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Effect of deep transcranial magnetic stimulation on inhibitory control processes

A study on obsessive-compulsive disorder patients and healthy volunteers

Vliv hluboké transkraniální magnetické stimulace na kontrolně inhibiční procesy

Studie na pacientech s obsedantně kompulzivní poruchou a zdravých dobrovolnících

Supervisor: Doc. MUDr. Monika Klírová, Ph.D.

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Abstract

Background: Inhibitory control (IC) is a core executive function impaired in obsessive-compulsive disorder (OCD), often linked to hyperactivity in the anterior cingulate cortex (ACC). Repetitive transcranial magnetic stimulation (rTMS), particularly deep TMS (dTMS) targeting the ACC, may modulate inhibitory control, providing therapeutic potential. This study investigates the effects of anterior cingulate double cone (ACDC) TMS on inhibitory control in healthy individuals and patients with OCD.

Aims: The primary aim was to assess the impact of ACDC TMS on inhibitory control in healthy participants and patients with OCD using the interference Stroop effect. The secondary aim was to compare other behavioral and electrophysiological (EEG) effects of ACDC TMS across groups, including changes in reaction times (RT), number of errors, and error-related negativity (ERN) amplitude.

Methods: The study comprised three parts: (1) ACDC TMS in 30 healthy participants, (2) ACDC TMS in 30 OCD patients, and (3) a comparative analysis of ACDC TMS effects between the two groups. The study was double-blind and sham-controlled. Participants underwent one session of high-frequency ACDC TMS. During the session, participants completed the Stroop task pre- and post-stimulation with simultaneous EEG recording. Stroop task results and ERN were analyzed using two-way ANOVA and mixed-model ANOVA for EEG amplitudes. Statistics were conducted using R 4.3.0 and BESA and Python software for EEG data.

Results: 58 participants completed the study (28 healthy, 30 OCD). In healthy participants, ACDC TMS didn't show any significant effect. In OCD patients, ACDC TMS led to a significant impact on error rates ($p < .05$); however, active stimulation "worsened" the result. Alongside the increased ERN amplitude was shown, in accordance with the literature. Comparative analysis revealed no significant difference between groups.

Conclusions: ACDC TMS can impact inhibitory control, with a marked effect in patients with OCD. Enhanced ERN and affected error rates suggest that ACDC TMS may modulate neural circuitry underlying inhibitory control in patients with OCD. Further studies with larger sample sizes and modified TMS parameters are warranted to optimize TMS protocols for cognitive research and clinical applications.

Abstrakt

Úvod: Inhibiční kontrola (IC) je jedna z klíčových exekutivních funkcí narušená u pacientů s obsedantně-kompulzivní poruchou (OCD), a její poruchy jsou často spojeny s hyperaktivitou v oblasti předního cingulárního kortexu (ACC). Repetitivní transkraniální magnetická stimulace (rTMS), zejména hluboká TMS (dTMS) zaměřená na ACC, může modulovat inhibiční kontrolu, a tím poskytnout terapeutický potenciál. Tato studie zkoumá vliv TMS s využitím double-cone cívký nad předním cingulem (ACDC TMS) na inhibiční kontrolu u zdravých jedinců a pacientů s OCD.

Cíle: Primárním cílem bylo posoudit vliv ACDC TMS na inhibiční kontrolu u zdravých dobrovolníků a pacientů s OCD pomocí interferenčního scóre ve Stroopově testu. Sekundárním cílem bylo porovnat další behaviorální a elektrofyziologické (EEG) účinky ACDC TMS uvnitř a mezi skupinami, včetně změn v reakčních časech (RT) a počtu chyb, a amplitudy error-related negativity (ERN).

Metodologie: Studie měla tři části: (1) ACDC TMS u 30 zdravých dobrovolníků, (2) ACDC TMS u 30 pacientů s OCD a (3) srovnávací analýza účinků ACDC TMS mezi oběma skupinami. Studie byla dvojité zaslepená a kontrolovaná sham stimulací. Účastníci podstoupili jednu aplikaci vysokofrekvenční ACDC TMS. Před a po stimulaci za současného snímání EEG záznamu absolvovali Stroopův test. Výsledky Stroopova testu a ERN byly následně analyzovány pomocí dvoucestné ANOVA a smíšeného modelu ANOVA pro amplitudy EEG. Statistická analýza byla provedena pomocí softwaru R 4.3.0, BESA a Python pro EEG data.

Výsledky: Celkem 58 účastníků dokončilo studii (28 zdravých, 30 OCD). U zdravých účastníků nebyl po ACDC TMS zaznamenán žádný významný efekt. U pacientů s OCD vedla ACDC TMS k významnému efektu v počtu chyb ($p < .05$); aktivní stimulace však výsledky „zhoršila“. Současně byla prokázána zvýšená amplituda ERN, v souladu s dosavadní literaturou. Srovnávací analýza neodhalila významné rozdíly mezi skupinami.

Závěr: ACDC TMS může ovlivnit inhibiční kontrolu se signifikantním efektem u pacientů s OCD. Zvýšené ERN a ovlivněný počet chyb naznačují, že ACDC TMS může modulovat nervové okruhy inhibiční kontroly u pacientů s OCD. Další studie s většími vzorky a upravenými parametry TMS jsou nutné pro optimalizaci TMS protokolů v kognitivním výzkumu a klinických aplikacích.

List of the main abbreviations used in the text

ACDC - Anterior Cingulate Double Cone (coil/stimulation)

ACC - Anterior Cingulate Cortex

CBT - Cognitive Behavioral Therapy

CANTAB - Cambridge Neuropsychological Test Automated Battery

CalCAP - California Computerized Assessment Package

CGI - Clinical Global Impression

CSTC - Cortico-Striato-Thalamo-Cortical (circuitry)

DLPFC - Dorsolateral Prefrontal Cortex

dTMS - Deep Transcranial Magnetic Stimulation

EEG - Electroencephalography

ERN - Error-Related Negativity

FDA - Food and Drug Administration (US)

HC - Healthy Controls

H-coil - Specific coil types (e.g., H7, H8, HAUT) used in TMS

IC - Inhibitory Control

LF - Low-Frequency

mPFC - Medial Prefrontal Cortex

OCD - Obsessive-Compulsive Disorder

PASAT - Paced Auditory Serial Addition Task

RT - Reaction Time

rTMS - Repetitive Transcranial Magnetic Stimulation

SSAS - Situational Self-Awareness Scale

SSD - State Scale of Dissociation

TCA - Tricyclic Antidepressant

TES-Antal - Adverse Effects Questionnaire (specific to the study)

Y-BOCS - Yale-Brown Obsessive Compulsive Scale

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1 Introduction

1.1 Inhibitory control

Cognition refers to mental processes and contains “all forms of knowing and awareness, such as conceiving, remembering, judging, imagining, and problem-solving” (VandenBos, 2007). A big part of cognition is dedicated to executive functions (or executive functions and cognitive control), which present a group of mental processes necessary for controlling our behavior. This is a part of our cognition that helps us to select and support behavior to achieve goals. This group includes several elements, such as attentional control, working memory, cognitive flexibility, and inhibitory control (see Fig. 1). It was the function that became the object of study for researchers in the last few years, as it becomes clear its significant role in the physiology of many neuropsychiatric disorders and even our "healthy" daily behavior.

