Response inhibition in OCD: predicting symptom severity before and after treatment: An investigation of the pre-SMA, IFG, and IPC

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Response inhibition in OCD: predicting symptom severity before and after treatment

An investigation of the pre-SMA, IFG, and IPC

Master Thesis

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Preface

Before you lies the thesis “Response inhibition in OCD: predicting symptom severity before and after treatment”, in which SST-related BOLD activity in three brain areas was investigated. The thesis was done in cooperation with the Amsterdam University Medical Centre (location VUmc) and was preceded by an internship where I first got introduced to the research and patient group. During my thesis I was engaged in part of the data collection, digitalising data, performing fMRI pre-processing and MRI quality checks, and adjusting in-house fMRIprep scripts for smoothing and first levels. I was engaged in these activities from April till July 2022.

The research question for the thesis was formulated in cooperation with my supervisors and fits the ACP master because factors are manipulated (through stimulating different sites of the brain) to enhance cognition, indicated by an absolute change in Y-BOCS symptom severity score post-treatment compared to before treatment. The overall goal is to predict treatment outcome, using fMRI BOLD activity during successful inhibition versus successful go responses as a measure of response inhibition.

I would like to thank my field supervisors, Tjardo Postma and Sophie Fitzsimmons, as well as my university supervisor Dr. Guido Band for the excellent guidance and support during this process. I also want to thank Dr. Odile Van den Heuvel who leads the Tipicco research and the rest of the Neuropsychiatry team for always being available and willing to answer questions. Finally, I want to thank my sisters and my partner for the support and brainstorming sessions during this trajectory.

Farah el Hakkouni

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Abstract

Obsessive compulsive disorder (OCD) is a prevalent disorder for which response inhibition deficits is a suggested endophenotype. Due to unknown reasons, current treatments for the disorder are only effective in 30-40% of patients. Therefore, the aim of this research was to identify relevant predictors of treatment outcome. The treatment consisted of an 8-week intervention including 2 weekly rTMS sessions followed by exposure therapy. The research question was whether Blood Oxygenation Level Dependent (BOLD) activity during successful inhibition in a Stop Signal Task could significantly predict baseline symptom severity and treatment outcome in OCD patients. It was investigated whether lower pre-supplementary motor area (pre-SMA), inferior frontal gyrus, and/or inferior parietal cortex BOLD activity would predict higher symptom severity scores at baseline and a larger decrease in Y-BOCS scores. The total sample consisted of 51 participants, spread over two experimental (pre-SMA and dorsolateral prefrontal cortex (DLPFC)) and one control (vertex) condition. Symptom severity scores were recorded before and after treatment using the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS). Results revealed that none of the regions of interest significantly predicted treatment outcome. Lower pre-SMA BOLD activity did however significantly predict higher symptom severity before treatment. In addition, an exploratory analysis of BOLD activity in the right DLPFC during successful inhibition was not a significant predictor of treatment outcome, while it was a significant predictor when based on executive control-related BOLD activity. It may be concluded from the results that pre-SMA BOLD activity significantly predicts baseline Y-BOCS scores, and that right DLPFC BOLD activity is not a relevant predictor when based on successful response inhibition.

Keywords: OCD, inhibition, pre-supplementary motor area, inferior frontal gyrus, inferior parietal cortex

Author contributions: the study had been designed before writing the thesis by the Tipicco research team. I have been engaged in part of the data collection and the digitalisation of data. Also, I have been engaged in data analysis with the help of Dr. Chris Vriend and my supervisors. For data analysis I have conducted fMRI pre-processing steps and performed MRI quality checks, and I adjusted in-house made scripts for smoothing and first levels. The report has been written and edited by me, together with the help of Dr. Guido Band, Tjardo Postma, Dr. Odile van den Heuvel, and Dr. Ysbrand van der Werf through the providence of feedback throughout the thesis project.

Introduction

About 2-3% of the population is thought to develop Obsessive Compulsive Disorder (OCD) symptoms at some point in their lives (Stein et al., 2019; Fitzsimmons et al., 2022). Development of the psychiatric disorder is the result of complex gene-environment interactions, where multiple genes' expression may be triggered by environmental factors such as birth complications or stressful or traumatic events. OCD is characterised by the presence of obsessions and compulsions, defined as repetitive, intrusive and unwanted "thoughts, images, impulses or urges" and "behaviours or mental acts that the individual feels driven to perform [...]" respectively (Stein et al., 2019, p.1). Although obsessions and compulsions may vary greatly between individuals, many patients have them related to contamination (obsession) resulting in excessive cleaning (compulsion), aggressiveness (obsession, and mental rituals as compulsive behaviour in response to it), and symmetry (obsession, and ordering and counting as compulsions). Experiencing OCD is found to significantly affect one's quality of life (Stein et al., 2019).

Researchers suggest several neurobiological mechanisms underlying OCD, such as alterations in cortico-striato-thalamo-cortical (CSTC) circuits. The CSTC circuits are proposed to be involved in cognitive, affective and motivational processes, and involve, amongst other brain areas, the pre-supplementary motor area (pre-SMA) and inferior frontal gyrus (IFG) which separately interact with the parietal network (Stein et al., 2019). Alterations in these three brain areas of the CSTC circuits are suggested to reflect response inhibition impairments in OCD patients (Stein et al., 2019; van Velzen et al., 2014); impairments that in theory would explain patients' inability to stop their obsessions and compulsions (de Wit et al., 2012; Grützmann et al., 2022).

Due to unknown reasons, only 30-40% of patients sufficiently benefit from current treatments which include (cognitive) behavioural therapy (CBT), such as exposure therapy (ERP), and medication (e.g., SSRIs) (Stein et al., 2019). Especially ERP is a form of CBT that has been found to be effective in treating OCD symptoms in a part of the population, by gradually exposing patients to fear-evoked stimuli while instructing them on how to refrain from performing compulsive behaviour (Stein et al., 2019; Wootton, 2016). Other successful, but less common treatments involve deep brain stimulation (DBS) and repetitive transcranial magnetic stimulation (rTMS) (Tastevin et al., 2019). DBS is an invasive treatment that is only used in severe cases, where the patient gets a physical stimulator implanted in the brain.

A non-invasive alternative treatment method suggested to be effective is rTMS, which is already a licensed treatment in the Netherlands for depression and bipolar disorder, but not for OCD. rTMS is usually performed on (pharmaco-)therapy resistant OCD patients in addition to CBT and is used to inhibit or excite brain areas with low- and high frequency magnetic field pulses respectively (Rossi et al., 2009; Pell et al., 2011). Which brain areas should be stimulated remains debated under researchers, but they most commonly include the pre-SMA and dorsolateral prefrontal cortex (DLPFC) (Fitzsimmons et al., 2022). It is however suggested that effects of the stimulation spread from the direct stimulation site, through its connections with other brain areas (Douw et al., 2020). This makes it uncertain what specific stimulation sites or intensities yield the highest effectiveness, leaving the variability in the effectiveness of rTMS between different individuals unexplained. It is thus important to identify other variables that explain this heterogeneity.

The construct of response inhibition

One suggested useful indicator of OCD symptoms is an impairment in response inhibition (de Wit et al., 2012; van Velzen et al., 2014). Response inhibition is defined as the ability to suppress responses that are unwanted or inappropriate, and it is suggested to be crucial for flexible and goal-directed behaviour (Verbruggen et al., 2019). In OCD patients, response inhibition deficits represent a suggested endophenotype, meaning that it could be a heritable trait (de Wit et al., 2012). Response inhibition can exist in many forms, as can be demonstrated with different paradigms. Not only have OCD patients been found to perform worse on response inhibition tasks than healthy controls, but they also showed alterations in their neural circuits during performance (de Wit et al., 2012; Norman et al., 2019; Grützmann et al., 2022). Such differences are useful to investigate as potential predictors for patients' symptom severity and treatment outcome of rTMS combined with CBT.

Before doing so, however, it is important to reduce the scope of 'response inhibition' to the form that OCD patients have been found to perform worst at; action cancelation (van Velzen et al., 2014). Action cancelation is measured by a Stop Signal Task (SST) (see **Figure 1**) where participants are instructed to respond as fast as possible to an arrow pointing either left or right (named 'go' trials), while inhibiting their response when an arrow is followed by an 'X'. The SST hereby measures the late stage of response inhibition and reflects one's ability to repress an action that is already initiated, namely inhibiting a motor response after a go' cue.

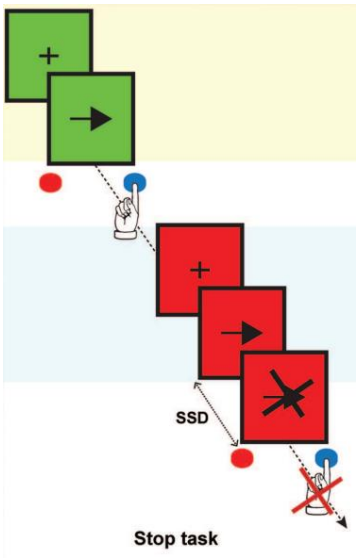

Figure 1: depiction of an adjusted version of the original SST used in the current research (with black backgrounds). The green and red backgrounds used in the figure represent a go- and stop-trial respectively. SSD = Stop Signal Delay. From "Response inhibition and interference control in obsessive–compulsive spectrum disorders", by L.S. Velzen, C. Vriend, S.J. de Wit and O.A. van den Heuvel, 2014, Frontiers in Human Neuroscience. Copyright 2014 by van Velzen, Vriend, de Wit and van den Heuvel. This is an open access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice.

