, J. Y., Langbour, N., Guehl, D., Bioulac, B., Jaafari, N., Allard, M., Aouizerate, B., & Burbaud, P. (2010). Gray matter alterations in obsessive-compulsive disorder: an anatomic likelihood estimation meta-analysis. *Neuropsychopharmacology*, *35*(3), 686-691. https://doi.org/10.1038/npp.2009.175
Roth, R. M., Saykin, A. J., Flashman, L. A., Pixley, H. S., West, J. D., & Mamourian, A. C. (2007). Event-related functional magnetic resonance imaging of response inhibition in obsessive-compulsive disorder. *Biol Psychiatry*, *62*(8), 901-909. https://doi.org/10.1016/j.biopsych.2006.12.007
Rubia, K., Cubillo, A., Smith, A. B., Woolley, J., Heyman, I., & Brammer, M. J. (2010). Disorder-specific dysfunction in right inferior prefrontal cortex during two inhibition tasks in boys with attention-deficit hyperactivity disorder compared to boys with obsessive-compulsive disorder. *Hum Brain Mapp*, *31*(2), 287-299. https://doi.org/10.1002/hbm.20864
Rubia, K., Cubillo, A., Woolley, J., Brammer, M. J., & Smith, A. (2011). Disorder-specific dysfunctions in patients with attention-deficit/hyperactivity disorder compared to patients with obsessive-compulsive disorder during interference inhibition and attention allocation. *Hum Brain Mapp*, *32*(4), 601-611. https://doi.org/10.1002/hbm.21048
Ruscio, A. M., Stein, D. J., Chiu, W. T., & Kessler, R. C. (2010). The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry*, *15*(1), 53-63. https://doi.org/10.1038/mp.2008.94
Russell, M. J., Goodman, T., Pierson, R., Shepherd, S., Wang, Q., Groshong, B., & Wiley, D. F. (2013). Individual differences in transcranial electrical stimulation current density. *J Biomed Res*, *27*(6), 495-508. https://doi.org/10.7555/JBR.27.20130074
Saturnino, G. B., Antunes, A., & Thielscher, A. (2015). On the importance of electrode parameters for shaping electric field patterns generated by tDCS. *Neuroimage*, *120*, 25-35. https://doi.org/10.1016/j.neuroimage.2015.06.067
Saturnino, G. B., Puonti, O., Nielsen, J. D., Antonenko, D., Madsen, K. H., & Thielscher, A. (2019). SimNIBS 2.1: a comprehensive pipeline for individualized electric field modelling for transcranial brain stimulation. *Brain and human body modeling: computational human modeling at EMBC 2018*, 3-25.

Saturnino, G. B., Siebner, H. R., Thielscher, A., & Madsen, K. H. (2019). Accessibility of cortical regions to focal TES: Dependence on spatial position, safety, and practical constraints. *Neuroimage*, *203*, 116183. https://doi.org/10.1016/j.neuroimage.2019.116183

Saturnino, G. B., Thielscher, A., Madsen, K. H., Knosche, T. R., & Weise, K. (2019). A principled approach to conductivity uncertainty analysis in electric field calculations. *Neuroimage*, *188*, 821-834. https://doi.org/10.1016/j.neuroimage.2018.12.053

Schoenbaum, G., Nugent, S. L., Saddoris, M. P., & Setlow, B. (2002). Orbitofrontal lesions in rats impair reversal but not acquisition of go, no-go odor discriminations. *Neuroreport*, *13*(6), 885-890.

Schridde, U., Khubchandani, M., Motelow, J. E., Sanganahalli, B. G., Hyder, F., & Blumenfeld, H. (2008). Negative BOLD with large increases in neuronal activity. *Cereb Cortex*, *18*(8), 1814-1827. https://doi.org/10.1093/cercor/bhm208

Schroeder, P. A., Schwippel, T., Wolz, I., & Svaldi, J. (2020). Meta-analysis of the effects of transcranial direct current stimulation on inhibitory control. *Brain Stimul*, *13*(5), 1159-1167. https://doi.org/10.1016/j.brs.2020.05.006

Sebastian, A., Pohl, M. F., Kloppel, S., Feige, B., Lange, T., Stahl, C., Voss, A., Klauer, K. C., Lieb, K., & Tuscher, O. (2013). Disentangling common and specific neural subprocesses of response inhibition. *Neuroimage*, *64*, 601-615. https://doi.org/10.1016/j.neuroimage.2012.09.020

Shephard, E., Stern, E. R., van den Heuvel, O. A., Costa, D. L. C., Batistuzzo, M. C., Godoy, P. B. G., Lopes, A. C., Brunoni, A. R., Hoexter, M. Q., Shavitt, R. G., Reddy, Y. C. J., Lochner, C., Stein, D. J., Simpson, H. B., & Miguel, E. C. (2021). Toward a neurocircuit-based taxonomy to guide treatment of obsessive-compulsive disorder. *Mol Psychiatry*, *26*(9), 4583-4604. https://doi.org/10.1038/s41380-020-01007-8