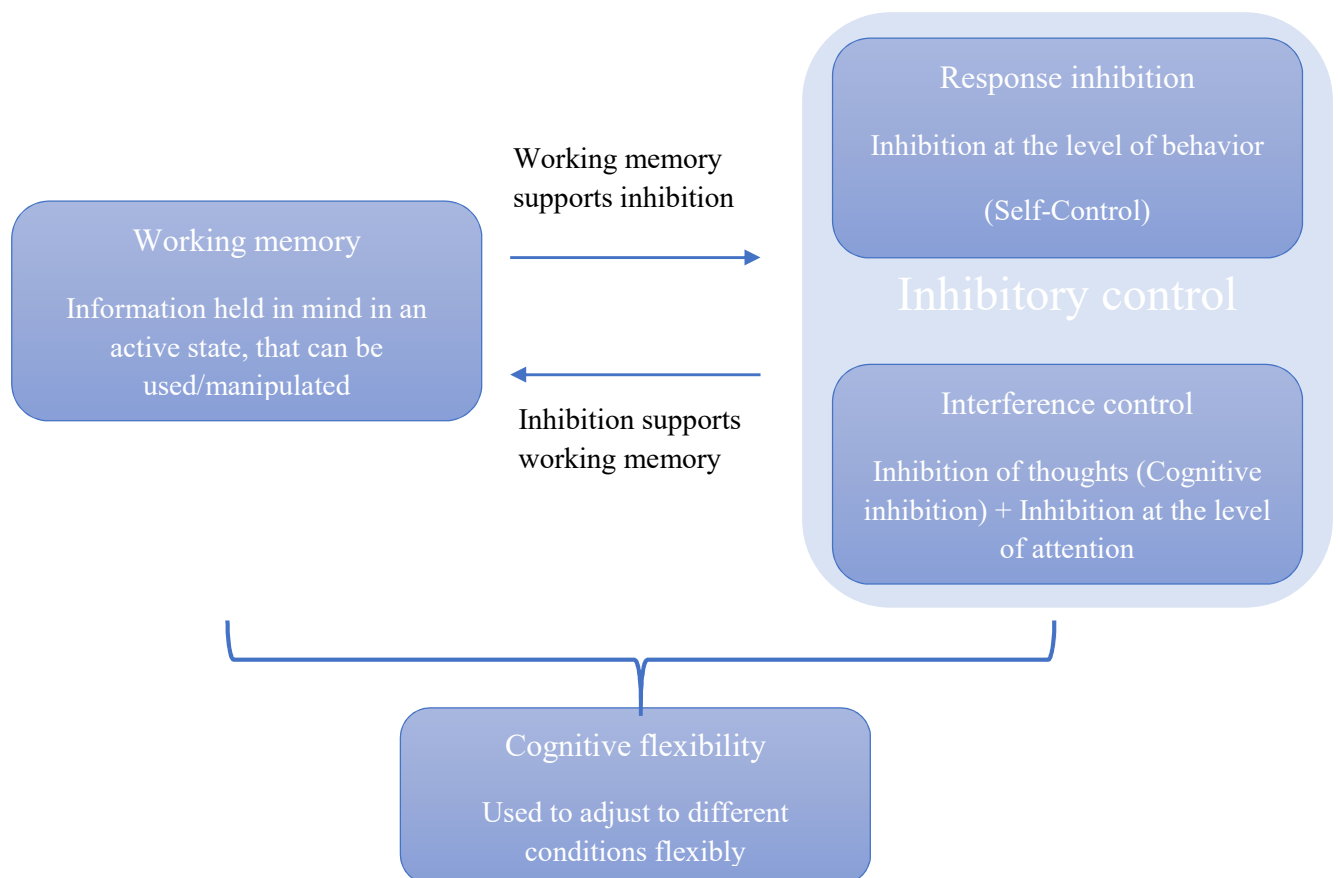


Figure 1. Relationship between core executive functions (adapted from (Diamond, 2013)). Basic abilities like working memory (WM) and inhibition depend on one another. It is necessary to prevent distractions from entering working memory (i.e., to avoid attention from

being drawn to them). The current aim or task must also be maintained firmly in WM to inhibit irrelevant information. The ability to adapt quickly to various contextual demands and conditions is known as cognitive flexibility, which depends on working memory and inhibition (Diamond, 2013).

The inhibitory control is tightly connected to such cognitive processes as decision-making and response selection. Inhibitory control plays a crucial role in both processes. Response selection is choosing a specific action or behavior from possible alternatives. It can involve selecting a motor response, a verbal response, or a combination of both in various contexts. For example, in a game, response selection could include choosing whether to move a character left or right in response to a specific stimulus. Inhibitory control here helps prevent the execution of inappropriate or premature responses. It allows individuals to withhold or modify their actions based on the context and goals, ensuring that the chosen answer is the most appropriate.

Decision-making is choosing a course of action or a solution from several alternatives. It involves evaluating available options, considering their potential outcomes, and selecting the most appropriate one based on one's goals or preferences. In everyday life, for example, decision-making could involve choosing between job offers or deciding what to have for dinner. Inhibitory control, in this case, is essential for suppressing impulsive decisions and actions that may not align with long-term goals or rational thinking. It allows individuals to take the time to consider various options, weigh the consequences, and make decisions that are more reflective and aligned with their objectives.

In summary, inhibitory control is like the "brake system" in the cognitive processes of response selection and decision-making, helping individuals regulate their behaviors and make choices that align with their goals and values.

Without inhibitory control, we would be at the mercy of impulses or the environment. Inhibitory control allows us to choose and regulate how we react and behave rather than being hostages of habit. Inhibitory control helps us not to take another piece of birthday cake, not to drink another shot at the party, or not to spend all night gaming online. Inhibitory control, unfortunately, can't help patients with obsessive-compulsive disorder to stop doing their compulsive rituals. Or support the person with addiction not to take another line or drink even

after a long time of soberness. Inhibitory control also can't assist the child with attention deficit hyperactivity disorder in finally finishing the math homework and not following those cars outside. Inhibitory control doesn't make our life easier. It's not entirely "automatic," and a big part of this is self-control, which involves control over one's behavior and emotions in the service of controlling one's behavior. Self-control is about resisting temptations and not acting impulsively. But for some of us, a "bad job" of self- (and inhibitory in the complex) control means a few more kilos of weight and one more sleepless night. In contrast, for others, it means disability and severe disorder, which complicates life and sometimes makes it impossible to withstand.

Before discussing inhibitory control in detail, we should notice two essential processes that help us produce inhibitory control in everyday life: error processing and conflict monitoring. Both these processes are also tightly connected to decision-making (see above). Error processing and conflict monitoring help identify when something is amiss or conflicting signals are present in decision-making.

Error processing is a cognitive mechanism that detects and responds to errors or discrepancies between an intended action or response and the actual outcome. It plays a crucial role in adaptive learning and performance improvement. If you realize that you pressed the wrong key on your keyboard while typing, your brain detects this error, and you may correct the mistake in the next keystroke. Inhibitory control is closely tied to error processing as it helps individuals regulate their responses and prevent errors. It involves the ability to inhibit impulsive or incorrect answers.

Conflict monitoring is a cognitive process that involves detecting conflicting information or competing response options. It is essential for managing and resolving mental conflicts, ensuring that the most appropriate response is selected. In a Stroop task, where the color of a word is different from the word itself (e.g., the term "red" written in blue ink), conflict monitoring is needed to overcome the automatic tendency to read the word and instead focus on the color. Inhibitory control is also connected to conflict monitoring. The ability to inhibit or resolve conflicting responses is critical to inhibitory control. When faced with competing options, inhibitory control allows individuals to select the most appropriate response while suppressing irrelevant or conflicting alternatives.

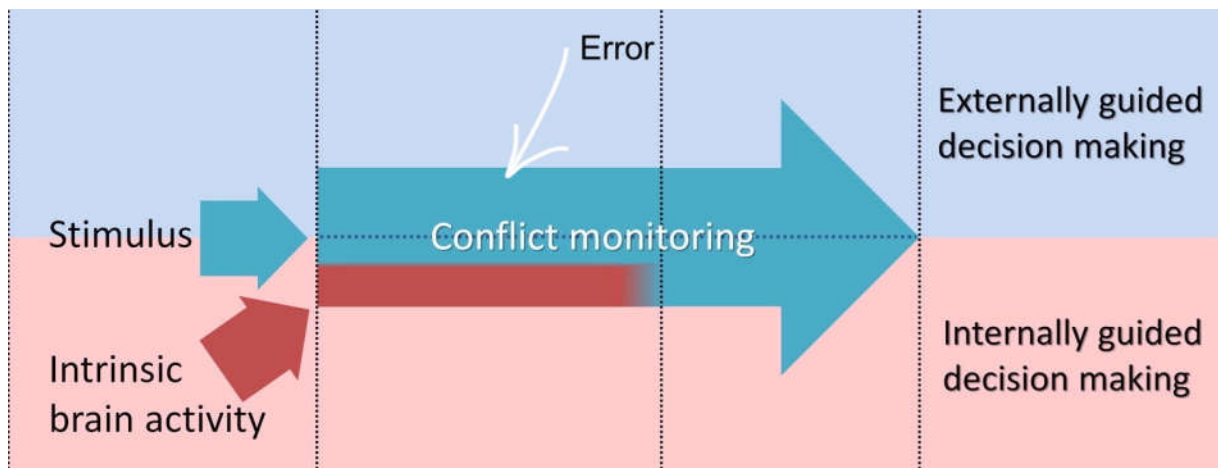


Figure 2 shows the decision-making process (the response selection process is similar). Under intrinsic brain activity, inhibitory control can be imagined. The red line inside the conflict monitoring is error processing. The image is adapted with changes from (Nakao et al., 2013).

1.1.1 Types of inhibitory control

Response inhibition (also known as "behavioral inhibition," "motor inhibition," "prepotent response inhibition," and "(attention) restraint") and attentional inhibition (also known as "interference control," "interference suppression," "resistance to (distracter) interference," and "attention constraint") are two critical cognitive processes that have been studied under the umbrella of inhibitory control (Friedman and Miyake, 2004; Nigg, 2000).

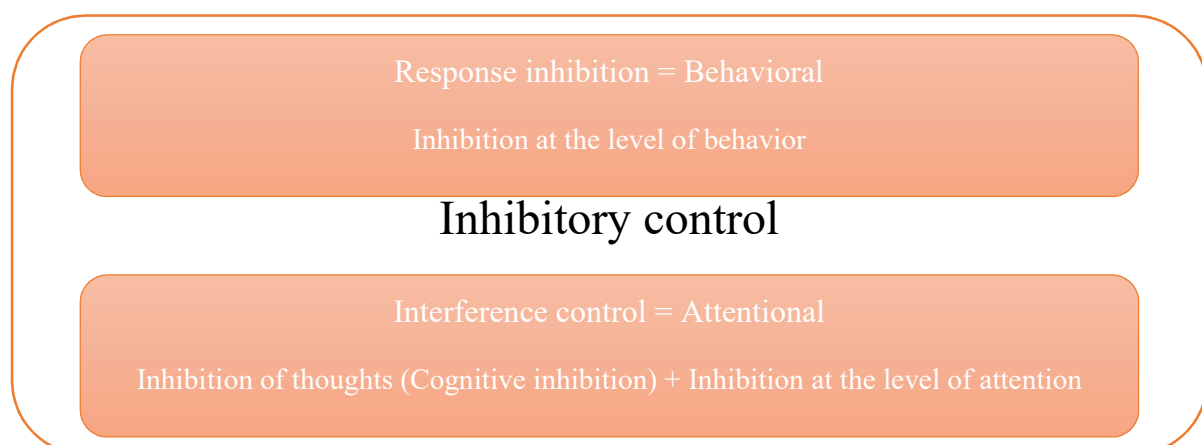


Figure 3. Inhibitory control and its parts: response inhibition = behavioral and interference control = attentional.