Logan and Cowan (1984) explain the concept of inhibition as an independent race between a 'go runner' and a 'stop runner'. When the 'stop runner' (triggered by presentation of a stop signal) finishes before the next 'go runner' (triggered by presentation of a go-signal), inhibition is successful. Inhibition is unsuccessful however, when a 'go runner' finishes before the 'stop runner'. By defining this difference, the independent race model allows to estimate the covert latency of the stop process. That is, the time frame from the moment one got the cue to initiate a response until the moment one gets the cue to inhibit this response. This is useful as the latency of inhibition-control capabilities cannot be observed directly with all inhibition tasks (Verbruggen et al., 2019). The SST has the advantage of being able to provide a timeframe of the stop process, due to the latency between the arrow and the 'X' covering it on stop-trials.

Brain areas associated with response inhibition in OCD

Using SST performance as an indicator of OCD symptom severity might already explain some of the variability in treatment outcome between individuals. It may however be complemented by other indicators to serve as a more accurate predictor. By investigating task-related fMRI Blood Oxygenation Level Dependent (BOLD) activity during a SST, alterations may be identified. Several CSTC circuits have already been suggested to be involved in response inhibition processes, directly and indirectly. The dorsal cognitive CSTC circuit, involving the pre-SMA, has been suggested to underlie working memory, planning and emotion regulation. The ventral cognitive CSTC circuit, however, has been suggested to have a more direct relationship with response inhibition, and includes the IFG. Finally, the frontoparietal network has been found to be involved in coordination of cognitive control, and to also have impaired function in OCD patients during response inhibition (Stein et al., 2019). To identify accurate predictors of treatment outcome, each of these brain areas' involvements in response inhibition and other functions must be investigated.

Pre-supplementary motor area (pre-SMA)

The pre-SMA has been found to be hyperactive in unmedicated OCD patients and their unaffected siblings compared to healthy controls during successful inhibition on a SST (de Wit et al., 2012; Thorsen et al. 2020). This negative correlation, where higher pre-SMA BOLD activity is associated with shorter Stop Signal reaction times (SSRTs), implicates a compensatory role of this brain region. As this negative correlation is present in patients as well as unaffected siblings, compensatory hyperactivity in the pre-SMA is suggested to be another endophenotype of OCD (de Wit et al., 2012). The idea of compensation is in line with the findings of Ruan et al. (2018), who found that BOLD activity in the pre-SMA appeared to be especially high just before performing a physical motor response in healthy

individuals. These, and the findings by de Wit et al. (2012) implicate an important role of the pre-SMA in action planning, which may facilitate successful response inhibition.

Indeed, research on the effectiveness of rTMS reported that exciting the pre-SMA through high frequency (HF) stimulation was associated with improved performance on a SST, while the opposite was found for low frequency (LF) stimulation to the pre-SMA (Watanabe et al., 2015). Other research however, found that even LF stimulation to the pre-SMA positively affected response inhibition compared to a sham stimulation condition (i.e., condition that got a non-working coil, to serve as a control condition) (Fitzsimmons et al., 2022).

Inferior frontal gyrus (IFG)

The IFG has also been suggested to play a role in response inhibition, and to show altered activation in OCD patients during a SST (de Wit et al., 2012). The IFG was found to be hypoactive during (un)successful inhibition in OCD patients, while increased BOLD activity of the IFG in healthy individuals was correlated with successful inhibition. Some studies suggest that activation is lateralised in patients, but not in unaffected siblings (Grützmann et al., 2021) and unrelated healthy controls (Roth et al., 2007). In a patient group with lesions to the IFG, similar inferences about the IFG's involvement can be made as a positive association between severity of the lesion and inhibition impairments was found (Aron et al., 2003).

Besides directly engaging in response inhibition, the IFG is also suggested to be involved in functions such as selection processes and switching (Moss et al., 2005; Hirshorn & Thompson-Schill, 2006), which may be part of the process of response inhibition. In a simple picture naming task measuring automatic retrieval, left IFG BOLD activity was found to increase with increasing demands in selection processes (Moss et al., 2005). This would explain why OCD patients are mostly impaired in action cancelation compared to other forms

of response inhibition such as action restraint and interference control. Action cancelation reflects one's ability to inhibit their response after initiation, while action restraint requires one to repress a response that is not initiated (i.e., instead of being presented with the stop-signal shortly after an arrow, one is presented with the stop-signal right at the beginning of the inhibition trial). As action cancelation is thus more demanding than action restraint, this would explain why the IFG's engagement is implicated both in this form of response inhibition and when cognitive demands increase. It may also be explained by the similarity in the sequence of triggers OCD patients might experience, where patients only have difficulty refraining from their compulsions once they experienced an obsessive thought (as the initiator).

In addition, IFG BOLD activity has been found to be increased in healthy individuals during switching, for example when doings so between clusters on a verbal fluency task (Hirshorn & Thompson-Schill, 2006). The hypoactivity in the IFG in OCD patients may reflect rigidity in one's ability to switch after a majority of go-trials to an unsuspected stop-trial. Finally, the division between the direct and indirect pathways proposed to result in dysfunctional behaviours, such as response inhibition impairments, provides a theoretical explanation for the impact of IFG hypoactivity in OCD patients (Van den Heuvel et al., 2010). The direct pathway is hypothesized to serve as a "self-reinforcing positive feedback loop" that impacts initiation and continuation of behaviours. The indirect pathway in turn responds to the output of this loop and serves as a regulator for inhibiting behaviours and switching between them. Although the IFG's involvement in the direct pathway may be counterargued by the findings of Cai & Leung (2011) showing that the inferior frontal cortex was active in healthy individuals both during successful and unsuccessful inhibition, it may potentially be that the IFG plays a role in the indirect pathway during successful inhibition in OCD.

Inferior parietal cortex (IPC)

In addition to the IFG, the IPC was found to be hypoactive during response inhibition in the study by de Wit et al. (2012). This was only the case for OCD patients compared to healthy controls, but not for unaffected siblings. This inability to recruit the IPC (and IFG) is suggested to reflect attention impairments to the stop signal on stop-trials, or an impairment in action reprogramming. The (inferior) parietal cortex has been implicated to be a key region for supervisory attentional control (Cieslik et al., 2015), which is suggested to play a role in suppressing one response in favour of the other as is the case in response inhibition as well. A lack of supervisory attention may thus account for patients' inability to successfully inhibit their response.

Aim and implications

There are many unexplained differences in treatment effectiveness between individuals, for CBT, pharmacotherapy, and rTMS. With inhibition impairments suggested to be a trait marker for OCD, SST performance could be a useful indicator of symptom severity. As research suggests the involvement of the pre-SMA, IFG and IPC in response inhibition, the aim was to investigate the effectiveness of using these brain areas' BOLD activity during successful inhibition in a SST to serve as a predictor for symptom severity and treatment outcome. Identifying predictors of treatment outcome would allow to select patients for the treatment, preventing unnecessary time, effort and costs made for patients that are not expected to benefit from the treatment. The Yale-Brown Obsessive Compulsive Scale (Y-BOCS), a widely used and validated questionnaire, was used as an indicator of symptom severity (Goodman et al., 1989; Storch et al., 2010).

In the current study, the effectiveness of an 8-week intervention containing 20 minutes of HF rTMS twice a week followed by a 45 minute ERP session, is investigated. Participants were randomly assigned to either of the three stimulation sites: the DLPFC, pre-

SMA or, for the control condition, the vertex. Although TMS is not directly targeted towards the regions of interest (ROIs) in the current study, except for the pre-SMA in 1 of the 3 conditions, they are still expected to be affected through their connections within the CSTC circuits (Rossi et al., 2009; Pell et al., 2011; Grützmann et al., 2022).

Hypotheses

To answer the research question whether SST-related BOLD activity in the pre-SMA, IFG and IPC in OCD patients during successful inhibition can predict symptom severity and treatment outcome, six two-part hypotheses were tested. The dependent variable was the Y-BOCS severity score for each of the hypotheses. The first part of the hypotheses included Y-BOCS scores prior to treatment as the dependent variable, while the second was the absolute change post-treatment compared to before treatment. The independent variable was the SST-BOLD activity in the specified ROI in either the left or right hemisphere, as an indicator of recruitment and involvement of this area in response inhibition.

Specifically, it was first of all hypothesized that lower left or right pre-SMA BOLD activity during successful inhibition on a SST is associated with higher symptom severity and more improvement post-treatment. This was based on the findings by de Wit et al. (2012), who suggest a compensatory role of the pre-SMA in inhibition in OCD, as higher activation was found to correlate with shorter SSRTs; as well as the findings by Ruan et al. (2018) who found higher activation to be correlated negatively with SSRTs in healthy individuals.