Shinde, A. B., Lerud, K. D., Munsch, F., Alsop, D. C., & Schlaug, G. (2021). Effects of tDCS dose and electrode montage on regional cerebral blood flow and motor behavior. *Neuroimage*, *237*, 118144. https://doi.org/10.1016/j.neuroimage.2021.118144

Simmonds, D. J., Pekar, J. J., & Mostofsky, S. H. (2008). Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia*, *46*(1), 224-232. https://doi.org/10.1016/j.neuropsychologia.2007.07.015

Snyder, H. R., Kaiser, R. H., Warren, S. L., & Heller, W. (2015). Obsessive-compulsive disorder is associated with broad impairments in executive function: A meta-analysis. *Clin Psychol Sci*, *3*(2), 301-330. https://doi.org/10.1177/2167702614534210

Soleimani, G., Kupliki, R., Paulus, M., & Ekhtiari, H. (2023). Dose-response in modulating brain function with transcranial direct current stimulation: From local to network levels. *PLoS Comput Biol*, *19*(10), e1011572. https://doi.org/10.1371/journal.pcbi.1011572

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. *Proceedings of the National Academy of Sciences*, *105*(34), 12569-12574.

Stecher, H. I., Notbohm, A., Kasten, F. H., & Herrmann, C. S. (2021). A Comparison of Closed Loop vs. Fixed Frequency tACS on Modulating Brain Oscillations and Visual Detection. *Front Hum Neurosci*, *15*, 661432. https://doi.org/10.3389/fnhum.2021.661432

Stein, D. J., Hollander, E., Mullen, L. S., Decaria, C. M., & Liebowitz, M. R. (1992). Comparison of clomipramine, alprazolam and placebo in the treatment of obsessive—compulsive disorder. *Human Psychopharmacology: Clinical and Experimental*, *7*(6), 389-395. https://doi.org/10.1002/hup.470070604

Stern, E. R., Fitzgerald, K. D., Welsh, R. C., Abelson, J. L., & Taylor, S. F. (2012). Resting-state functional connectivity between fronto-parietal and default mode networks in obsessive-compulsive disorder. *PLoS One*, *7*(5), e36356. https://doi.org/10.1371/journal.pone.0036356

Storch, E. A., Abramowitz, J. S., & Keeley, M. (2009). Correlates and mediators of functional disability in obsessive-compulsive disorder. *Depress Anxiety*, *26*(9), 806-813. https://doi.org/10.1002/da.20481

Swedo, S. E., Schapiro, M. B., Grady, C. L., Cheslow, D. L., Leonard, H. L., Kumar, A., Friedland, R., Rapoport, S. I., & Rapoport, J. L. (1989). Cerebral Glucose Metabolism in Childhood-Onset Obsessive-Compulsive Disorder. *Archives of General Psychiatry*, *46*(6), 518-523. https://doi.org/10.1001/archpsyc.1989.01810060038007

Talairach, J., Hecaen, H., David, M., Monnier, M., & De Ajuriaguerra, J. (1949). Recherches sur la coagulation thérapeutique des structures sous-corticales chez l'homme. *Rev Neurol*, *81*, 4-24.

Thair, H., Holloway, A. L., Newport, R., & Smith, A. D. (2017). Transcranial Direct Current Stimulation (tDCS): A Beginner's Guide for Design and Implementation. *Front Neurosci*, *11*, 641. https://doi.org/10.3389/fnins.2017.00641

Thorsen, A. L., Hagland, P., Radua, J., Mataix-Cols, D., Kvale, G., Hansen, B., & van den Heuvel, O. A. (2018). Emotional Processing in Obsessive-Compulsive Disorder: A Systematic Review and Meta-analysis of 25 Functional Neuroimaging Studies. *Biol Psychiatry Cogn Neurosci Neuroimaging*, *3*(6), 563-571. https://doi.org/10.1016/j.bpsc.2018.01.009

Tomiyama, H., Murayama, K., Nemoto, K., Tomita, M., Hasuzawa, S., Mizobe, T., Kato, K., Ohno, A., Tsuruta, S., Togao, O., Hiwatashi, A., & Nakao, T. (2022). Increased functional connectivity between presupplementary motor area and inferior frontal gyrus associated with the ability of motor response inhibition in obsessive-compulsive disorder. *Hum Brain Mapp*, *43*(3), 974-984. https://doi.org/10.1002/hbm.25699

Tricomi, E., Balleine, B. W., & O'Doherty, J. P. (2009). A specific role for posterior dorsolateral striatum in human habit learning. *Eur J Neurosci*, *29*(11), 2225-2232. https://doi.org/10.1111/j.1460-9568.2009.06796.x

Truong, D. Q., Magerowski, G., Blackburn, G. L., Bikson, M., & Alonso-Alonso, M. (2013). Computational modeling of transcranial direct current stimulation (tDCS) in obesity: Impact of head fat and dose guidelines. *Neuroimage Clin*, *2*, 759-766. https://doi.org/10.1016/j.nicl.2013.05.011