Response Inhibition is the process of restraining a prepotent motor response. It is typically measured by non-selective stopping tasks like the stop signal, go/no-go, and antisaccade tasks, which call for participants to momentarily suppress a motor response in response to a conditional stimulus or cue (Aron et al., 2014; Chambers et al., 2009; Verbruggen and Logan, 2008) presentation.

Attentional inhibition is the capacity to resist interference from stimuli in the external environment. Visual matching tasks that require participants to determine whether the target and comparison stimuli are the same or different while ignoring task-irrelevant distracters have been used to study attentional inhibition (Friedman and Miyake, 2004; Nigg, 2017).

Response Inhibition and Attentional Inhibition are frequently assessed using Stimulus-Response Compatibility (SRC) procedures such as the Stroop, Eriksen Flanker (Flanker), and Simon tasks (Eriksen and Eriksen, 1974; Simon, 1969; Stroop, 1935). These forced-choice reaction time tasks demand that participants selectively pay attention to and respond to target stimuli while disregarding distracting stimuli irrelevant to the goal. SRC tasks typically have three main conditions: (1) control, (2) congruent (or compatible), and (3) incongruent (or incompatible) (Eriksen, 1995; Kornblum et al., 1990; Lu and Proctor, 1995; MacLeod, 1991).

Control trials are defined by presenting task-relevant stimuli, or stimulus dimensions, without task-irrelevant stimuli and response features. In contrast, incongruent and congruent trials have response possibilities and task-irrelevant stimuli. Task-relevant and task-irrelevant stimuli and response attributes match on congruent trials, enabling automated stimulus identification and response creation (Kornblum, 1994; Kornblum and Lee, 1995). On the other hand, the task-relevant and task-irrelevant stimuli and response inclinations are mismatched in incongruent trials, competing for further processing. According to several studies (Eriksen, 1995; Kornblum et al., 1990; Lu and Proctor, 1995; MacLeod, 1991), mean reaction times on incongruent trials are often longer than on congruent or control trials.

The 'interference effect,' or difference in mean reaction time, reflects the extra time needed to resolve the conflict between competing sensory representations and response tendencies (Fan et al., 2002; Rueda et al., 2004). Studies have employed variations of the Flanker task to evaluate Attentional Inhibition and the interference effect gained from the performance of the Stroop and Simon tasks to test Response Inhibition (Forstmann et al., 2008; Friedman and Miyake, 2004; Kane and Engle, 2003).

1.2 Tasks to measure inhibitory control

To better understand how inhibitory control functions and the underlying brain network involved, various tasks have been used to study it. These have been used behaviorally, in conjunction with neuroimaging and neurostimulation techniques, in clinical populations and normal subjects. The Stroop task (MacLeod, 1991) is one task that has been used in multiple studies combined with both transcranial magnetic stimulation and direct current stimulation.

1.2.1 Stroop task

Many studies use the Stroop task for the “quantification” of inhibitory control, one of the most well-known paradigms in cognitive psychology (Hommel, 2011; Lu and Proctor, 1995). During the test, color words are presented in various ink colors, with the participants’ goal being to report the ink color (ignoring the word color) (see Fig. 4). Compared to incongruent trials, congruent trials elicit faster reaction times and fewer errors. Most popular theories on the Stroop effect (the difference between congruent and incongruent trials) assume that the meaning of the words is automatically processed, which interacts with responding to the incongruent ink color, resulting in slower reaction times and more errors.



Figure 4. Different stimulus conditions in the Stroop task: congruent and incongruent.

The Stroop task is frequently used to assess the capacity to inhibit cognitive interference. However, it has also been used to determine cognitive abilities like working memory, attention, processing speed, and cognitive flexibility (Jensen and Rohwer, 1966; Kane

and Engle, 2003). Therefore, assessing several cognitive functions using the Stroop task might be feasible.

Different Stroop task measurements can be used to access different cognitive functions (such as reaction time for the processing speed). In its turn, Stroop interference is commonly interpreted as a measure of inhibitory control. It is quantified as the difference in latency or accuracy between (a) the incongruent and neutral or (b) the incongruent and congruent conditions (MacLeod, 1991). In our studies, we use the difference between answer latency in incongruent and congruent stimuli as one of the measurements of inhibitory control.

1.2.2 Other tasks

Several other psychological measures can be used to access inhibitory control, such as the Stop signal task (Lipszyc and Schachar, 2010), Simon task (Hommel, 2011), Flanker task (Eriksen and Eriksen, 1974; Mullane et al., 2009), antisaccade tasks (Luna, 2019; Munoz and Everling, 2004), delay-of-gratification tasks (Kochanska et al., 2001; Sethi et al., 2000), and go/no-go tasks (Cragg and Nation, 2008).

1.3 Neural mechanisms of inhibitory control

Inhibitory control involves several brain structures that suppress or inhibit inappropriate or prepotent responses. Some of the central brain regions involved in inhibitory control are (also see Fig. 5):

- 1) The prefrontal cortex, particularly the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC) (Koechlin and Franck, 2003; MacDonald et al., 2000). The DLPFC is involved in the cognitive aspects of inhibitory control, such as working memory, attention, and the ability to stop an ongoing action. The VLPFC is more associated with emotional and social aspects of inhibitory control and regulates emotional responses and impulse control.

- 2) The ACC is involved in detecting and signaling the presence of conflicts or errors (Badre and Wagner, 2004). It helps monitor for discrepancies and conflicts in information, which is crucial in recognizing the need for inhibitory control. Deficiencies in these functions represent a common element across psychiatric disorders (Downar et al., 2016). During conflict monitoring and error processing, the medial prefrontal cortex (mPFC), which covers the ACC,

generates theta oscillatory activity called Frontal Midline Theta (FMT) (Cavanagh and Shackman, 2015; Cohen et al., 2008).

3) The basal ganglia, including structures like the caudate nucleus and the putamen, play a role in motor control and action selection (Wei and Wang, 2016). They are involved in inhibitory control by helping suppress automatic or habitual responses in favor of more controlled and goal-directed actions.

4) One of the fundamental components of behavioral flexibility and control is the suppression of premature or inappropriate motor responses, and the right inferior frontal gyrus (rIFG) is considered an essential center for this process (Aron et al., 2014; Leung and Cai, 2007). Research on patients with lesions has demonstrated that damage to the right IFG is linked to issues with inhibitory control (Aron et al., 2003).

5) The orbitofrontal cortex (OFC) involves higher-order cognitive functions, including strategic planning and decision-making (Fettes et al., 2017). It contributes to inhibitory control by evaluating response options and selecting the most appropriate one.

These brain structures do not work in isolation but form a network allowing effective inhibitory control.

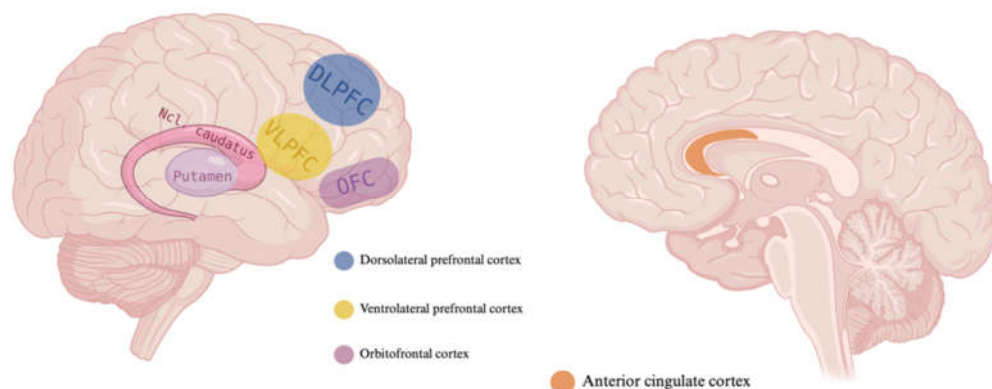


Figure 5. The main brain areas involved in inhibitory control. The caudate nucleus and putamen are parts of the basal ganglia. The figure does not show the inferior frontal gyrus since VLPFC is on it. ACC anterior cingulate cortex, DLPFC dorsolateral prefrontal cortex, OFC orbitofrontal cortex, VLPFC ventrolateral prefrontal cortex.

Numerous methods have examined the brain areas connected to inhibitory control. Electrophysiological and neuroimaging research indicates that other regions can also be involved in the inhibitory control circuit.

According to neuroimaging studies, the middle frontal gyrus (MFG) and the right parietal lobe may play a role in cognitive control (Rubia et al., 2003). Numerous EEG studies have shown pre-supplementary motor area (pre-SMA) activation before starting a planned action (Brinkman and Porter, 1979; Swann et al., 2009). Studies of populations that exhibit high levels of instrumental violence have provided information about other possible related brain areas—for example, Blair et al. (Blair, 2003) discovered proof of the orbitofrontal cortex and amygdala's involvement. As a result, information gathered using diverse techniques points to many brain regions implicated in inhibitory control.