Secondly, it was hypothesized that lower left or right IFG BOLD activity during the SST is associated with higher symptom severity and better treatment outcome. This was based on findings of previous researchers on the IFG's role in response inhibition, revealing impairments corresponded with an inability to recruit the IFG (de Wit et al., 2012). IFG lesions were also found to correlate positively with SSRTs in non-OCD patients, and the IFG has been implicated in a number of other functions that may reflect sub-aspects of response

inhibition, such as switching and selection processes (Van den Heuvel et al., 2010; Aron et al., 2003; Moss et al., 2005; Hishorn & Thompson-Schill, 2006).

Thirdly, it was hypothesized that lower left or right IPC BOLD activity is correlated with higher symptom severity and a larger Y-BOCS change post-treatment. The IPC was found to be hypoactive in OCD patients, which was negatively correlated with SSRTs (de Wit et al., 2012). Also, the IPC has been suggested to take part in supervisory attention, which may be a sub-component in response inhibition as well (Cieslik et al., 2015).

Methods

Design

The current research was part of a larger 'proof-of-concept' randomized controlled trial on ERP and rTMS-induced neurobiological and behavioural changes in OCD patients for which symptoms remained after trying (pharmaco-)therapy in the past. The study consisted of 3 conditions, each receiving 10 Hz rTMS either on the left DLPFC, pre-SMA or, as control condition, over the vertex before going to ERP. Although the study included 3 conditions and has a typical between-subjects design, this particular research did not compare each of the conditions. Instead, the aim was to identify predictors for rTMS and ERP treatment outcome based on BOLD activity in the brain being high or low in a ROI during successful inhibition, regardless of one's treatment condition.

The independent variable in each of the hypotheses was thus the fMRI BOLD response in either the left or right pre-SMA, IFG, or IPC, during the inhibition contrast. This contrast compared BOLD activity during successful go-trials with that during successful stop trials in the SST measured in arbitrary units (au). The dependent variable was the Y-BOCS score at baseline and the absolute change post-treatment for each of the hypotheses. Both fMRI BOLD activity and Y-BOCS scores have an interval measurement level. To account for regression to the mean when measuring Y-BOCS scores a second time for the change post-treatment, a model including baseline Y-BOCS scores as a covariate was be compared to one without. Other covariates were age, gender, education, and medication status (yes/no). As participants were not deblinded, the vertex (control) condition is included in the current analyses which is an important consideration when interpretating the results.

Participants

The sample size for the current analysis consisted of 51 OCD-diagnosed individuals (N females=34; N males=17) between the age of 18 and 65 years old (M=37, SD=12.98). Participants were recruited throughout the Netherlands via GGZ in Geest and advertisement on OCD patient association websites (e.g., www.dwang.eu).

Inclusion criteria were previous (cognitive) behavioural therapy (≥8 sessions), and the use of medication (in the past) without sufficient effects. Furthermore, a minimum Y-BOCS score of 16 was required and participants' medication use had to be stable or absent for at least 12 weeks before being assigned to a treatment condition. Individuals were excluded from research if they had previous experience with rTMS as treatment, or if they did not meet the TMS and MRI screening requirements (see **Appendix I**). Other exclusion criteria included severe heart disease, Tourette's syndrome, and/or (past) use of antipsychotics or medication affecting cortical excitability. Furthermore, patients whose resting motor threshold exceeded 75% or had no useful motor-evoked potential (MEP) elicitable were excluded. The MEP was determined based on recorded motor responses in the right hand while stimulating the left motor cortex. The intensity on which a MEP was elicited was assumed to indicate one's excitability threshold for other brain areas in the cortex and thus used to calculate treatment intensity (110% of the resting motor threshold for the pre-SMA and DLPFC, 60% for the vertex).

Patients were compensated for completing intake questionnaires and procedures, baseline cognitive and clinical assessments, and for taking part in MRI and TMS motor threshold sessions, separately, adding up to a total of €90,- euros. Ethical approval from the METC VUmc has been obtained for the study on January 15th 2019 and is registered under protocol number 2018/522. Also, prior to participation, informed consent was obtained in accordance with the declaration of Helsinki (World Medical Association, 2013).

Procedure

Before participation, screening for eligibility was conducted by a clinical neuropsychiatrist after which informed consent was obtained and an appointment to complete clinical and cognitive assessments was scheduled. Some assessment questionnaires completed at baseline included the SCID-I, demographic characteristics, BDI, BAI, and Tourette's and tic disorder screening questionnaire. The Y-BOCS was completed both at baseline and post-treatment.

Right after clinical assessment, participants were invited to the policlinic of the Amsterdam UMC, location VUmc. Here, two practice tasks were conducted followed by 4 cognitive assessments. Practice tasks were the Tower of London (ToL) and the SST, which both had to be performed inside the MRI scanner after completing the 4 cognitive assessments. This included a N-back, temporal discounting, risk choice, and emotional Stroop task. During the tasks a supervisor was present to provide explanation. After completion, the participant was escorted to the MRI scanner where they performed the ToL and SST. Then, an introduction session was scheduled to determine the MEP and for patients to have their second ERP. The MEP was used to calculate stimulation intensity, after which the 8 week intervention started. This included 20-minute rTMS sessions twice a week in a room at the Amsterdam VUmc, where patients were instructed to sit still and relax. Each rTMS session was followed by a 45-minute ERP at GGz in Geest located next to the medical centre. For purposes of the current analysis, only clinical outcomes and the BOLD activity during successful inhibition will be investigated, without using performance on either of the other 4 cognitive assessments.

Apparatus

To visually examine (f)MRI scans, MobaXterm, an online data server, was used. Data was then analysed through SPM, which allows to select coordinates in the brain and access to a numerical output of this fMRI data with MarsBar. Furthermore, the Magstim Rapid2 TMS stimulator and Magstim Double 70mm Air Film coil were used for the 16 rTMS sessions. In addition, the Localite TMS Navigator was used to allow real-time localisation of the rTMS target areas on an uploaded MRI scan presented on screen. It was also used to determine the location of the pre-SMA to put on the MRI scan, based on SST-related BOLD activity at baseline (while the location of the DLPFC and vertex were based on coordinates from the literature).

Scans were obtained at the VUmc with a 3T whole-body scanner consisting of a 32 channel phased-array head coil. Using a gradient echoplanar imaging sequence (repetition time= 2200 ms, echo time= 28 ms, 64 x 64 matrix, field of view= 211 mm, flip angle= 90°), images were acquired with 42 ascending slices per volume (3.3 x 3.3 mm in-plane resolution, slice thickness= 3 mm, inter-slice gap= 0.33 mm). Before entering the scanner, participants were provided with earbuds to protect them from noise and a headset for communication with the researcher.

Task & questionnaire

Stop-Signal Task (SST)

The SST was used as an indicator of response inhibition and to locate successful inhibition related BOLD activity at the time of performance. Participants were instructed to respond as fast as possible to arrows pointing left or right after seeing a fixation cross, requiring a button press on a remote in patients' left and right hands respectively on go-trials. Stop-trials included an arrow pointing either way, followed by an "X" covering it, where participants must inhibit their response. SSRTs were recorded for successful stop and

successful go responses, using the inhibition contrast (SS>SG). Regardless of when/whether a response is given, arrows remained on screen for 1500ms. A total of 250 trials were included in 13 minutes, where the minority of the trials (20%) were stop-trials. This led to a stop-success-to-error ratio of approximately 50%, in accordance with the recommendations of Verbruggen et al. (2019).

Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)

The dependent variable for each of the hypotheses were the Y-BOCS score at baseline, and separately investigated, the Y-BOCS score post-treatment. The Y-BOCS is an OCD-symptom checklist developed by Goodman et al. (1989), consisting of 5 questions related to obsessions and 5 to compulsions, and is suggested to have high validity (Goodman et al., 1989; Storch et al., 2010). In a longitudinal study on the psychometric properties of the Y-BOCS, it was found that it has acceptable to good within-person change reliability over time, as well as high between-person change reliability (Kuckertz et al., 2021). Questions were translated from English to Dutch to fit the patient group and the questionnaire was conducted in an interview setting, writing the answers on paper to digitalise them at a later point in time. Higher Y-BOCS scores implicate higher symptom severity, fitting either of the 5 categories: “mild” (scores 0-13), “moderate” (scores 14-25), “moderate-severe” (scores 26-34), or “severe” (scores ≥35), although the participants were not reduced to these categories in current analyses. Based on previous research, the cut-off point for reductions to reliably predict full treatment response was at 35%, with partial treatment response at a 25% symptom severity score reduction relative to their baseline scores (Farris et al., 2013; Mataix-Cols et al., 2016). This calculation was only used for the categorisation of responders.

Observations

During the rTMS sessions a researcher or research-assistant and intern were present. The experienced researcher or assistant observed possible displacements of the coil during the stimulation on a screen using the Localite TMS Navigator. Interns were placed in the corner of the room, facing the patient to observe possible changes in their state. A short questionnaire had to be filled in to record the presence of neurological side-effects, potential uncomfortable, involuntary facial movements (e.g., eye(brow) twitches), and whether the patient was falling asleep.