Turner, R. (2016). Uses, misuses, new uses and fundamental limitations of magnetic resonance imaging in cognitive science. *Philos Trans R Soc Lond B Biol Sci*, *371*(1705). https://doi.org/10.1098/rstb.2015.0349

van de Veerdonk, M. M. G. H., Bouwens van der Vlis, T. A. M., Ackermans, L., Schruers, K. R. J., Temel, Y., & Leentjens, A. F. G. (2023). The role of the dorsal anterior cingulate cortex in obsessive-compulsive disorder. *Deep Brain Stimulation*, *3*, 1-7. https://doi.org/10.1016/j.jdbs.2023.07.001

van den Heuvel, O. A., van Wingen, G., Soriano-Mas, C., Alonso, P., Chamberlain, S. R., Nakamae, T., Denys, D., Goudriaan, A. E., & Veltman, D. J. (2016). Brain circuitry of compulsivity. *Eur Neuropsychopharmacol*, *26*(5), 810-827. https://doi.org/10.1016/j.euroneuro.2015.12.005

van Roessel, P. J., Grassi, G., Aboujaoude, E. N., Menchon, J. M., Van Ameringen, M., & Rodriguez, C. I. (2023). Treatment-resistant OCD: Pharmacotherapies in adults. *Compr Psychiatry*, *120*, 152352. https://doi.org/10.1016/j.comppsych.2022.152352

van Velzen, L. S., Vriend, C., de Wit, S. J., & van den Heuvel, O. A. (2014). Response inhibition and interference control in obsessive-compulsive spectrum disorders. *Front Hum Neurosci*, *8*, 419. https://doi.org/10.3389/fnhum.2014.00419

Verbruggen, F., & Logan, G. D. (2008). Response inhibition in the stop-signal paradigm. *Trends Cogn Sci*, *12*(11), 418-424. https://doi.org/10.1016/j.tics.2008.07.005

Videira, A. S., Canadas, D., De, O. P. L., Andrade, A., Ferreira, H. A., Miranda, P. C., & Fernandes, S. R. (2022). How the Number and Distance of Electrodes Change the Induced Electric Field in the Cortex during Multichannel tDCS. *Annu Int Conf IEEE Eng Med Biol Soc*, *2022*, 2357-2360. https://doi.org/10.1109/EMBC48229.2022.9871114

Visser-Vandewalle, V., Andrade, P., Mosley, P. E., Greenberg, B. D., Schuurman, R., McLaughlin, N. C., Voon, V., Krack, P., Foote, K. D., & Mayberg, H. S. (2022). Deep brain stimulation for obsessive–compulsive disorder: a crisis of access. *Nature medicine*, *28*(8), 1529-1532.

Voroslakos, M., Takeuchi, Y., Brinyiczki, K., Zombori, T., Oliva, A., Fernandez-Ruiz, A., Kozak, G., Kincses, Z. T., Ivanyi, B., Buzsaki, G., & Berenyi, A. (2018). Direct effects of transcranial electric stimulation on brain circuits in rats and humans. *Nat Commun*, *9*(1), 483. https://doi.org/10.1038/s41467-018-02928-3

Wall, M. B. (2023). Multiband acquisition sequences for fMRI: Proceed with caution. *Aperture Neuro*, *3*. https://doi.org/10.52294/001c.91292

Weeland, C. J., Kasprzak, S., de Joode, N. T., Abe, Y., Alonso, P., Ameis, S. H., Anticevic, A., Arnold, P. D., Balachander, S., & Banaj, N. (2022). The thalamus and its subnuclei—a gateway to obsessive-compulsive disorder. *Translational psychiatry*, *12*(1), 70.

Welter, M. L., Burbaud, P., Fernandez-Vidal, S., Bardinet, E., Coste, J., Piallat, B., Borg, M., Besnard, S., Sauleau, P., Devaux, B., Pidoux, B., Chaynes, P., Tezenas du Montcel, S., Bastian, A., Langbour, N., Teillant, A., Haynes, W., Yelnik, J., Karachi, C., . . . French Stimulation dans Trouble Obsessionnel Compulsif Study, G. (2011). Basal ganglia dysfunction in OCD: subthalamic neuronal activity correlates with symptoms severity and predicts high-frequency stimulation efficacy. *Transl Psychiatry*, *1*(5), e5. https://doi.org/10.1038/tp.2011.5

Wink, A. M., Hoogduin, H., & Roerdink, J. B. (2008). Data-driven haemodynamic response function extraction using Fourier-wavelet regularised deconvolution. *BMC Med Imaging*, *8*, 7. https://doi.org/10.1186/1471-2342-8-7

Wittchen, H. U., & Jacobi, F. (2005). Size and burden of mental disorders in Europe--a critical review and appraisal of 27 studies. *Eur Neuropsychopharmacol*, *15*(4), 357-376. https://doi.org/10.1016/j.euroneuro.2005.04.012