It's also crucial to remember that inhibition is related to behavior regulation (Chambers et al., 2007). Therefore, it is necessary to discuss the brain regions that may be connected to behavioral regulation and the nature of their involvement in inhibitory control before further addressing them.

Studies using brain stimulation provide the opportunity to look at implicated areas required for efficient inhibitory control and provide insight into their mechanistic contributions.

1.4 EEG and inhibitory control in a healthy brain

Several EEG measurements were used to describe it in neurophysiological studies concerning inhibitory control. Mostly the ERPs such as N2, P3, and ERN were used. A detailed analysis of these signals can be found below.

1.4.1 N2

The term "event-related potentials" (ERP) refers to voltage variations that occur directly in connection with the brain's reaction to stimuli. They are measured by recording EEG during specific sensory, cognitive, or motor events (Coles et al., 2005). They are often used to study cognitive interference in addition to brain imaging methods. Negative-going potentials with a fronto-medial scalp distribution, which are increased in interference conditions requiring higher cognitive control, are prominent ERP components in interference tasks. The "conflict-related N2" is a negative difference potential at fronto-central electrode sites that appears 250–350 ms after stimulus onset (see Fig. 8). It has consistently been seen in NoGo trials

(Nieuwenhuis et al., 2003), incongruent trials in the Eriksen flanker task (Heil et al., 2000; Kopp et al., 1996), and the Simon task (Leuthold, 2004).

Since overlapping movement-related potentials are complicated when comparing Go and NoGo ERPs, it has been challenging to interpret N2 effects in the NoGo paradigms (Bruin and Wijers, 2002). Because conflict-related N2 appears in such a wide range of interference conditions, whether this component reflects a single process or a combination of different processes occurring in the MFC and surrounding regions is emphasized (Falkenstein, 2006; Ullsperger and von Cramon, 2001).

1.4.2 P3

The frontocentral P300, or P3a, is one event-related potential (ERP) that has frequently been mentioned as a potential indicator of inhibition (Enriquez-Geppert et al., 2010; Huster et al., 2013; Wessel and Aron, 2015) (see Fig. 6). When participants are given instructions not to respond to a stimulus in a situation where responding is the prepotent inclination, this positive potential, hereafter referred to as P3, is consistently observed. The P3 ERP is driven by increased frontocentral activity in the low theta and delta frequency range with a reasonably high time- or phase-locking (Huster et al., 2014; Raud and Huster, 2017).

Under the circumstances theoretically connected to a high inhibitory load, the P3 is persistently elevated. Increased P3 amplitudes are related to reduced stop-signal probabilities, cue-induced response preparation before stop-signal presentation, or faster average reaction times (Huster et al., 2013). Additionally, lower P3 amplitudes are frequently linked to potential deficits in inhibitory control, as is the case with conditions like ADHD (Bekker et al., 2005; Lansbergen et al., 2007).

Additionally, it has been demonstrated that P3 peak latencies in failure stop trials are longer than in successful stop trials (Kok et al., 2004; Ramautar et al., 2006, 2004). Because the timing of the P3 beginning matches with the SSRT, Wessel et al. (Wessel and Aron, 2015) hypothesized that it may be a more accurate indicator of response inhibition than the P3's peak amplitude or peak latency. Indeed, a significant positive connection was discovered, with subjects with longer SSRTs showing later P3 onsets.

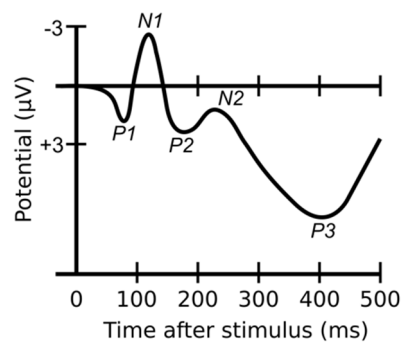


Figure 6. A waveform showing several ERP components, including the N2 and P3.

1.4.3 Problem with N2 and P3

However, according to the most recent data, neither the N2 nor the P3 amplitudes exhibit a reliable correlation with the latency of the stop process during stop-signal paradigm (stop-signal reaction time; SSRT). This is unexpected because a previous EEG literature review indicated higher inhibitory loads are associated with larger P3s (Huster et al., 2013). This finding is typically replicated when contrasting healthy control groups with patient populations who may have impaired inhibitory control, with the latter showing attenuated P3 amplitudes.

On the other hand, latency measures consistently demonstrate a connection with the SSRT with generally moderate effect sizes. The P3 peak and onset latencies are positively linked with SSRTs, so shorter SSRTs accompany earlier P3s.

This effect would typically be consistent with the idea that the P3's latency may indicate an inhibitor's control skills (Wessel and Aron, 2015). Since the N2 peak latency exhibits the same connection, this impact is not unique to the P3. However, it's still being determined whether this holds for the N2 onset as well (just one study looked at this association and came up with a null result).

Overall, this raises the possibility that neither N2 nor P3 latencies are precise markers of the temporal dynamics of inhibition proper, but rather that these associations may be influenced by the timing of earlier processing stages (such as sensory processing) or by general processing capacity constraints for higher-order cognitive processing. Examples of more general behaviorally adaptable patterns that may contribute to these correlations include the weighing of going and halting or general behavioral adaptations resulting from performance-tracking processes (Huster et al., 2020).

1.4.4 ERN

The error-related negativity (ERN; see for an overview Falkenstein et al. (2000)) is another fronto-centrally distributed negative ERP component produced in the MFC and is consistently seen in the error commission (Falkenstein et al., 2000). The response-locked error processing is believed to be reflected by the ERN, which appears 60–100 ms after an incorrect response (Gehring et al., 1993) (see Fig. 7).

According to one theory, the ERN is just another instance of conflict monitoring because the conflict-related N2 and ERN reflect the same process (Burle et al., 2005; Masaki et al., 2007; Matsushashi et al., 2021; Yeung et al., 2004).

According to a review by Folstein and van Petten, fronto-medial distributed ERP negativities should be split into two subcomponents (Folstein and Van Petten, 2008). When the triggering stimuli are attended, one component detects novelty or mismatch from a perceptual template. In contrast, a second component is connected to cognitive control and includes response inhibition, response conflict, and error monitoring.

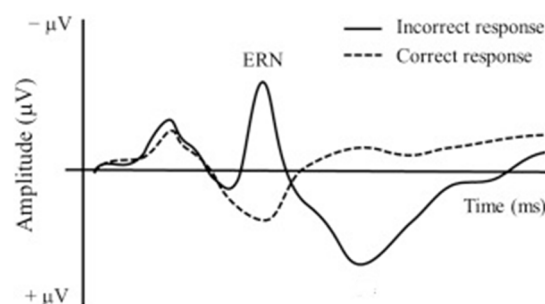


Figure 7. Illustration of error-related negativity (ERN) (adapted from (Chang, 2016)).

1.5 Inhibitory control in patients with obsessive-compulsive disorder

Impaired cognitive control may lead to adverse personal and social outcomes or even to psychiatric disturbances, such as drug and alcohol abuse, gambling, eating disorders, attention deficit hyperactivity disorder (ADHD), or obsessive-compulsive disorder (OCD). In the thesis, we focus on the features of inhibitory control in patients with OCD.

1.5.1 Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is a mental disorder that can be described as a group of symptoms that include intrusive thoughts, rituals, preoccupations, and compulsions (Shavitt et al., 2014). With a lifetime prevalence in the general population estimated at 2 to 3

percent, OCD is now the fourth most prevalent psychiatric diagnosis, behind major depressive disorder, substance use disorders, and phobias (Ruscio et al., 2010). According to some experts, the illness may be present in as many as 10% of outpatients in psychiatric clinics. These rates have been supported by epidemiological research conducted across cultural boundaries in Europe, Asia, and Africa.

The recurrent obsessions or compulsions bring about severe distress to the patients. They are time-consuming and considerably obstruct the person's regular schedule, ability to carry out daily tasks, everyday social interactions, or relationships. A persistent and bothersome thought, emotion, idea, or sensation is referred to as an obsession. A compulsion is a behavior instead of an obsession, a mental process. A compulsion is defined explicitly as a conscious, regular, reoccurring behavior, such as counting, checking, or avoiding. The OCD patient recognizes the preoccupation as being unreasonable, and both the obsession and the compulsion are perceived as ego-dystonic (unwanted behavior) (Freedman et al., 1975).

Neuroimaging in individuals with OCD has revealed converging findings showing abnormal function in the neurocircuitry linking the orbitofrontal cortex, caudate, and thalamus (see Fig. 8 and 9). Various functional brain-imaging studies - for example, positron emission tomography (PET) - have demonstrated increased activity (e.g., metabolism and blood flow) in the frontal lobes, the basal ganglia (particularly the caudate), and the cingulum of patients with OCD. The role of these regions in the pathology of OCD seems to be more closely linked to cortico-striato-thalamo-cortical (CSTC) (see Fig. 8) circuits (which for now believed to play a central role in the pathophysiology of OCD) than to the amygdala pathways, which are currently the subject of many studies on another anxiety disorders. According to reports, behavioral and pharmaceutical therapies can correct these problems (Bolton et al., 2001). The findings of functional and structural brain imaging studies are consistent with the result that OCD can occasionally be treated with neurological techniques affecting the cingulum.