Analysis

fMRI data

The independent variable for each of the hypotheses was the fMRI BOLD response during inhibition, as investigated with the inhibition contrast (successful stop > successful go). This contrast has been used by other researchers to measure inhibitory control (de Wit et al., 2012; Norman et al., 2018; van Velzen et al., 2014). First levels were run to extract this information, followed by a second level analysis in which this BOLD activity was averaged across participants. MNI coordinates from the research by de Wit et al. (2012) were used to localise the pre-SMA (right: x=9, y=17, z=67; left: x=-15, y=14, z=67), the IFG (right: x=33, y=23, z=-11; left: x=-33, y=23, z=-8) and the IPC (right: x=42, y=-55, z=43; left: x=-51, y=-55, z=43) with a 5mm sphere around the coordinates. Exploratory analyses included another region of interest, the right dorsolateral prefrontal cortex (DLPFC), of which coordinates (x=40, y=36, z=35) were used from the research by Mylius et al. (2013).

To ensure the quality of the imaging data, pre-existing ‘fMRIprep’ scripts were run for pre-processing, which were visually inspected once more before statistical analysis. Steps included slice timing correction, susceptibility derived distortion correction, realignment, and

checking noise through the use of ICA components. After that, quality checks were conducted. For structural data, checks included: checking field inhomogeneity, head motion, extension on the signal-to-noise ratio (CNR), and image energy within the head relative to outside of the head. Functional data steps included: head motion, image quality, variation, framewise displacement (FD), and time-series signal-to-noise ratio. Participants were excluded from the analyses in case they were outliers on the boxplots for each of the checks and when visual inspection confirmed movement and unreliability of the results, or if FD >0.5 mm.

Statistical analyses

Each of the hypotheses was tested by means of a linear regression as the hypotheses consist of (in)dependent variables with a continuous measurement level, and all have a predictive direction. The statistical program used for the analyses was R studio (R version 4.1.1), while figures were made in IBM SPSS Statistics (version 28). Prior to statistical analyses the six assumptions for regression models were checked for violations (i.e., linearity, normally distributed independent and dependent variables, homoscedasticity, multicollinearity, independence of observations, and normality of residuals).

Baseline Y-BOCS scores were taken into account when testing treatment outcome, as low-severity groups were already close to “normal” brain function, providing them with the least room for improvement. Also, baseline Y-BOCS scores were controlled for when testing treatment outcome to counteract regression to the mean as is expected with extreme values of BOLD activity at baseline. In addition to that, a model with baseline Y-BOCS scores as a covariate was compared to a model without controlling for this variable. Besides, age, gender, and medication use (yes/no) were included as covariates, as these were found to influence the course of the disorder. Their individual contributions were tested in post-hoc exploratory analyses.

Results

A total sample of 51 participants remained after excluding drop-outs (N=16), people that are still in treatment (N=13), and people whose fMRI data was not usable due to motion artefacts (N=2). No outliers or missing data were detected after inspecting (box)plots and frequency tables and thus the sample of N=51 remained. Participants' age range was between 19 and 65 years old (M=37, SD=12.98) and two-third of the sample consisted of females (see **Table 1**). 60% of participants used medication and each participant completed a form of education, with 82% having an educational level of HAVO or higher (see **Appendix III**).

		Age			**Y-BOCS score pre-treatment**			**Treatment response (absolute change in Y-BOCS score)**		
	N	*Min.*	*Max.*	*M(SD)*	*Min.*	*Max.*	*M(SD)*	*Min.*	*Max.*	*M(SD)*
Female	34	19	65	38(13.16)	19	37	28.18(4.49)	0	23	11.82(5.59)
Male	17	20	58	36(12.94)	18	39	27.35(4.78)	0	18	9(6.05)
Medicated	31*	19	65	37(13.98)	21	39	27.77(4.36)	1	21	10.61(4.71)
Unmedicated	20**	19	57	37(11.59)	18	36	28.1(4.95)	0	23	11.3(7.39)

*Of which 71% was female. **Of which 66% was female.

Table 1: descriptive statistics for age, baseline Y-BOCS score and treatment response by gender and medication status

For the linear regression analysis, the absolute change in Y-BOCS score was investigated (see $\Delta\, YBOCS\ score$ in **Figure 2**). However for the categorisation of responders, in full-, partial and non-responders, treatment response was calculated relative to baseline Y-BOCS scores (see $Relative\ treatment\ response$ in **Figure 2**). A full treatment response was found for 57% of the participants, indicating a reduction in symptom severity of 35% or more relative to baseline severity scores. Partial treatment response was found for 18% of the participants and 25% did not significantly decrease in Y-BOCS scores after treatment compared to their scores before.

As can be seen in **Table 2**, the standard deviation in treatment outcome and the proportion of non-responders is larger for the unmedicated group than for the medicated group. Also, females had a better treatment response on average, a larger proportion of partial and full-responders, and less variability in treatment response between individuals than males.

$$\Delta\, YBOCS\ score = YBOCS\ after\ treatment - YBOCS\ before\ treatment$$

$$Relative\ treatment\ response = \frac{\Delta\, YBOCS\ score}{YBOCS\ score\ before\ treatment}$$

Figure 2: formula for linear regression (top) and categorisation of responders (bottom)

	No response (0%-24% improvement)	*Partial response (25%-34% improvement)*	*Full response (≥35% improvement)*
N	13	9	29
Y-BOCS score pre-treatment (M, SD)	27.62(5.62)	28.11(5.11)	27.97(4)
Age (M, SD)	39(14.36)	37(13.75)	36(12.52)
Female	6 | 17.65%	7 | 20.59%	21 | 61.76%
Male	7 | 41.18%	2 | 11.76%	8 | 47.06%
Medicated	6 | 19.35%	7 | 22.58%	18 | 58.06%
Unmedicated	7 | 35%	2 | 10%	11 | 55%

*Percentages presented next to the absolute values add up horizontally to a 100% of the gender/(un)medicated group

Table 2: descriptive statistics for age and baseline Y-BOCS score by gender, and medication and response status

A total of 112 analyses were tested against $\alpha = 0.05$, of which 84 were exploratory. First of all, BOLD activity during successful inhibition was investigated for each of the three ROIs

(pre-SMA, IFG, and IPC) in each hemisphere separately to predict Y-BOCS scores before treatment. None of the six analyses turned out to be significant (see **Table 3**). Then, an exploratory analysis was added to see the contribution of each of the covariates (age, gender, education, and medication status) to the model (see **Appendix IV**). The analyses revealed significant F-statistics for lower pre-SMA BOLD activity predicting lower Y-BOCS scores pre-treatment, when only controlling for age [left: F(2,48)=3.599, p=0.035; right: F(2,48)=3.931 p=0.026]. This implies that the model using left or right pre-SMA BOLD activity including age might still be a significant predictor of one's Y-BOCS score pre-treatment.

Relationship ROI and Y-BOCS score pre-treatment

	Significance left	*Significance right*
Pre-SMA	F(9,41)=2.001, **p=0.064**	F(9,41)=1.922, **p=0.076**
IFG	F(9,41)=1.407, **p=0.217**	F(9,41)=1.372, **p=0.232**
IPC	F(9,41)=1.385, **p=0.227**	F(9,41)=1.445, **p=0.201**
DLPFC**	-	F(9,41)=1.367, **p=0.23**

*****Each analysis included age, gender, education, and medication status as covariates.

**The right DLPFC was added as an exploratory analysis

Table 3: results of the first part of hypotheses (predicting Y-BOCS scores pre-treatment)

The significance of the pre-SMA predicting baseline Y-BOCS scores is confirmed by both the regression coefficient for age (i.e., slope) [left: $\beta_{1=}$-0.11, t(1)=-2.286, p=0.027; right: $\beta_{1=}$-0.11, t(1)=-2.215, p=0.032] and the intercept [left: β_0 =32.01, t(1)=16.876, p<0.001; right: $\beta_{0=}$31.331, t(1)=16.982, p<0.001] being significant for the pre-SMA. The significant relationship disappeared for the left pre-SMA when adding gender as another covariate [F(3,47)=2.588, p=0.064], but remained for the right pre-SMA [F(3,47)=2.896, p=0.045]. In

contrast to what was hypothesized, the association between pre-SMA BOLD activity and Y-BOCS scores was positive, as depicted in **Figure 3** and **Figure 4.**

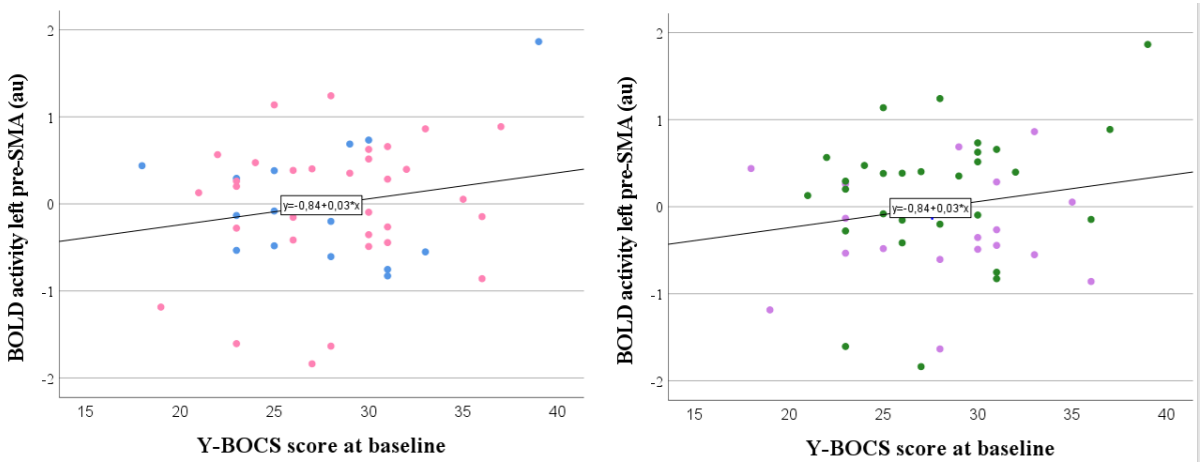

*Figure 3: significant relationship between left pre-SMA BOLD activity and baseline Y-BOCS scores while controlling for age, categorised by gender (left) and medication status (right). *Gender: pink reflects females. **Medication status: purple reflects no use*