Woods, A. J., Antal, A., Bikson, M., Boggio, P. S., Brunoni, A. R., Celnik, P., Cohen, L. G., Fregni, F., Herrmann, C. S., Kappenman, E. S., Knotkova, H., Liebetanz, D., Miniussi, C., Miranda, P. C., Paulus, W., Priori, A., Reato, D., Stagg, C., Wenderoth, N., & Nitsche, M. A. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clin Neurophysiol*, *127*(2), 1031-1048. https://doi.org/10.1016/j.clinph.2015.11.012

Woolley, J., Heyman, I., Brammer, M., Frampton, I., McGuire, P. K., & Rubia, K. (2008). Brain activation in paediatric obsessive compulsive disorder during tasks of inhibitory control. *Br J Psychiatry*, *192*(1), 25-31. https://doi.org/10.1192/bjp.bp.107.036558

Wu, C. W., Chen, C. L., Liu, P. Y., Chao, Y. P., Biswal, B. B., & Lin, C. P. (2011). Empirical evaluations of slice-timing, smoothing, and normalization effects in seed-based, resting-state functional magnetic resonance imaging analyses. *Brain Connect*, *1*(5), 401-410. https://doi.org/10.1089/brain.2011.0018

Xu, B., Sandrini, M., Wang, W. T., Smith, J. F., Sarlls, J. E., Awosika, O., Butman, J. A., Horwitz, B., & Cohen, L. G. (2016). PreSMA stimulation changes task-free functional connectivity in the fronto-basal-ganglia that correlates with response inhibition efficiency. *Hum Brain Mapp*, *37*(9), 3236-3249. https://doi.org/10.1002/hbm.23236

Xu, J., Moeller, S., Auerbach, E. J., Strupp, J., Smith, S. M., Feinberg, D. A., Yacoub, E., & Uğurbil, K. (2013). Evaluation of slice accelerations using multiband echo planar imaging at 3 T. *Neuroimage*, *83*, 991-1001.

Yu, J., Tseng, P., Hung, D. L., Wu, S. W., & Juan, C. H. (2015). Brain stimulation improves cognitive control by modulating medial-frontal activity and preSMA-vmPFC functional connectivity. *Hum Brain Mapp*, *36*(10), 4004-4015. https://doi.org/10.1002/hbm.22893

Zborowski, M., Ostera, G. R., Moore, L. R., Milliron, S., Chalmers, J. J., & Schechter, A. N. (2003). Red blood cell magnetophoresis. *Biophysical journal*, *84*(4), 2638-2645.

Zhang, W., Xiong, B., Wu, Y., Xiao, L., & Wang, W. (2023). Local field potentials in major depressive and obsessive-compulsive disorder: a frequency-based review. *Front Psychiatry*, *14*, 1080260. https://doi.org/10.3389/fpsyt.2023.1080260

Zheng, Z. S., & Monti, M. M. (2022). Cortical and thalamic connections of the human globus pallidus: Implications for disorders of consciousness. *Front Neuroanat*, *16*, 960439. https://doi.org/10.3389/fnana.2022.960439

Zhou, Z., Zhen, J., Karpowich, N. K., Law, C. J., Reith, M. E., & Wang, D. N. (2009). Antidepressant specificity of serotonin transporter suggested by three LeuT-SSRI structures. *Nat Struct Mol Biol*, *16*(6), 652-657. https://doi.org/10.1038/nsmb.1602

Zhu, Y., Fan, Q., Zhang, H., Qiu, J., Tan, L., Xiao, Z., Tong, S., Chen, J., & Li, Y. (2016). Altered intrinsic insular activity predicts symptom severity in unmedicated obsessive-compulsive disorder patients: a resting state functional magnetic resonance imaging study. *BMC Psychiatry*, *16*, 104. https://doi.org/10.1186/s12888-016-0806-9

Zou, Q. H., Zhu, C. Z., Yang, Y., Zuo, X. N., Long, X. Y., Cao, Q. J., Wang, Y. F., & Zang, Y. F. (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: fractional ALFF. *J Neurosci Methods*, *172*(1), 137-141. https://doi.org/10.1016/j.jneumeth.2008.04.012

Zuo, X. N., Di Martino, A., Kelly, C., Shehzad, Z. E., Gee, D. G., Klein, D. F., Castellanos, F. X., Biswal, B. B., & Milham, M. P. (2010). The oscillating brain: complex and reliable. *Neuroimage*, *49*(2), 1432-1445. https://doi.org/10.1016/j.neuroimage.2009.09.037

Acknowledgements

„It takes a village“ is also true of a PhD. The innumerous conversations and input I received before even embarking on the PhD and throughout the process, show the level of teamwork that goes into such a project. Without the resources and support that were made available to me through München Rechts der Isar, the LMU and the Deutsche Forschungsgemeinschaft, all incredibly research oriented, I would not have been able to complete this feat.