The anterior cingulate cortex, which plays an essential role in performance monitoring (Ridderinkhof et al., 2004), has been consistently reported by neuroimaging studies as overactivated in patients with OCD along with fronto-medial and striatal brain regions (Aouizerate et al., 2004).

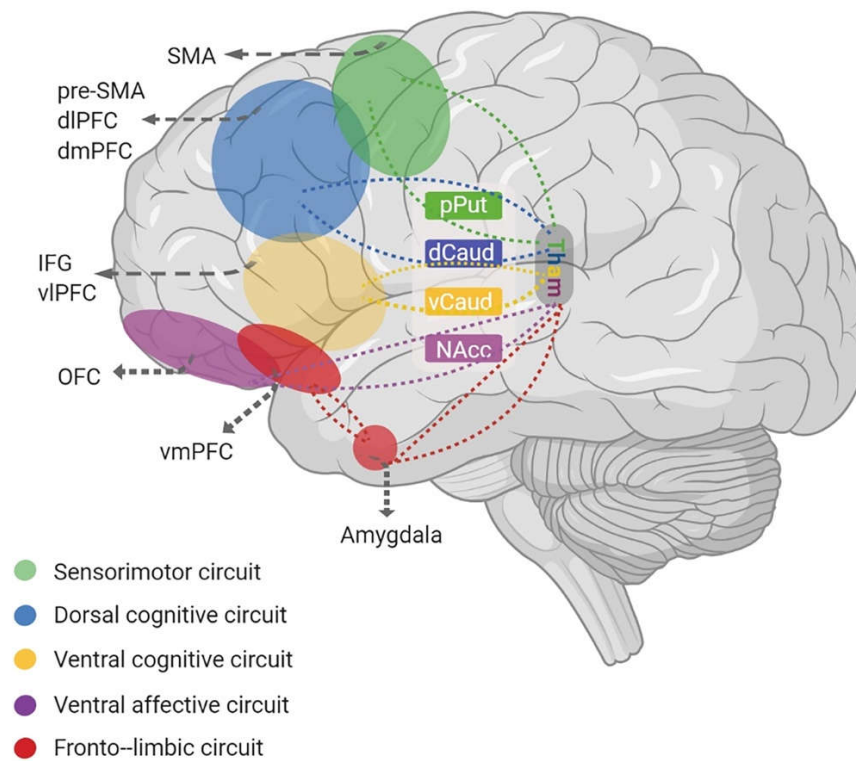


Figure 8. OCD is associated with five circuits, according to van den Heuvel et al. (van den Heuvel et al., 2016). The amygdala and ventromedial prefrontal cortex (VMPFC) are parts of the fronto-limbic circuit (red) that elicit emotional reactions like anxiety and fear. The supplementary motor area (SMA), putamen, and thalamus are parts of the sensorimotor circuit (green) responsible for producing and regulating motor behavior and integrating sensory data. The inferior frontal gyrus (IFG), ventrolateral prefrontal cortex (VLPFC), ventral caudate, and thalamus comprise the ventral cognitive circuit (yellow), which is involved in self-regulatory behavioral control. The nucleus accumbens (NAcc), thalamus, and orbitofrontal cortex comprise the ventral affective circuit (purple) responsible for processing and reacting to rewards. The dorsolateral prefrontal cortex (DLPFC), dorsomedial prefrontal cortex (DMPFC), dorsal caudate, and thalamus form the dorsal cognitive circuit (blue), which is implicated in executive functions like working memory and planning as well as emotion regulation—figure from (Shephard et al., 2021).

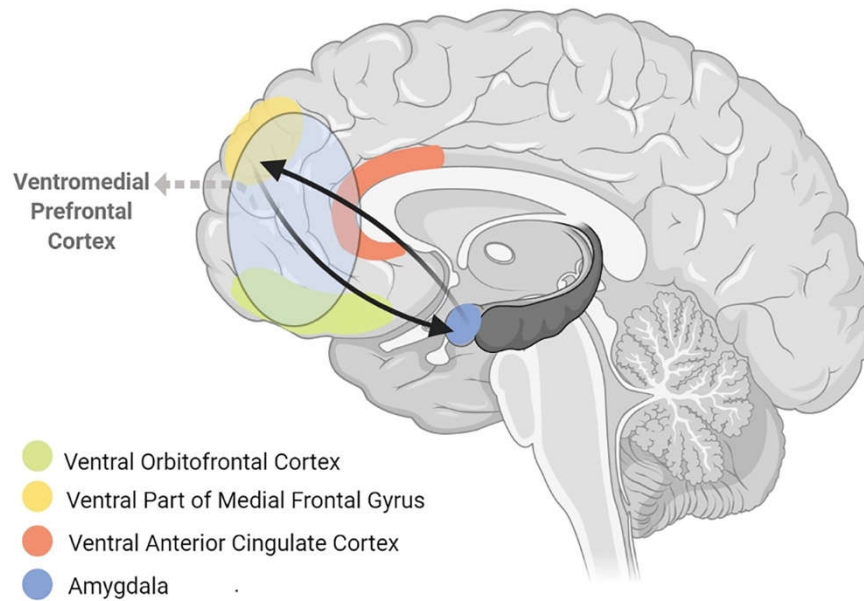


Figure 9. The ventromedial prefrontal cortex (VMPFC, which consists of the ventral orbitofrontal cortex, ventral anterior cingulate cortex, and the ventral portion of the medial frontal gyrus) and the amygdala are components of the fronto-limbic circuit. The dorsolateral prefrontal cortex (DLPFC) from the dorsal cognitive circuit and other circuit regions involved in top-down behavioral control is connected to the fronto-limbic circuit. By recruiting these regions, the fronto-limbic circuit can dampen fronto-limbic activity and thus facilitate emotional regulation—figure from (Shephard et al., 2021).

1.5.2 Inhibitory control in OCD brain

On inhibitory control tests, patients with OCD frequently exhibit abnormal brain activation during incorrect and correct responses (Norman et al., 2016; Stern et al., 2011). The go/no-go and stop tasks measure the ability to inhibit responses to no-go stimuli among prepotent go stimuli and to withdraw already triggered motor responses in response to stop signals. Additionally, interference inhibition tasks like the antisaccade, flanker, Simon, Stroop, and multisource interference tasks that call for participants to ignore interfering stimulus features and override prepotent responses to process relevant information are relevant tasks (Carlisi et al., 2017; Norman et al., 2016; van Velzen et al., 2014).

Poor control of obsessions and compulsions in OCD may be partially attributed to dysfunctional error processing and inhibitory control brain networks, as many patients are aware of their symptoms but engage in obsessive behavior (Chamberlain et al., 2005; Norman et al., 2016; Schlösser et al., 2010; van Velzen et al., 2014).

The error-related negativity, as shown by a higher amplitude of a midline frontal electrical potential, is undoubtedly the most reliable neurocognitive biomarker of OCD (Endrass and Ullsperger, 2014; Gillan et al., 2017; Mathews et al., 2012). In the latest fMRI meta-analysis, a longer inhibitory control reaction time and more inhibitory control errors were observed in OCD patients compared to healthy controls. Patients' brains displayed hyperactivity during error processing in the bilateral dorsal ACC, SMA, and pre-SMA, as well as the right anterior insula/frontal operculum and anterior lateral prefrontal cortex. Hypoactivity during inhibitory control was found in the rostral and ventral ACC, bilateral thalamus/caudate, the right anterior insula/frontal operculum, supramarginal cortex, and medial orbitofrontal cortex (Norman et al., 2019).

1.6 EEG and inhibitory control in an OCD brain

Many electrophysiological studies have found neurobiological alterations that seem connected to OCD-related behavioral and psychological impairments.

1.6.1 P3 and N2

P3 and N2 are other ERPs that are frequently connected to OCD. When performing tasks like the Go/NoGo (Malloy et al., 1989), auditory oddball (Sanz et al., 2001; Yamamuro et al., 2015), and selective attention (Towey et al., 1994) tasks, patients with OCD displayed lower P3 amplitudes than healthy controls. Additionally, it was discovered that OCD patients' reduced P3 amplitude was related to an incorrect allocation of cognitive resources to task-relevant stimuli (Towey et al., 1994). Instead, an increase in P3b (Gohle et al., 2008; Ischebeck et al., 2011; Mavrogiorgou et al., 2002), as well as a general rise in P3 (Andreou et al., 2013) found in several research, showed over-focused attention and hyperarousal in OCD patients.

In research using the auditory oddball (Miyata et al., 1998; Towey et al., 1993, 1990), Flanker (Riesel et al., 2017), and selective attention (Towey et al., 1994) tasks, the N2 amplitude was considerably higher in people with OCD compared to healthy controls. According to Näätänen et al. (Näätänen et al., 1978), this may be accounted for by OCD patients' hyper-arousal and excessively focused attention. However, research using the Go/NoGo (Kim et al., 2007) and auditory oddball tasks revealed a reduced N2 amplitude in other studies (Morault et al., 1998); according to a survey by Upton et al. (Upton et al., 2010) and analyses of conflict monitoring (Cavanagh et al., 2012), N2 is thought to represent a decision process that governs behavioral reactions. Because of this, the reduced N2 seen in

OCD patients may be a result of poorly managed stimulus information processing, which affects both behavioral responses and inhibition. Furthermore, many studies found that OCD patients had shorter P3 and N2 latencies when compared to healthy controls (Miyata et al., 1998; Morault et al., 1998; Towey et al., 1990). This might indicate cortical hyperarousal in OCD, speeding up cognitive processing and shortening P3 and N2 latencies (Beech et al., 1983).