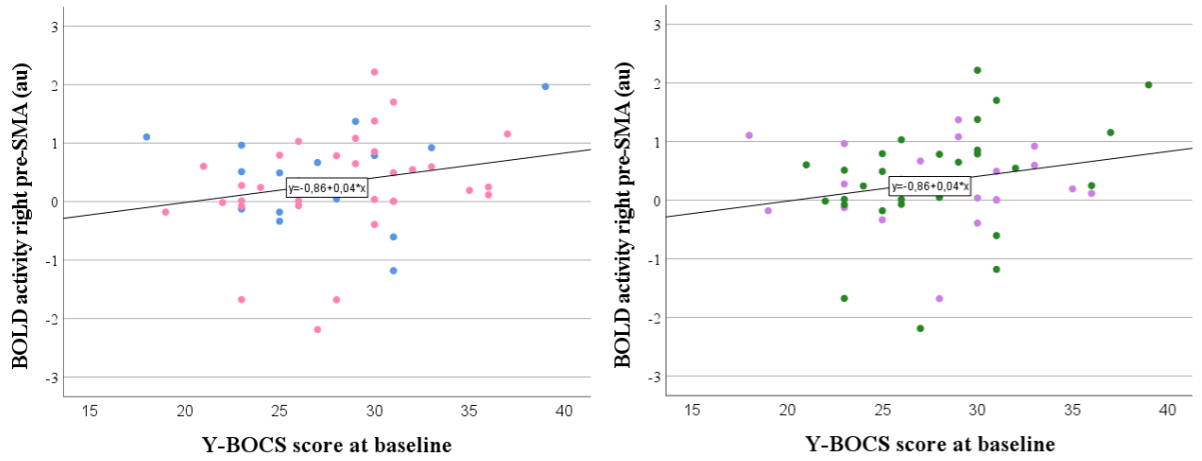

*Figure 4: significant relationship between right pre-SMA BOLD activity and baseline Y-BOCS scores while controlling for age, categorised by gender (left) and medication status (right). *Gender: pink reflects females. **Medication status: purple reflects no use*

Age explained 13% of the variance in Y-BOCS scores prior to treatment for the left pre-SMA, with an adjusted R^2 of 9%. The deviation implies that the regression equation would not generalize as accurately to other samples taken from the same population. For the right pre-SMA, age explained 14% of the variance in baseline Y-BOCS scores, with an adjusted R^2 of 10%.

After the first part of each of the hypotheses was tested, it was investigated whether the particular ROI's SST-related BOLD activity significantly predicted treatment outcome. For each of the hypotheses, a model controlling for Y-BOCS symptom severity score at baseline was compared against a model excluding this covariate. None of the F-statistics turned out to be significant (see **Table 4**), indicating that neither pre-SMA nor IFG or IPC BOLD activity during a SST significantly predicts treatment outcome. Noticeably, the insignificant relationship found between pre-SMA BOLD activity and treatment outcome fits a negative correlation, as can be seen in **Figure 5** and **Figure 6**. This implies higher BOLD activity in the pre-SMA at baseline would predict less improvement if it were to be a significant predictor. In addition, no significant difference was found between any of the ROIs' models' controlling and not controlling for Y-BOCS score pre-treatment.

Relationship ROI and difference in Y-BOCS score (after treatment – before treatment)

	Excl. Y-BOCS score pre-treatment as covariate	*Incl. Y-BOCS score pre-treatment as covariate*	*Model with Y-BOCS score pre-treatment versus model without*
pre-SMA (left)	F(9,41)=1.04, **p=0.426**	F(10,40)=1.243, **p=0.295**	F(1,40)=2.682, **p=0.109**
pre-SMA (right)	F(9,41)=1.034, **p=0.43**	F(10,40)=1.223, **p=0.307**	F(1,40)=2.565, **p=0.117**
IFG (left)	F(9,41)=1.561, **p=0.16**	F(10,40)=1.708, **p=0.113**	F(1,40)=2.514, **p=0.121**
IFG (right)	F(9,41)=1.53, **p=0.17**	F(10,40)=1.584, **p=0.147**	F(1,40)=1.801, **p=0.187**
IPC (left)	F(9,41)=1.49, **p=0.184**	F(10,40)=1.609, **p=0.139**	F(1,40)=2.267, **p=0.14**
IPC (right)	F(9,41)=1.39, **p=0.224**	F(10,40)=1.556, **p=0.156**	F(1,40)=2.567, **p=0.117**
DLPFC (right)	F(9,41)=1.501, **p=0.18**	F(10,40)=1.607, **p=0.14**	F(1,40)=2.172, **p=0.148**

*Each analysis included age, gender, education, and medication status as covariates.

Table 4: results of the second part of hypotheses (treatment outcome)

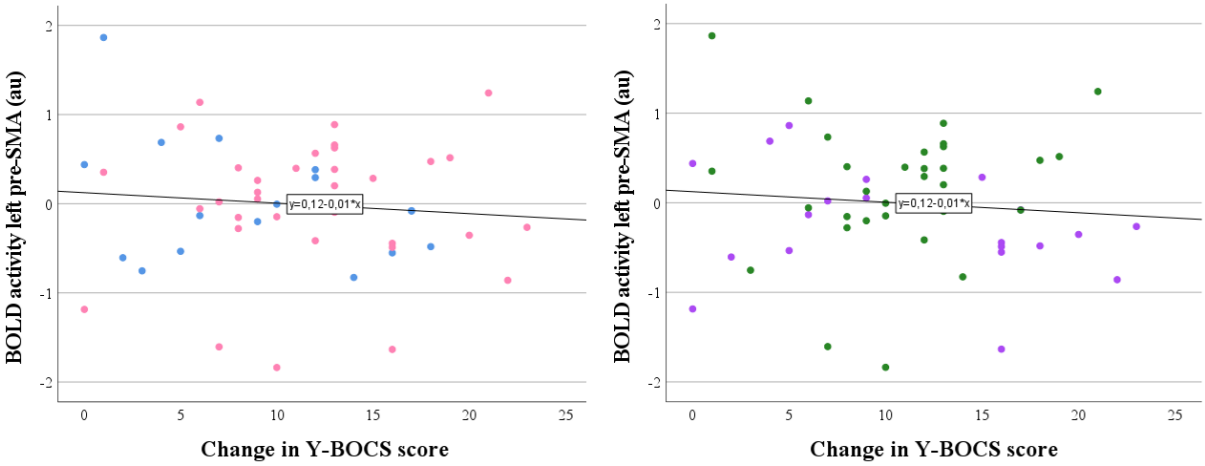

*Figure 5: insignificant relation between left pre-SMA BOLD activity and the absolute change in Y-BOCS score excluding baseline Y-BOCS score as covariate, categorised by gender (left) and medication status (right). *Gender: pink reflects females. **Medication status: purple reflects no use*

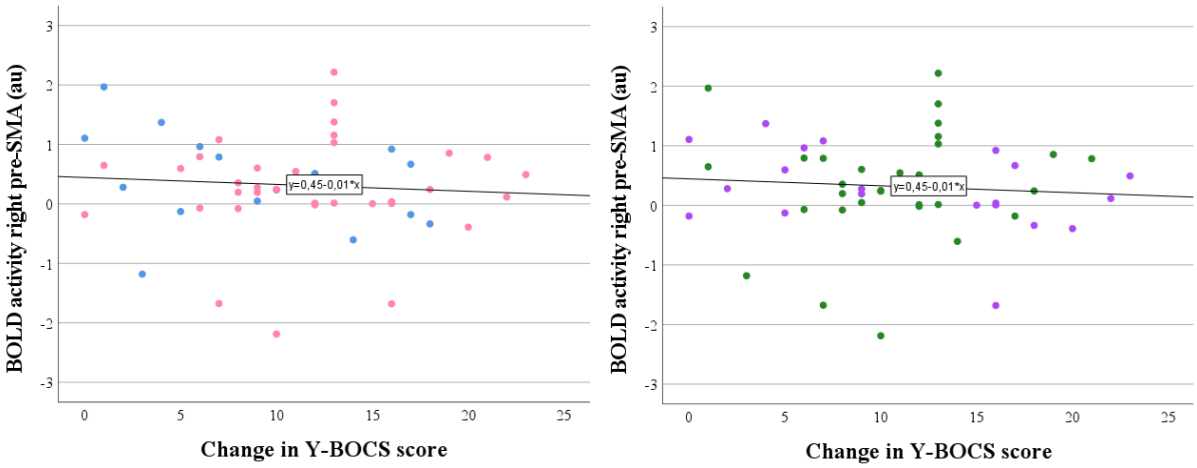

*Figure 6: insignificant relation between right pre-SMA BOLD activity and the absolute change in Y-BOCS score excluding baseline Y-BOCS score as covariate, categorised by gender (left) and medication status (right). *Gender: pink reflects females. **Medication status: purple reflects no use*

After completing the 24 main analyses (both parts of the three hypotheses, for left and right hemispheric activation), separate covariate contributions were investigated (see **Appendix IV**). This was followed by the addition of another ROI, the right DLPFC, after a parallel thesis on the same sample showed right DLPFC BOLD activity during an executive control task (Tower of London) was found to significantly predict treatment outcome. For the current research, right DLPFC BOLD activity turned out to be another insignificant predictor

of treatment outcome [including baseline Y-BOCS score as a covariate: $F(10,40)=1.607$, $p=0.14$], indicating the right DLPFC's BOLD activity predicting treatment outcome is task-specific. Right DLPFC BOLD activity during successful inhibition was also not a significant predictor of baseline Y-BOCS scores [$F(9,41)=1.367$, $p=0.23$].