Thank you **Kathrin** for providing me with the trust and freedom needed to own and shape the project. Thank you also for encouraging me to explore methods and courses outside of the original scope of the PhD, it definitely made me a more well-rounded candidate. Most importantly, thank you for providing me with the real Münchener insider tips on the least-visited hiking paths and skiing resorts.

Thank you to my TAC members **Afra**, **Paul**, **Valentin** and **Franziska** for sharing their points of view and opinions with me so openly and guiding me through important decisions.

Thank you to **Christine** for your sincere support and guidance in all things scanning related, especially for letting us knock on your door in moments of stress.

Thank you to **Prof. Zimmer** for your enthusiasm for research and support throughout my PhD.

Thank you to the **Graduate School of Systemic Neurosciences** for the opportunity to take insightful soft skills and hard skills seminars. I especially thank you for organising the annual retreat which was always a highlight.

Thank you to **Martin Gruber** for your patience when answering our never-ending questions. Thank you for taking the trouble to get to know us students. Thank you **Daniel Fröbel** for taking us students under your wing and teaching us the intricacies and politics of scanning.

Thank you to the **TUM-NIC** for our game nights, park lunches, ice cream walks, hat-crafting sessions and Isar picnics. Special mentions to **Elisabeth, Laura** and **Mahnaz** for the atmosphere you create.

Thank you to my “predecessors” **Samira**, **Andre**, **Toni** and **Alyssa** for setting an example and helping me navigate the unpredictable landscape of a PhD. You showed me that even the most meticulous and dedicated workers know how to have a good time. Thank you to the **Bergz** for the unwavering emotional support – could not have done it without you!

Thank you to **Alyssa**, the PhD-encyclopaedia, there was not a question you could not guide me through. You adopted me into our lab even before I even set foot in the office.

Thank you to the energising students I got to work with during my PhD. Thank you, **Julian**, **Manuel** and **Chelsea**, for enduring some agitated times with me at the scanner. Special thanks to **Gülce, Begüm** and **Onur**: I hope to continue to follow your path and continue to learn from you in the future.

Gracias **Ma** y **Pa** por introducirme a una multitud de ambientes y culturas. Con ello la enseñanza de la complejidad que ofrece este mundo y que nada tiene una simple explicación. Gracias por enseñarme que en cualquier situación y lugar hay aprendizajes. La curiosidad y

atención que se requiere en un proyecto así es algo que ustedes nos demostraron. Nos han hechos a mis hermanos y mí unos seres independientes que cuestionan y reforman sus alrededores. Gracias por haberme empujado a medirme a este nuevo desafío en 2020, vieron en mí una candidata a doctorando antes de que yo pudiera. Gracias **Mom** por cruzar Alemania cada vez que te necesitaba y gracias por escucharme por horas en el teléfono, aprecio saber que nunca te aburro.

Gracias al **abuelito Gustavo** por mostrarme que las oportunidades son para tomarlas y no cuestionarlas.

Cami and **Santi,** thank you for accepting and respecting me the way I am yet never missing a chance to make fun of me or undermine my authority – I know I am a huge pain in the butt and you have make my edges a bit smoother.

Fabio, we (coincidentally) embarked on this journey together in a library in England. Thank you for acting as my sound board, letting me discuss the minutest decisions and predicaments so they did not ruminate endlessly in my head. I want to thank you for your endless energy and motivational speeches, for reminding me of my capability when I couldn't fend off the self-doubt. But also, thank you for your honesty and for holding me accountable when I get lazy, and my presentation is "just a bit shit" (in Fabs accent). You trust in me to demand more of me and for that I am thankful. Thank you above all, for being a brilliant personal chef during thesis writing and other stressful times.

Selma, **Liv**, **Adele, Stan** and **Matilde** thank you to for letting me unplug and reminding me not to take any of this too seriously. Thank you **Maddy** for being my rock and embarking on endless FlixBus journeys to see me. I wish everyone a friend like you.

List Of Publications

Published:

Ahnaou, A., D. Rodriguez-Manrique, R. Biermans, S. Embrechts, N. V Manyakov, and W. H. Drinkenburg. 2020a. "Functional Alterations in the Olfactory Neuronal Circuit Occur before Hippocampal Plasticity Deficits in the P301s Mouse Model of Tauopathy: Implications for Early Diagnosis and Translational Research in Alzheimer's Disease." *International Journal of Molecular Sciences* 21, no. 15: 5431.

Ahnaou, A., D. Rodriguez-Manrique, S. Embrechts, R. Biermans, N. V. Manyakov, S. A. Youssef, and W. H. Drinkenburg. 2020b. "Aging Alters Olfactory Bulb Network Oscillations and Connectivity: Relevance for Aging-Related Neurodegeneration Studies." *Neural Plasticity* 2020.