1.6.2 ERN

Abnormal ERPs can be found in many psychiatric disorders (Neshige et al., 1988; Pritchard, 1986; Spronk et al., 2008), including OCD.

A significant increase in ERN amplitude is consistently observed in OCD patients, suggesting excessive action monitoring during cognitive tasks. Substantial evidence supports the idea that ERN could be even a viable endophenotype for OCD.

The continuous ERN amplification in OCD patients may be due to hyperactive performance monitoring since ERN represents action monitoring processes (Tamnes et al., 2013). Interestingly, in most studies, anomalies associated with ERN were seen without any apparent behavioral changes in error rates or reaction times (Endrass et al., 2008; Nawani et al., 2018; Xiao et al., 2011). Numerous studies indicated that OCD patients had larger ERN amplitudes than healthy controls. These studies used the Stroop, Go/NoGo, and Eriksen Flanker (Eriksen and Eriksen, 1974) tasks. An early study using ERN on OCD patients discovered that their ERN amplitude and duration were increased after they finished a modified Stroop test (Gehring et al., 2000).

Results from a study by Grützmann et al. (Grützmann et al., 2016), using simultaneous EEG and fMRI, showed increased ERN in OCD to be more evident in the amygdala and subgenual anterior cingulate cortex, indicating a more robust affective response towards errors in OCD patients.

1.7 Repetitive transcranial magnetic stimulation (rTMS) and deep transcranial magnetic stimulation (dTMS)

Research using non-invasive brain stimulation (NIBS) techniques (Polanía et al., 2018) has significantly changed our neuroscience knowledge. Repetitive transcranial magnetic

stimulation (rTMS) is one of NIBS's most widely used instruments. rTMS is based on principles of electromagnetism and uses alternating magnetic fields to induce electric currents in the cortical tissue (Burt et al., 2002). It is affected by its non-invasiveness and safety for the research and treatment (Anand and Hotson, 2002). Repetitive TMS has been used to investigate almost all areas of cognitive neuroscience (Guse et al., 2010; Luber and Lisanby, 2014), and of course, it was used to study and influence inhibitory control.

1.7.1 TMS parameters

The effectiveness of rTMS in enhancing inhibitory control may depend on the stimulation protocol and parameters used, such as the frequency of stimulation (e.g., high-frequency or low-frequency rTMS), duration of stimulation session (Simonetta-Moreau, 2014), or targeted area for stimulation.

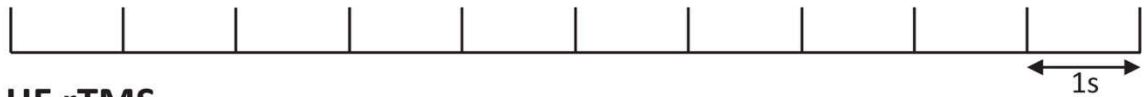
1.7.1.1 Frequency of stimulation

High-frequency stimulation (> 5 Hz) causes excitatory effects in the brain, while low-frequency stimulation (1 Hz) has inhibitory effects.

New rTMS protocols have been developed in addition to basic ones. Theta burst stimulation (TBS) is the most popular. It has been shown to promote synaptic plasticity in animal experiments. The theta rhythm, which naturally occurs in the brain's hippocampus, is the basis for the TBS pattern. High-frequency stimulation bursts compose TBS (see Fig. 10). The effects of various TBS patterns on motor cortex excitability vary. Motor cortex excitability is increased by an intermittent TBS (iTBS) protocol, in which TBS is applied for two seconds and then repeated every ten seconds. The motor-evoked potential is consistently lowered by a continuous TBS (cTBS) protocol, in which TBS is repeated for 40 s without a break.

Only one study with cognitive inhibition measures reported significant improvement in the Stroop task following iTBS of the left DLPFC (Viejo-Sobera et al., 2017). More studies using cTBS showed significant attenuating effects on cognitive functions, including inhibition (Lowe et al., 2018).

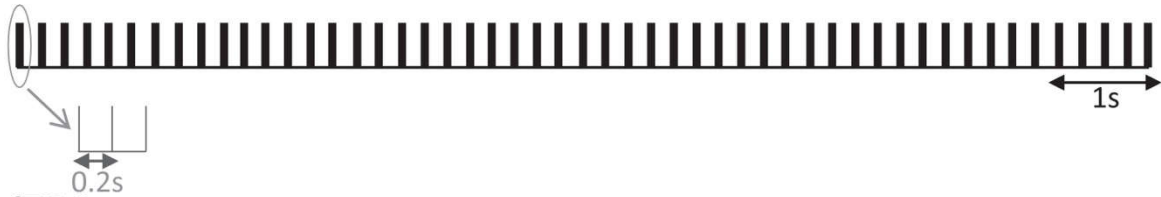
LF rTMS



HF rTMS



cTBS



iTBS

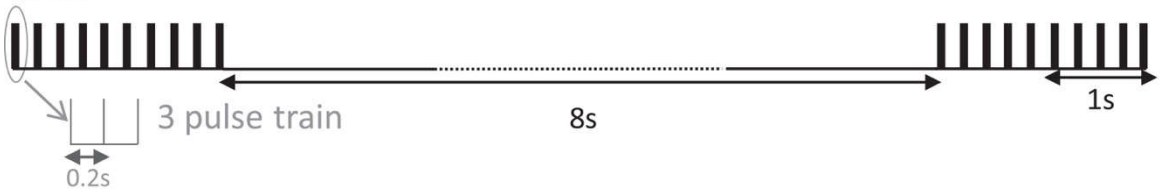


Figure 10. Basic rTMS protocols are identical stimuli spaced by an equal inter-stimulus interval. Effects depend on stimulation frequency: LF rTMS < 1 Hz depresses excitability in the motor cortex, whereas HF rTMS > 5 Hz increases it. TBS involves bursts of high-frequency stimulation (3 pulses at 50 Hz) repeated with an interval of 200 ms (5 Hz). In an intermittent TBS (iTBS) protocol, bursts are delivered for 2 s, then repeated every 10 s (2 s of TBS followed by a pause of 8 s). In a continuous TBS protocol (cTBS), bursts are repeated for 40 s without any pause (Klomjai et al., 2015).

1.7.1.2 Duration of stimulation session

The aftereffects' duration appears to change directly to the stimulation's duration. More prolonged stimulation results in after-effects that last longer. These after-effects are believed to result from rTMS impacting the strength of glutamatergic synapses through the actions of the NMDA receptor, AMPA receptor, and calcium channel (Hallett, 2007; Huang et al., 2007; Nitsche et al., 2012; Vlachos et al., 2012). Additional mechanisms, such as nonlinear time-dependent actions on inhibitory GABAergic neurons, may mediate these effects. Changes in brain-derived neurotrophic factor (BDNF) and even neurogenesis are examples of non-synaptic mechanisms underlying the after-effects of rTMS (Ueyama et al., 2011).

1.7.1.3 Targeted area

Different stimulation areas are used in rTMS cognitive research.

Since the DLPFC is associated with cognitive control processes and plays a role in inhibition, it is one area commonly targeted to enhance inhibitory control. Studies with left DLPFC rTMS utilizing the Go/No Go paradigm or Stroop task with healthy participants didn't significantly affect the inhibitory control (Huang et al., 2004; Vanderhasselt et al., 2006; Wagner et al., 2006). On the other hand, some studies with similar methodology could detect improvements, mainly in depressive patients (Hausmann et al., 2004; Martis et al., 2003; Rektorova et al., 2005). Only one study with patients suffering from OCD with DLPFC rTMS was performed with simultaneous cognitive testing and no significant change in cognitive function after rTMS was reported (Kang et al., 2009). However, the authors in this study used the stimulation of right (and not left) DLPFC with the low-frequency protocol.

We should notice that the use of terms in cognitive neuroscience is not uniform, which makes proper reviewing almost impossible.

As we can see, the effect of DLPFC rTMS on cognition could be more impressive, particularly in healthy participants. So nowadays new target areas suggest themselves. For example, the deeply located ACC functions as a monitor of discrepancies and conflicts in information. This plays a crucial role in recognizing the need for inhibitory control. So, modern studies focused on inhibition more often try to influence this area precisely, and they are forced to face the limitations of classic rTMS.

Standard rTMS has limitations, one of which is the depth of the induced field. Standard rTMS coils cause an effective field in a depth of approximately 1cm (Cohen et al., 1990; Roth et al., 2007, p. 200; Zangen et al., 2005). It was hypothesized that deeper stimulation could improve results (Roth et al., 2002), and various newly innovative coils were developed. Two main coil types for deeper stimulation or deep TMS (dTMS) are H-coils and double-cone coils (see Fig. 13). They were designed to reach a depth of 3cm without a significant increase of electric fields induced in superficial cortical regions (Roth et al., 2007).