Before conducting the linear regression analyses five assumptions were checked against violations. Only the linearity assumption was violated, for the bilateral IFG and the right IPC for predicting pre-treatment Y-BOCS scores and treatment outcome. This indicates biases in these models, negatively affecting the reliability of the results. The normality assumption was statistically checked by means of a Shapiro-Wilks (SW) test for the 7 independent and the 2 dependent variables which turned out to be insignificant for the bilateral pre-SMA and the right IPC and DLPFC. Visual inspection of the histograms did not confirm this non-normality. Homoscedasticity of variances was statistically tested by means of Breusch-Pagan tests and visually inspected with standardized residuals plotted against observed values. Both inspections showed no sign of heteroscedasticity of variances. Multicollinearity was also not significant, based on the tolerance and variance inflation factor. Besides, the independence of observation assumption was not violated, as checked by plotting standardized residuals against ID variables and by means of Durbin-Watson's tests for autocorrelation. Finally, normality of residuals was confirmed with a SW-test for standardized individuals.

Discussion

The aim of the research was to identify relevant predictors of treatment outcome in (pharmaco-)therapy-resistant OCD patients. As current treatments for OCD are often effective for only a small part of the population, identifying predictors would benefit the strategy of allocating patients to the appropriate treatment. Response inhibition is a suggested endophenotype of OCD, reason for SST-related BOLD activity to be a potential useful predictor of symptom severity. The one-time investment for performing a fMRI would outweigh the high costs associated with treatments, in time, money, and effort, especially when given to people that will not benefit from them. First and foremost, it would speed up the treatment process and allow patients to quicker improve their quality of life.

In order to achieve this goal BOLD activity during successful inhibition was investigated for each of the three ROIs (pre-SMA, IFG, and IPC) in each hemisphere separately, complemented by exploratory analyses of the right dorsolateral prefrontal cortex (DLPFC) and individual covariate contributions to the models. The hypothesis that lower pre-SMA BOLD activity would significantly predict higher symptom severity and a better treatment outcome, turned out to be insignificant. Pre-SMA BOLD activity did however become a significant predictor for Y-BOCS scores before treatment when controlling only for age. This significance remained for the right pre-SMA when adding gender as another covariate, but not when education was added to the model. This implies that educational levels impact the significance of pre-SMA BOLD activity predicting baseline Y-BOCS scores. However, considering the high amount of covariates relative to the sample size, education may possibly be excluded from the model. Nevertheless, even without controlling for education, the hypothesis that lower pre-SMA BOLD activity predicts higher baseline Y-BOCS scores and more improvement cannot be confirmed.

Instead, the current results suggest a positive correlation between pre-SMA BOLD activity and Y-BOCS scores at baseline, meaning that higher BOLD activity predicts higher Y-BOCS scores before treatment. This may seem in contrast to the findings from previous research by de Wit et al. (2012), who found hyperactivity in the pre-SMA correlated with shorter SSRTs, indicating a compensatory role of the brain area. The tested hypothesis was formulated based on the interpretation that this compensation reflects a positive trait, namely one's ability to cope with symptom severity, and that higher abilities to compensate would possibly improve one's chance of benefitting from treatment. However, current results imply that although pre-SMA BOLD activity may be compensatory, it may in fact be a negative biomarker of clinical symptoms reflecting the increased need for compensation and thus one's true symptom severity, instead of one's ability to cope with them.

For the IFG and IPC, the results also suggested that BOLD activity during the SST is not a significant predictor of baseline Y-BOCS scores nor for the change in Y-BOCS scores post-treatment. This is in contrast to what was hypothesized, namely that lower BOLD activity in either of the ROIs would predict higher symptom severity at baseline and a higher improvement post-treatment. Interestingly, the insignificant correlation remains for the bilateral IFG when controlling for age only, although the predictiveness of bilateral pre-SMA BOLD activity became significant. This is unexpected, since pre-SMA-IFG interactions are suggested to be critical for response inhibition (Tomiyama et al., 2021). In SST-related fMRI, alterations in connectivity have been found, showing an interaction between hyperactivity of the pre-SMA and hypoactivity of the IFG when response inhibition was impaired (Tomiyama et al., 2021). With both ROIs being functionally connected, it would be expected that together with the pre-SMA, IFG BOLD activity would be a significant predictor for baseline Y-BOCS scores. The lack of significance may imply that the pre-SMA's involvement is more relevant for response inhibition than that of the IFG.

Lastly, BOLD activity in the right DLPFC during successful inhibition was found to not significantly predict Y-BOCS scores before treatment or the improvement after treatment. This insignificant finding is not necessarily contradicting theory, as the DLPFC is not suggested to be as involved in response inhibition as it is in executive control. In an executive control task, right DLPFC BOLD activity was found to be a significant predictor of treatment outcome in the same OCD sample, implicating that the significance of using DLPFC's BOLD activity as a predictor for treatment outcome is task specific.

There are several possible explanations for the insignificant findings in this research. First of all, the study design included the stimulation of three brain areas, of which one is a placebo condition with stimulation to the vertex. For the two experimental conditions, only the pre-SMA is engaged in response inhibition, while the DLPFC is engaged in executive control. Although (r)TMS effects are suggested to spread besides the direct stimulation site (Douw et al., 2020), this is only for brain areas that it is connected with. Since the DLPFC is not implicated in response inhibition and not directly connected to respective brain areas, this leaves only one of three conditions that stimulate a site related to response inhibition. Regardless of both response inhibition and executive control impairments reflecting symptom severity, response inhibition related BOLD activity has now been used as a predictor for a treatment that was directed towards an engaged brain area only in one of three conditions.

Besides, including the control condition in the sample is a limitation in itself as rTMS treatment effects cannot be isolated. Since brain activity is not expected to change as a result of rTMS, and unknown to change from ERP, it is not possible to use this knowledge to identify and exclude the control condition. This may be another explanation for the insignificant findings when predicting treatment outcome, as the rTMS treatment effects may now be invisible when outweighed by non-responders in the vertex condition.

In addition to that, there was found to be a large standard deviation from the mean in scores of improvement in the unmedicated group (see **Table 1**) compared to the medicated group and both genders. The large standard deviation may reflect pre-existing differences between medication and non-medication users, or an overarching effect of medication outweighing other between-individual variability. Regardless of the theoretical interpretation of the cause of this variability, it is plausible that unmedicated patients caused the relationship to become insignificant.

Moreover, it may be that the coordinates that were used in the current study were not suitable for the population. The coordinates used were based on peak BOLD activity during a SST in unmedicated OCD patients as found in the research by de Wit et al. (2012). As the current sample contained medicated as well as unmedicated patients, the coordinates may not be generalisable. This may be supported by the large standard deviation found in improvement from treatment, as well as the large proportion of non-responders in the unmedicated group (see **Table 2**). From **Table 2** it also became clear that non- and partial responders have a larger standard deviation in baseline Y-BOCS scores than full-responders. Lastly, the sample size was small, which may have negatively affected the statistical power and reliability of the results.

Despite its limitations, the results of this research have theoretical significance to the field of research. The positive association found for pre-SMA BOLD activity predicting baseline Y-BOCS scores have led to a possibly new perspective on the nature of the compensatory activity and what it indicates. This association together with the insignificant findings for the IFG also put a new perspective on the relevance of each ROI in their functional connectivity during successful response inhibition. The fact that results were significant for the pre-SMA but not for the IFG may imply that pre-SMA recruitment is more important than inhibition of the IFG during response inhibition when predicting symptom severity. Furthermore, the

finding that right DLPFC activity does not significantly predict treatment outcome demonstrates the DLPFC's activity only serves as a predictor when measured during a task it is typically engaged in. It also adds to the idea that the stimulation sites in the current research may not have been suitable when using SST-related BOLD activity as a proxy for symptom severity.

Future research is therefore suggested to investigate SST-related BOLD activity as a predictor for symptom severity when treatment includes stimulation sites that are engaged in response inhibition, such as the IFG and IPC. This could be a more direct measure of the treatment effects. It is also suggested to repeat the current research when deblinding of the sample is possible, to exclude the control condition from the experimental conditions, and to investigate each experimental condition separately. Moreover, future research is suggested to separate medication users from non-medication users, and to include participants that have not used psychoactive medication before. Including participants with no history of medication use would potentially allow to infer whether differences between those who use medication and those who do not are pre-existing or a result of medication use.