Bruin, W. B., Y. Abe, P. Alonso, A. Anticevic, L. L. Backhausen, S. Balachander, N. Bargallo, M. C. Batistuzzo, F. Benedetti, S. Bertolin Triquell, S. Brem, F. Calesella, B. Couto, Dajp Denys, M. A. N. Echevarria, G. K. Eng, S. Ferreira, J. D. Feusner, R. G. Grazioplene, P. Gruner, J. Y. Guo, K. Hagen, B. Hansen, Y. Hirano, M. Q. Hoexter, N. Jahanshad, F. Jaspers-Fayer, S. Kasprzak, M. Kim, K. Koch, Y. Bin Kwak, J. S. Kwon, L. Lazaro, C. R. Li, C. Lochner, R. Marsh, I. Martinez-Zalacain, J. M. Menchon, P. S. Moreira, P. Morgado, A. Nakagawa, T. Nakao, J. C. Narayanaswamy, E. L. Nurmi, J. C. P. Zorrilla, J. Piacentini, M. Pico-Perez, F. Piras, F. Piras, C. Pittenger, J. Y. C. Reddy, D. Rodriguez-Manrique, Y. Sakai, E. Shimizu, V. Shivakumar, B. H. Simpson, C. Soriano-Mas, N. Sousa, G. Spalletta, E. R. Stern, S. Evelyn Stewart, P. R. Szeszko, J. Tang, S. I. Thomopoulos, A. L. Thorsen, T. Yoshida, H. Tomiyama, B. Vai, I. M. Veer, G. Venkatasubramanian, N. C. Vetter, C. Vriend, S. Walitza, L. Waller, Z. Wang, A. Watanabe, N. Wolff, J. Y. Yun, Q. Zhao, W. A. van Leeuwen, H. J. F. van Marle, L. A. van de Mortel, A. van der Straten, Y. D. van der Werf, Enigma-Ocd Working Group, P. M. Thompson, D. J. Stein, O. A. van den Heuvel, and G. A. van Wingen. 2023. "The Functional Connectome in Obsessive-Compulsive Disorder: Resting-State Mega-Analysis and Machine Learning Classification for the Enigma-Ocd Consortium." *Mol Psychiatry* 28, no. 10 (Oct): 4307-4319. https://dx.doi.org/10.1038/s41380-023-02077-0.

Ivanov, I., P. S. W. Boedhoe, Y. Abe, P. Alonso, S. H. Ameis, P. D. Arnold, S. Balachander, J. T. Baker, N. Banaj, N. Bargallo, M. C. Batistuzzo, F. Benedetti, J. C. Beucke, I. Bollettini, S. Brem, B. P. Brennan, J. Buitelaar, R. Calvo, Y. Cheng, K. I. K. Cho, S. Dallaspezia, D. Denys, J. B. Diniz, B. A. Ely, J. D. Feusner, S. Ferreira, K. D. Fitzgerald, M. Fontaine, P. Gruner, G. L. Hanna, Y. Hirano, M. Q. Hoexter, C. Huyser, K. Ikari, A. James, F. Jaspers-Fayer, H. Jiang, N. Kathmann, C. Kaufmann, M. Kim, K. Koch, J. S. Kwon, L. Lazaro, Y. Liu, C. Lochner, R. Marsh, I. Martinez-Zalacain, D. Mataix-Cols, J. M. Menchon, L. Minuzzi, A. Morer, P. Morgado, A. Nakagawa, T. Nakamae, T. Nakao, J. C. Narayanaswamy, E. L. Nurmi, S. Oh, C. Perriello, J. C. Piacentini, M. Pico-Perez, F. Piras, F. Piras, Y. C. J. Reddy, D. Rodriguez-Manrique, Y. Sakai, E. Shimizu, H. B. Simpson, N. Soreni, C. Soriano-Mas, G. Spalletta, E. R. Stern, M. C. Stevens, S. E. Stewart, P. R. Szeszko, D. F. Tolin, D. van Rooij, D. J. Veltman, Y. D. van der Werf, G. A. van Wingen, G. Venkatasubramanian, S. Walitza,

Z. Wang, A. Watanabe, L. H. Wolters, X. Xu, J. Y. Yun, M. Zarei, F. Zhang, Q. Zhao, N. Jahanshad, S. I. Thomopoulos, P. M. Thompson, D. J. Stein, O. A. van den Heuvel, J. O'Neill, and Enigma-Ocd Working Group. 2022. "Associations of Medication with Subcortical Morphology across the Lifespan in Ocd: Results from the International Enigma Consortium." *J Affect Disord* 318 (Dec 1): 204-216. https://dx.doi.org/10.1016/j.jad.2022.08.084.

Kaiser, J., A. Gentsch, D. Rodriguez-Manrique, and S. Schütz-Bosbach. 2023. "Function without Feeling: Neural Reactivity and Intercommunication During Flexible Motor Adjustments Evoked by Emotional and Neutral Stimuli." *Cerebral Cortex* 33, no. 10: 6000-6012.