Compared to the classic (not deep) figure-8 coil, the H-coil produces a summation of the electric field from several coil elements located at different positions around the specific brain region, all carrying current in the same direction. However, the H-coils' ability to effectively stimulate deeper neuronal structures is obtained at the cost of wider electrical field

distribution in the brain (Zangen et al., 2005) (for a schematic view of coils and inducing field, please see Fig.11).

The “double cone” angulated coil (DCC) consists of two large circular coils forming an obtuse angle. At the expense of less focality, this coil type helps reach deeper targets. In particular, such coils may enable stimulation of the anterior cingulate cortex (Hayward et al., 2007).

In conclusion, dTMS, a modern and refined method of NIBS, shows promise for neurocognitive research and therapy.

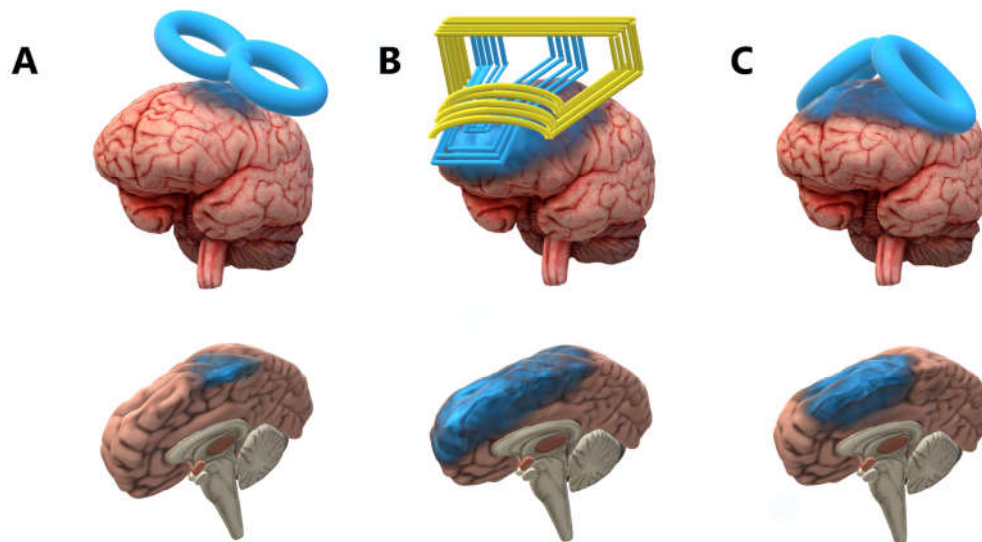


Figure 11. Approximate schematic induced field distribution of A) the figure-8 rTMS coil, B) the H-coil, and C) the double-cone coil (adapted from (Laskov and Klírová, 2021)).

1.7.2 dTMS and cognitive functions in healthy participants

Based on recent research in healthy adults, excitatory classic rTMS (high-frequency) was associated with statistically reliable effects for improving executive functioning, and inhibitory rTMS (low-frequency) was associated with statistically reliable effects for improving episodic memory and visual perception. However, these effects were minor (Patel et al., 2020).

Only seven dTMS trials with healthy participants and assessed cognitive functions have been published. Two addressed (Gruberger et al., 2015; Krause et al., 2012) very specific cognitive functions – such as self-awareness and cognitive Theory of Mind (ToM); the other two (Lee et al., 2019; Spagnolo et al., 2019) focused on the cognitive functions connected with addictive behavior and therefore tested only „decision making.” The study by Zangen et al. (Zangen et al., 2005) showed no significant differences in immediate and delayed memory in healthy participants. In this study, other cognitive functions were not assessed, and the low-frequency (1 Hz) dTMS was applied. The only study with high-frequency dTMS (up to 20Hz) was conducted by Levkovitz et al. (Levkovitz et al., 2007), in which more cognitive functions were tested (including the executive function). Still, the only improvement was shown in spatial working memory.

The inhibitory control was assessed in healthy controls in the study by Modirrousta et al.. They compared the performance of healthy participants and patients with OCD in the Eriksen Flanker task before and after one session of deep 1 Hz rTMS (1200 pulses) over the mPFC. A pairwise post hoc comparison showed that there was a drop in error rate for OCD patients from baseline to post-TMS ($p < 0.05$), but at the same time, the healthy group did not show a similar reduction in errors ($p > 0.05$) (Modirrousta et al., 2015a). However, this study was focused mainly on OCD patients and has only limited information about the execution of healthy participants.

For the whole overview, please see Table 1.

Study	Coil type	Frequency	No. of sessions	Diagnosis (participant type)	Mean age	% female	Adverse effects + Clinical effects	Study design	Functions assessed	Scales	Cognitive outcomes
Healthy participants											
Zangen et al. (2005)	H	1	1	Healthy n=6			No	Open-label	Immediate and Delayed memory	CalCAP	No significant differences
Levkovitz et al. (2007)	H1, H2, 8-coil	1 pulse/day 1; 10 Hz/day 3; 20 Hz/day 5	3	Healthy n=35	27	56	No	Double-blind, parallel-group, sham-controlled; 4 groups: H1 n=9, H2 n=9, 8-coil n=8, sham n=9	Psychomotor speed, Executive functions, Sustained attention, Visuospatial memory	CANTAB	Transient reduction in short-term effect on spatial recognition memory (1st day in H1 group); Spatial Working Memory significantly improved in H2 group
Krause et al. (2012)	HAUT	1	1	Healthy n=16	27	62	No	Single-blind, sham-controlled, cross-over	Cognitive ToM	Yoni Task	No significant differences
Gruberger et al. (2015)	H1	1	1	Healthy n=55			N/a	Double-blind, six parallel groups: dTMS + rest, dTMS + task, standard task, standard rTMS + rest, standard rTMS + task, sham-rTMS + rest or sham-rTMS + task.	Self-awareness	Word-recognition measure of self-awareness, SSAS, SSD	dTMS affected situational self-awareness - disrupted activity induced reports of lowered self-awareness and strong feelings of dissociation.
Lee et al. (2019)	H	1; 10	4	Healthy n=28	30	57	3 facial twitching, 4 headaches	Double-blind, cross-over, sham-controlled, two active stimulations + two sham	Decision making, Facial perception	Risk Task, Faces Task	No significant differences
Spagnolo et al. (2019)	H8	1	2	Healthy n=16	38	56	2 mild headaches	Double-blind, cross-over, sham-controlled	Decision making	Blink Task, Risk Task	No significant differences
Modirrousta et al. (2015)	ACDC	1	1	Healthy n=10 (and OCD n=10)	30		N/a	Open-label, with healthy controls n=10 after 1 session	Executive functions (Inhibitory control)	Eriksen Flanker task (three versions)	No significant difference was reported in healthy volunteers

Table 1. Characteristics of the included studies, stimulation parameters, demographic characteristics, type of cognitive evaluations, and cognitive outcomes – studies with healthy participants. Table adapted from (Laskov and Klírová, 2021).

Abbreviations: ACDC Anterior Cingulate Double Cone (coil/stimulation); CalCAP California Computerized Assessment Package; CANTAB Cambridge Neuropsychological Test Automated Battery; dTMS deep transcranial magnetic stimulation; H, H1, H2, H8 or HAUT H-coil types; N number of participants; OCD obsessive-compulsive disorder; rTMS repetitive transcranial magnetic stimulation; SSAS Situational Self-Awareness Scale; SSD State Scale of Dissociation; 8-coil conventional figure-of-eight coil.

1.7.3 dTMS as a treatment for OCD

rTMS has been explored as a possible treatment for OCD (Fitzsimmons et al., 2022; Hyde et al., 2022; Lefaucheur et al., 2020) since cognitive-behavioral therapy (CBT), and SSRI antidepressants (both as first-line treatments) are effective in only 50% of patients (Hirschtritt et al., 2017). Different stimulation parameters (frequency, number of stimulation sessions, etc.) with varying stimulation targets of cortical-striato-thalamo-cortical circuits have been explored. Except for rTMS of the pre-SMA (Mantovani et al., 2010; Zhang et al., 2019), which belongs to the motor CSTC circuit, the most studied rTMS targets to date were the components of associative CSTC circuit, such as dorsolateral prefrontal cortex (DLPFC) or limbic CSTC circuit that includes mPFC and ACC. These studies stimulated especially the left DLPFC (Badawy et al., 2010), right DLPFC (Elbeh et al., 2016; Mansur et al., 2011), and bilateral DLPFC (Shayganfard et al., 2016) by standard rTMS using an eight-figure coil, or mPFC, together with the ACC (Carmi et al., 2019, 2018; McCathern et al., 2020) by dTMS using an H7-coil or a double-cone coil, so-called “the Anterior Cingulate Double Cone“ (ACDC) when stimulating the ACC (Kreuzer et al., 2019). Nowadays, low-frequency rTMS of the right DLPFC is recommended by rTMS European guidelines (Lefaucheur et al., 2020) as the treatment for OCD with possible efficacy (level C evidence). The latest rTMS-OCD meta-analysis also supports this recommendation (Fitzsimmons et al., 2022). Nevertheless, brain imaging studies have shown that the ACC plays a crucial role in the neurophysiology of OCD (Fitzgerald et al., 2005; Herrmann et al., 2004), and recent mPFC-dTMS studies targeting the ACC with H7 or a double-cone coil have demonstrated the effect of high-frequency mPFC-dTMS in OCD treatment. Finally, high-frequency ACDC rTMS and the H7-coil have been approved by the US Food and Drug Administration (FDA) for OCD treatment.