All in all it can be concluded that SST-related pre-SMA BOLD activity is a relevant predictor of Y-BOCS scores before treatment, but that none of the ROIs' BOLD activity could significantly predict treatment outcome. Also, right DLPFC BOLD activity is only a significant predictor of treatment outcome when the task is related to executive control, but not when it is to response inhibition. Despite the insignificant findings, there are several theoretical implications to the results of this research. The proposed improvements for future research have the potential to explain current intra-individual variability in treatment outcome and fulfil the aim of identifying relevant predictors of treatment outcome.

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Appendix I: TMS and MRI screening (Nederlands)

MRI contra-indicaties:

Datum van afname: ../../….

[Vink het juiste antwoord aan van de volgende vragen:]

"Hebt u …

- Eerder een MRI scan gehad?
  - ▫ Ja
  - ▫ Nee
  - ▫ Weet ik niet
- Een pacemaker of (oude) pacemaker draden?
  - ▫ Ja
  - ▫ Nee
  - ▫ Weet ik niet
- Clips in het hoofd sinds een operatie?
  - ▫ Ja
  - ▫ Nee
  - ▫ Weet ik niet
- Een medicijnpomp (bijvoorbeeld een insulinepomp)?
  - ▫ Ja
  - ▫ Nee
  - ▫ Weet ik niet
- Een port a cath?
  - ▫ Ja

- Nee
- Weet ik niet

- Een neuro-stimulator?
  - Ja
  - Nee
  - Weet ik niet
- Een kunstlens met metalen clips?
  - Ja
  - Nee
  - Weet ik niet
- Een gehoorapparaat?
  - Ja
  - Nee
  - Weet ik niet
- Metalen oorbuisjes of een gehoorbeen prothese?
  - Ja
  - Nee
  - Weet ik niet
- Een cochleair implantaat?
  - Ja
  - Nee
  - Weet ik niet
- Een prothese (bijv. kunstarm)?

- Eén of meerdere piercings?
    - ▫ Ja
    - ▫ Nee
    - ▫ Weet ik niet
- Eén of meerdere tatoeages?
    - ▫ Ja
    - ▫ Nee
    - ▫ Weet ik niet
- Een niet verwijderbare metalen beugel in uw mond?
    - ▫ Ja
    - ▫ Nee
    - ▫ Weet ik niet
- Problemen met langer dan 30 minuten stil liggen?
    - ▫ Ja
    - ▫ Nee
    - ▫ Weet ik niet
- In de afgelopen 6 weken een operatie ondergaan?
    - ▫ Ja
    - ▫ Nee
    - ▫ Weet ik niet
- Een endoscopie met videocapsule ondergaan en is de capsule nog aanwezig?
    - ▫ Ja
    - ▫ Nee

- Weet ik niet

- Een implanteerbare cardioverter defibrilator (ICD)?
  - Ja
  - Nee
  - Weet ik niet
- Een behandeling met accupunctuurnaalden ondergaan en zijn deze nog aanwezig?
  - Ja
  - Nee
  - Weet ik niet
- (oud) Metaalbewerker of bestaat er een kans op metaalsplinters in de oogkas?
  - Ja
  - Nee
  - Weet ik niet
- Claustrofobisch (bang in kleine ruimtes)?
  - Ja
  - Nee
  - Weet ik niet
- Kortademig bij plat liggen?
  - Ja
  - Nee
  - Weet ik niet
- Hoe lang bent u (in cm)? …
- Hoeveel weegt u (in kg)? …

- Bent u (mogelijk) zwanger?
    - ☐ Ja
    - ☐ Nee
    - ☐ Weet ik niet

Eventuele bijzonderheden/opmerkingen: …….

TMS contra-indicaties:

Datum van afname: ../../….

[Vink het juiste antwoord aan op de volgende vragen:]

- Hebt u epilepsie? Of ooit een toeval of insult gehad?
    - ☐ Ja
    - ☐ Nee
- Hebben naaste familieleden (ouders, broers/zussen, kinderen) last van epilepsie of ooit een toeval of insult gehad?
    - ☐ Ja
    - ☐ Nee
- Hebt u ooit hoofdletsel opgelopen dat als een hersenschudding vastgesteld of gepaard gegaan was met verlies van bewustzijn? Zo ja, wanneer was dit?
    - ☐ Ja
    - ☐ Nee
- Hebt u ooit hersenchirurgie of oogoperaties ondergaan?
    - ☐ Ja

- ☐ Nee

- Zou het kunnen dat u zwanger bent?
  - ☐ Ja
  - ☐ Nee
- Hebt u metaal in uw hersenen, schedel of ergens anders in uw lichaam (bijvoorbeeld fragmenten, clips, etc.)?
  - ☐ Ja
    - Soort metaal: ……
    - Locatie: ……
  - ☐ Nee
- Hebt u een neurostimulator?
  - ☐ Ja
  - ☐ Nee
- Hebt u een medicijnpomp (bijvoorbeeld een insulinepomp)?
  - ☐ Ja
  - ☐ Nee
- Hebt u een huidziekte of huidallergie?
  - ☐ Ja
    - Welke? ……
  - ☐ Nee
- Hebt u hartklachten?
  - ☐ Ja
    - Wat voor klachten? ……
  - ☐ Nee

- Bent u ooit flauwgevallen?
  - ☐ Ja
    - In welke gevallen? ……
    - Wanneer voor het laatst? ……
  - ☐ Nee
- Hebt u last van gehoorproblemen of tinnitus, of hoort u een constante pieptoon?
  - ☐ Ja
  - ☐ Nee
- Hebt u een cochleair implantaat?
  - ☐ Ja
  - ☐ Nee
- Hebt u ooit eerder TMS ondergaan?
  - ☐ Ja
    - Wanneer voor het laatst? ……
    - Waren er problemen? ……
- Hebt u ooit eerder MRI ondergaan?
  - ☐ Ja
    - Waren er problemen? ……
  - ☐ Nee
- Gebruikt u momenteel medicijnen?
  - ☐ Ja, ……
  - ☐ Nee
- Hebt u medicijnen of (recreatieve) drugs in de afgelopen week gebruikt?
  - ☐ Ja, ……

- ▫ Nee

- Hebt u alcohol geconsumeerd in de afgelopen 24 uur?
  - ▫ Ja
  - ▫ Nee
- Hebt u een voor u normale hoeveelheid cafeïne geconsumeerd in de afgelopen 24 uur?
  - ▫ Ja
  - ▫ Nee
- Hebt u vannacht een normale hoeveelheid slaap gehad?
  - ▫ Ja
  - ▫ Nee