Kim, B. G., and G. Kim, and Y. Abe, and P. Alonso, and S. Ameis, and A. Anticevic, and P. D. Arnold, and S. Balachander, and N. Banaj, and N. Bargallo, and M. C. Batistuzzo, and F. Benedetti, and S. Bertolin, and J. C. Beucke, and I. Bollettini, and S. Brem, and B. P. Brennan, and J. K. Buitelaar, and R. Calvo, and M. Castelo-Branco, and Y. Cheng, and R. B. Chhatkuli, and V. Ciullo, and A. Coelho, and B. Couto, and S. Dallaspezia, and B. A. Ely, and S. Ferreira, and M. Fontaine, and J. P. Fouche, and R. Grazioplene, and P. Gruner, and K. Hagen, and B. Hansen, and G. L. Hanna, and Y. Hirano, and M. Q. Hoxter, and M. Hough, and H. Hu, and C. Huyser, and T. Ikuta, and N. Jahanshad, and A. James, and F. Jaspers-Fayer, and S. Kasprzak, and N. Kathmann, and C. Kaufmann, and M. Kim, and K. Koch, and G. Kvale, and J. S. Kwon, and L. Lazaro, and J. Lee, and C. Lochner, and J. Lu, and D. Rodriguez-Manrique, and I. Martinez-Zalacain, and Y. Masuda, and K. Matsumoto, and M. P. Maziero, and J. M. Menchon, and L. Minuzzi, and P. S. Moreira, and P. Morgado, and J. C. Narayanaswamy, and J. Narumoto, and A. E. Ortiz, and J. Ota, and J. C. Pariente, and C. Perriello, and M. Pico-Perez, and C. Pittenger, and S. Poletti, and E. Real, and Y. C. J. Reddy, and D. van Rooij, and Y. Sakai, and J. R. Sato, and C. Segalas, and R. G. Shavitt, and Z. Shen, and E. Shimizu, and V. Shivakumar, and C. Soriano-Mas, and N. Sousa, and M. M. Sousa, and G. Spalletta, and E. R. Stern, and S. E. Stewart, and P. R. Szeszko, and R. Thomas, and S. I. Thomopoulos, and D. Vecchio, and G. Venkatasubramanian, and C. Vriend, and S. Walitza, and Z. Wang, and A. Watanabe, and L. Wolters, and J. Xu, and K. Yamada, and J. Y. Yun, and M. Zarei, and Q. Zhao, and X. Zhu, and Enigma-Ocd Working Group, and P. M. Thompson, and W. B. Bruin, and G. A. van Wingen, and F. Piras, and F. Piras, and D. J. Stein, and O. A. van den Heuvel, and H. B. Simpson, and R. Marsh, and J. Cha. 2024. "White Matter Diffusion Estimates in Obsessive-Compulsive Disorder across 1653 Individuals: Machine Learning Findings from the Enigma Ocd Working Group." *Mol Psychiatry* (Feb 7). https://dx.doi.org/10.1038/s41380-023-02392-6.

Koch, K., and D. Rodriguez-Manrique. 2023. "Unraveling the Neural Substrates of Insight in Obsessive-Compulsive Disorder." *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging* 8, no. 11: 1070-1071.

Koch, K., D. Rodriguez-Manrique, O. G. Rus-Oswald, D. A. Gürsel, G. Berberich, M. Kunz, and C. Zimmer. 2021. "Homogeneous Grey Matter Patterns in Patients with Obsessive-Compulsive Disorder." *NeuroImage: Clinical* 31: 102727.

Weeland, C. J., and S. Kasprzak, and N. T. de Joode, and Y. Abe, and P. Alonso, and S. H. Ameis, and A. Anticevic, and P. D. Arnold, and S. Balachander, and N. Banaj, and N. Bargallo, and M. C. Batistuzzo, and F. Benedetti, and J. C. Beucke, and I. Bollettini, and V. Brecke, and S. Brem, and C. Cappi, and Y. Cheng, and K. I. K. Cho, and D. L. C. Costa, and S. Dallaspezia, and D. Denys, and G. K. Eng, and S. Ferreira, and J. D. Feusner, and M. Fontaine, and J. P. Fouche, and R. G. Grazioplene, and P. Gruner, and M. He, and Y. Hirano, and M. Q. Hoexter, and C. Huyser, and H. Hu, and F. Jaspers-Fayer, and N. Kathmann, and C. Kaufmann, and M. Kim, and K. Koch, and Y. Bin Kwak, and J. S. Kwon, and L. Lazaro, and C. R. Li, and C. Lochner, and R. Marsh, and I. Martinez-Zalacain, and D. Mataix-Cols, and J. M. Menchon, and L. Minnuzi, and P. S. Moreira, and P. Morgado, and A. Nakagawa, and T. Nakamae, and J. C. Narayanaswamy, and E. L. Nurmi, and A. E. Ortiz, and J. C. Pariente, and J. Piacentini, and M. Pico-Perez, and F. Piras, and F. Piras, and C. Pittenger, and Y. C. J. Reddy, and D. Rodriguez-Manrique, and Y. Sakai, and E. Shimizu, and V. Shivakumar, and H. B. Simpson, and N. Soreni, and C. Soriano-Mas, and N. Sousa, and G. Spalletta, and E. R. Stern, and M. C. Stevens, and S. E. Stewart, and P. R. Szeszko, and J. Takahashi, and T. Tanamatis, and J. Tang, and A. L. Thorsen, and D. Tolin, and Y. D. van der Werf, and H. van Marle, and G. A. van Wingen, and D. Vecchio, and G. Venkatasubramanian, and S. Walitza, and J. Wang, and Z. Wang, and A. Watanabe, and L. H. Wolters, and X. Xu, and J. Y. Yun, and Q. Zhao, and Enigma Ocd Working Group, and T. White, and P. M. Thompson, and D. J. Stein, and O. A. van den Heuvel, and C. Vriend. 2022. "The Thalamus and Its Subnuclei-a Gateway to Obsessive-Compulsive Disorder." *Transl Psychiatry* 12, no. 1 (Feb 21): 70. https://dx.doi.org/10.1038/s41398-022-01823-2.

In progress:

- **Rodriguez-Manrique D**, Ruan H, Winkelmann C, Haun J, Berberich G, Zimmer C, Koch K. Investigating the effects of brain stimulation on the neural substrates of inhibition in patients with OCD: A simultaneous tDCS – fMRI study. https://doi.org/10.21203/rs.3.rs-3936529/v1 [under consideration in Transl. Psychiatry].
- **Rodriguez-Manrique D**, Bremer B, Berberich G, Zimmer C, Koch K. Examining Percent Amplitude of Fluctuations as a resting-state fMRI measure in Patients with Obsessive-Compulsive Disorder [in preparation].
- Ruan H, **Rodriguez-Manrique D**, Winkelmann C, Haun J, Berberich G, Zimmer C, Koch K. Changes in local effective connectivity after single-session transcranial direct current stimulation in obsessive-compulsive disorder patients [in preparation].

Declaration Of Author Contributions

Manuscript 1: Investigating the effects of brain stimulation on the neural substrates of inhibition in patients with OCD: A simultaneous tDCS – fMRI study

---

Rodriguez-Manrique D, Ruan H, Winkelmann C, Haun J, Berberich G, Zimmer C, Koch K.

DRM, KK designed the study. DRM implemented tDCS stimulation in the scanner, as it had not been done previously. DRM designed and coded the cognitive tasks. DRM acquired all data with help of CW and JH. DRM established cooperation with nearby clinics and recruited OCD patients with help of CW and JH. During data acquisition CW and JH were responsible for questionnaire assessment during the sessions. BG allowed us the use of the clinic facilities to conduct our pilot study on site. CZ gathered funding for the completion of this project. DRM preprocessed, analysed, interpreted all data and wrote the present manuscript. DRM, KK and RH performed data visualisations. HR additionally calculated cortical thickness values used in the mediation analysis and analysed data required for figure 5. KK provided supervision, funding and writing review.

My contributions to this manuscript in detail:

For this manuscript, I designed the study, implemented the stimulation procedure within the MR scanner, designed and coded all cognitive tasks. Furthermore, I was responsible for participant and data management and acquired all data. Subsequently, I preprocessed, analysed and interpreted the data, performed data visualizations and wrote this manuscript.

Munich, June 26, 2024

Daniela Rodriguez Manrique

Prof. Dr. Kathrin Koch, PhD

Manuscript 2: Examining Percent Amplitude of Fluctuations as a resting-state fMRI measure in Patients with Obsessive-Compulsive Disorder

---

Rodriguez-Manrique D, Bremer B, Gürsel D, Berberich G, Zimmer C, Koch K

DG recruited subjects and acquired all the data with help from BB. DRM, BB and KK designed the study based on the available data sample. BB advised on the preprocessing and methodological decisions. DRM completed all preprocessing, analyses and data interpretation. DRM additionally performed all data visualisations and wrote the present manuscript. Cooperation with BG allowed patients recruitment from the clinic. CZ supported data storage funding for project. KK and BB provided writing review. KK provided supervision and funding.

My contributions to this manuscript in detail:

For this manuscript, I designed the study based on the available data sample. Subsequently, I preprocessed, analysed and interpreted all the data. Furthermore, I performed all data visualisations and wrote this manuscript.

Munich, June 26, 2024

Daniela Rodriguez Manrique

Prof. Dr. Kathrin Koch, PhD

Affidavit / Eidesstattliche Versicherung

Hiermit versichere ich an Eides statt, dass ich die vorliegende Dissertation “Exploring Neuronal Correlates of Obsessive-Compulsive Disorder – Novel Approaches using Brain Stimulation and fMRI” selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

I hereby confirm that the dissertation “Exploring Neuronal Correlates of Obsessive-Compulsive Disorder – Novel Approaches using Brain Stimulation and fMRI“ is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

Munich, 26.06.2024 Daniela Rodriguez Manrique