Eventuele opmerkingen: ……

Appendix II: Tipicco study design

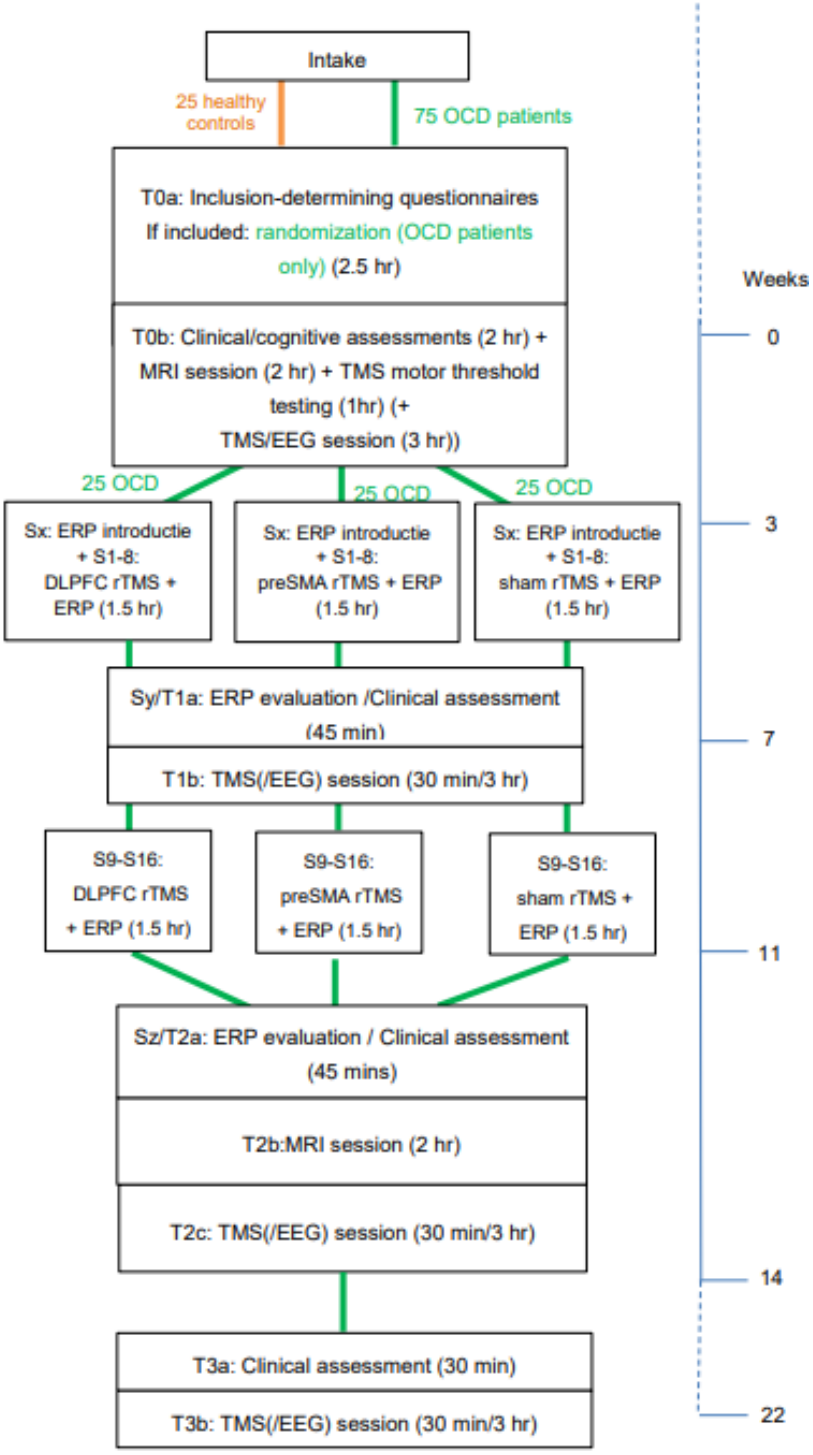

Figure 7: depiction of the study design of the Tipicco research project

Appendix III: Education levels

Education levels categorised by gender		
	Females	*Males*
VBO/LBO (huishoud-, ambacht-, technische school of interne bedrijfsopleiding)**, MBO kort**	0 (0%)	1 (6%)
MAVO/MULO/VMBO	2 (6%)	1 (6%)
MBO-LANG/internal corporate education at MBO-level	4 (12%)	1 (6%)
HAVO, VWO, Gymnasium	9 (26%)	3 (18%)
HBO	7 (20%)	6 (35%)
WO	12 (35%)	5 (29%)
Total	34 (99%)	17 (100%)

Table 5: depiction of educational levels categorised by gender

Appendix IV: Covariate contributions

Relationship ROI and Y-BOCS score pre-treatment		
	Significance left hemisphere	*Significance right hemisphere*
Pre-SMA (+A	F(2,48)=3.599, **p=0.035**	F(2,48)=3.931 **p=0.026**
Pre-SMA (+A, G)	F(3,47)=2.588, **p=0.064**	F(3,47)=2.896, **p=0.045**
Pre-SMA (+A, G, M)	F(4,46)=2.142, **p=0.091**	F(4,46)=2.187, **p=0.085**
Pre-SMA (+A, G, M, E)	F(9,41)=2.001, **p=0.064**	F(9,41)=1.922, **p=0.076**
IFG (+A)	F(2,48)=1.963, **p=0.152**	F(2,48)=1.773, **p=0.181**
IFG (+A, G)	F(3,47)=1.438, **p=0.244**	F(3,47)=1.325, **p=0.278**
IFG (+A, G, M)	F(4,46)=1.114, **p=0.362**	F(4,46)=1.005, **p=0.415**
IFG (+A, G, M, E)	F(9,41)=1.407 **p=0.217**	F(9,41)=1.372, **p=0.232**
IPC (+A)	F(2,48)=2.026, **p=0.143**	F(2,48)=2.478, **p=0.095**
IPC (+A, G)	F(3,47)=1.478, **p=0.233**	F(3,47)=1.791, **p=0.162**
IPC (+A, G, M)	F(4,46)=1.114, **p=0.362**	F(4,46)=1.343, **p=0.269**
IPC (+A, G, M, E)	F(9,41)=1.385, **p=0.227**	F(9,41)=1.445, **p=0.201**
DLPFC (+A)	-	F(2,48)=1.81, **p=0.175**
DLPFC (+A, G)	-	F(3,47)=1.349, **p=0.27**
DLPFC (+A, G, M)	-	F(4,46)=1.021, **p=0.407**
DLPFC (+A, G, M, E)	-	F(9,41)=1.367, **p=0.23**

Table 6: depiction of results of the first part of the hypotheses, predicting Y-BOCS scores prior to treatment based on BOLD activity during the SST in the ROIs in the left and right side of the brain (A=age, G=gender, M=medication, E=education)

Relationship ROI and difference in Y-BOCS score pre- versus post-treatment (treatment outcome)			
	Significance when no control for Y-BOCS score pre-treatment	*Significance while controlling for Y-BOCS score pre-treatment*	*Significance model with versus without Y-BOCS score pre-treatment*
Left pre-SMA (+A)	F(2,48)=0.234, p=0.792	F(3,47)=1.257, p=0.3	F(1,47)=3.282, p=0.076
Left pre-SMA (+A, G)	F(3,47)=1.049, p=0.38	F(4,46)=1.5, p=0.218	F(1,46)=2.738, p=0.105
Left pre-SMA (+A, G, M)	F(4,46)=0.824, p=0.517	F(5,45)=1.187, p=0.331	F(1,45)=2.531, p=0.119
Left pre-SMA (+A, G, M, E)	F(9,41)=1.04, **p=0.426**	F(10,40)=1.243, **p=0.295**	F(1,40)=2.682, **p=0.109**
Right pre-SMA (+A)	F(2,48)=0.183, p=0.833	F(3,47)=1.216, p=0.314	F(1,47)=3.265, p=0.077
Right pre-SMA (+A, G)	F(3,47)=0.984, p=0.408	F(4,46)=1.422, p=0.242	F(1,46)=2.631, p=0.112
Right pre-SMA (+A, G, M)	F(4,46)=0.81, p=0.526	F(5,45)=1.163 p=0.342	F(1,45)=2.475, p=0.123
Right pre-SMA (+A, G, M, E)	F(9,41)=1.034, **p=0.43**	F(10,40)=1.223, **p=0.307**	F(1,40)=2.565, **p=0.117**
Left IFG (+A)	F(2,48)=0.689, p=0.507	F(3,47)=1.455, p=0.239	F(1,47)=2.932, p=0.093
Left IFG (+A, G)	F(3,47)=1.545, p=0.215	F(4,46)=1.818, p=0.142	F(1,46)=2.488, p=0.122
Left IFG (+A, G, M)	F(4,46)=1.163, p=0.339	F(5,45)=1.434, p=0.231	F(1,45)=2.379, p=0.13
Left IFG (+A, G, M, E)	F(9,41)=1.561, **p=0.16**	F(10,40)=1.708, **p=0.113**	F(1,40)=2.514, **p=0.121**
Right IFG (+A)	F(2,48)=0.56, p=0.575	F(3,47)=1.272, p=0.295	F(1,47)=2.658, p=0.11
Right IFG (+A, G)	F(3,47)=1.487, p=0.23	F(4,46)=1.697, p=0.167	F(1,46)=2.21, p=0.144
Right IFG (+A, G, M)	F(4,46)=1.147, p=0.347	F(5,45)=1.361, p=0.257	F(1,45)=2.106, p=0.154

Right IFG (+A, G, M, E)	F(9,41)=1.53, **p=0.17**	F(10,40)=1.584, **p=0.147**	F(1,40)=1.801, **p=0.187**
Left IPC (+A)	F(2,48)=1.206, p=0.308	F(3,47)=1.913, p=0.14	F(1,47)=3.214, p=0.079
Left IPC (+A, G)	F(3,47)=1.972, p=0.131	F(4,46)=2.222, p=0.081	F(1,46)=2.752, p=0.104
Left IPC (+A, G, M)	F(4,46)=1.549, p=0.204	F(5,45)=1.806, p=0.131	F(1,45)=2.618, p=0.113
Left IPC (+A, G, M, E)	F(9,41)=1.49, **p=0.184**	F(10,40)=1.609, **p=0.139**	F(1,40)=2.267, **p=0.14**
Right IPC (+A)	F(2,48)=0.403, p=0.671	F(3.47)=1.311, p=0.282	F(1,47)=3.092, p=0.085
Right IPC (+A, G)	F(3,47)=1.225, p=0.311	F(4,46)=1.608, p=0.189	F(1,46)=2.628, p=0.112
Right IPC (+A, G, M)	F(4,46)=0.998, p=0.419	F(5,45)=1.325, p=0.271	F(1,45)=2.502, p=0.121
Right IPC (+A, G, M, E)	F(9,41)=1.39, **p=0.224**	F(10,40)=1.556, **p=0.156**	F(1,40)=2.567, **p=0.117**
Right DLPFC (+A)	F(2,48)=0.432, p=0.652	F(3,47)=1.189, p=0.324	F(1,47)=2.674, p=0.109
Right DLPFC (+A, G)	F(3,47)=1.32, p=0.279	F(4,46)=1.575, p=0.197	F(1,46)=2.234, p=0.142
Right DLPFC (+A, G, M)	F(4,46)=1.051, p=0.391	F(5,45)=1.286, p=0.287	F(1,45)=2.121, p=0.152
Right DLPFC (+A, G, M, E)	F(9,41)=1.501, p=0.18	F(10,40)=1.607, p=0.14	F(1,40)=2.172, p=0.148

Table 7: depiction of the second part of the hypotheses, models including Y-BOCS scores pre-treatment and excluding this covariate were tested against each other. Covariates were stepwise added to the test (A=age, G=gender, M=medication, E=education)