Randomized control trials targeting OCD have revealed consistent results of Y-BOCS reduction and induction of electrophysiological changes after the stimulation preceded by the provocation of OCD symptoms (exposure) that activates the CSTC circuit (Carmi et al., 2019, 2018; McCathern et al., 2020). It supports the well-documented finding that neuromodulation can be enhanced by activating the neural network of interest through specific cognitive or behavioral action (Lefaucheur et al., 2020). Thus, in our research, we used cognitive activation training in healthy participants and “exposure” in patients with OCD.

1.7.4 dTMS and inhibitory control in patients with OCD

OCD is associated with various neurobiological abnormalities, including structural abnormalities (Ahmari and Dougherty, 2015) and impaired function of CSTC circuits (Coles et al., 2005; Gehring et al., 2000; Lapidus et al., 2014) or its different components (Coles et al., 2005). The ACC and mPFC were found to be hyperactivated in patients with OCD when detecting cognitive conflicts (Fitzgerald et al., 2005) or making errors (Herrmann et al., 2004). Over-reaction to mistakes is a common feature in OCD patients (Coles et al., 2005) and can be recognized by tasks that include the commission of a mistake, such as the Stroop task (Alyagon et al., 2021). Notably, dTMS treatment over the mPFC using a double-cone, or H7-coil, improved both OCD symptoms and post-error slowing, which suggests a correlation between error monitoring impairment and OCD pathophysiology (Modirrousta et al., 2015b). Overall, mPFC-dTMS is effective in the treatment of OCD symptoms, including affecting cognitive functions and inducing EEG changes such as modified ERN response that can be offered as an electrophysiological marker for the treatment effect of OCD.

Only a few dTMS trials that tested inhibitory control were held with OCD patients. Two studies have been presented in the last few years, and four research papers have been printed based on these studies (Alyagon et al., 2021; Carmi et al., 2018; Modirrousta et al., 2015a, 2015b).

One double-blinded sham-controlled clinical trial with 41 patients was performed with low-frequency and high-frequency dTMS over the mPFC (Carmi et al., 2018). Only the HF dTMS (20 Hz) group showed clinical improvement, and the LF group was omitted. Participants performed a Stroop task with simultaneous EEG recordings at pre- and post-treatment time points. After stimulation, analyses of HF dTMS patients' Stroop task results indicated an effect of active dTMS on performance and improvement in executive functions (cognitive control). The beneficial effect of the treatment was also associated with modified theta activation over the mPFC (including the ACC).

Another study (Modirrousta et al., 2015a) was open-label with ten OCD patients who received ten sessions of LF ACDC TMS (1 Hz) stimulation and ten healthy controls who received only one session of LF ACDC TMS. All patients demonstrated an improvement in their OCD symptoms after ten sessions of dTMS. Participants completed three versions of the Eriksen Flanker task for cognitive function measurement. Measures did not reveal significant differences in the flanker effect, reaction times (RTs), percentage of reporting errors, or percentage of correcting errors in patients' performance. However, patients' error rates

significantly dropped after one and ten sessions of dTMS compared to healthy participants. Additionally, a trend toward normalizing post-correct slowing impairment was shown (RTs after correct responses dropped significantly after ten sessions)

For the whole overview, please see Table 2.

Study	Coil type	Frequency	No. of sessions	Diagnosis (participant type)	Mean age	% female	Adverse effects + Clinical effects	Study design	Functions assessed	Scales	Cognitive outcomes
Patients with OCD											
Modirrousta et al. (2015a; 2015b)	ACDC	1	10	OCD n=10	29		N/a; OCD patients showed a significant reduction in Y-BOCS scores following ten sessions of dTMS	Open-label, with healthy controls n=10 after 1 session	Executive functions (Cognitive control)	Eriksen Flanker task (three versions)	Significantly decreased post-correct slowing impairment and error rate
Carmi et al. (2018); Alyagon et al. (2020)	H7	1; 20	25	OCD n=41	33	47	4 headaches and fatigue; response rate following HF treatment was significantly higher	Double-blind, three-arm, parallel-group, sham-controlled; 1 Hz (LF) dTMS n=8, 20 Hz (HF) dTMS n=18, or sham n=15	Executive functions (Cognitive control)	Stroop test (E-Prime software)	Significantly reduced reaction time and post-error slowing in the active group

Table 2. Characteristics of the included studies, stimulation parameters, demographic characteristics, type of cognitive evaluations, and cognitive outcomes – studies with patients with OCD. Table adapted from (Laskov and Klírová, 2021).

Abbreviations: ACDC Anterior Cingulate Double Cone (coil/stimulation); dTMS deep transcranial magnetic stimulation; H7 type of H-coils; HF high-frequency; LF low-frequency; OCD obsessive-compulsive disorder; Y-BOCS Yale-Brown Obsessive Compulsive Scale.

Therefore, the ACC and mPFC present favorable targets for intervention in OCD. These brain regions can be stimulated (in)directly using high-frequency mPFC-dTMS with a double cone coil – ACDC TMS. Previous dTMS studies confirm that HF mPFC-dTMS can disrupt overactivity and induce clinical and electrophysiological long-term effects in OCD. Studies also state that stimulation of the mPFC and the mediated ACC stimulation lead to improvement of inhibitory (cognitive) control.

In this thesis, we were trying to close knowledge gaps in this area of research. We independently investigated the effect of ACDC TMS on inhibitory control in (1) healthy participants and (2) patients with OCD using behavioral and electrophysiological measures and then compared the results of the two studies.

2 Goals and hypothesis

Despite many partial findings summarized in this thesis's introduction, the influence of dTMS on inhibitory control processes still needs to be explored. In healthy populations, we have only a little information available, which is moreover only concerned with low-frequency protocols and does not correspond methodologically to studies on clinical populations. The studies conducted on OCD patients have been more focused on the clinical picture and the change in clinical status.

This thesis is part of a long-term research project investigating the effects of different neurostimulation methods on cognitive functions in patients and healthy populations. We focus on the impact of dTMS on inhibitory control in OCD patients and healthy volunteers. The third part of the current thesis is a head-to-head comparison between the two groups.

Our studies are one step towards understanding how dTMS functions in healthy and clinical populations. In the future, this could help us optimize the TMS protocols for treating OCD and develop new treatment strategies.

2.1 Goals

2.1.1 Study 1 – healthy volunteers

The primary objective of the actual study was to investigate the effect of ACDC TMS in healthy participants by evaluating pre- and post-stimulation changes in the interference effect in the Stroop task, measured as the reaction time to incongruent minus the reaction time to congruent stimuli.

The secondary objectives were:

To investigate the effect of ACDC TMS by evaluating pre- and post-stimulation changes on

- 1) Inhibitory control measured via the reaction times change and error count in the Stroop task (as less sensitive markers)
- 2) The electrophysiological marker - the ERN amplitude measured as mean theta power during the Stroop test.

2.1.2 Study 2 - a clinical population of patients with OCD

The primary objective of the second study was to investigate the effect of ACDC TMS in patients with OCD by evaluating pre- and post-stimulation changes in the interference effect in the Stroop task, measured as the reaction time to incongruent minus the reaction time to congruent stimuli.

The secondary objectives were:

To investigate the effect of ACDC TMS by evaluating pre- and post-stimulation changes on

- 1) Inhibitory control measured via the reaction times change and error count in the Stroop task (as less sensitive markers)
- 2) The electrophysiological marker - the ERN amplitude measured as mean theta power during the Stroop test.

And to find a correlation between the severity of symptoms measured by Y-BOCS and IC changes.

2.1.3 Study 3 – a compilation comparison study of healthy and clinical OCD populations

The primary objective of the actual study was to compare the effect of active and sham ACDC TMS on inhibitory control (measured via the interference effect in the Stroop task) between healthy participants and patients with OCD.

The secondary objectives were:

To compare the effect of ACDC TMS between groups (healthy/patient population) by evaluating pre- and post-stimulation changes on

- 1) Inhibitory control measured via the reaction times change and error count in the Stroop task
- 2) The electrophysiological marker - the ERN amplitude measured as mean theta power during the Stroop test.

2.2 Hypothesis

In connection with the objectives, we plan to test the following hypotheses.

2.2.1 Study 1 – healthy volunteers

A single active ACDC TMS application in healthy participants will lead to the following:

- 1) Enhancement of the inhibitory control performance as measured by the Stroop test – decrease in the interference, which means a lower difference between the reaction time to incongruent minus the reaction time to congruent stimuli,
- 2) Lower reaction times to incongruent stimuli (the same effect as was shown in the patients with OCD see Introduction 1.5.2),
- 3) There is no change in the error count,
- 4) Increase of the ERN amplitude*.

* The result is somewhat paradoxical, given that an increased ERN is typically observed in individuals with OCD compared to controls and that a general hyperactivation of the ACC is frequently noted in OCD patients (Gehring et al., 2000). Nonetheless, the same results were previously noted after advantageous therapies in OCD, such as enhanced resting state (Saxena et al., 2009) and task-related activity (Nakao et al., 2013) seen following successful CBT treatment. The main thing for us is the same result (increase in the amplitude of the ERN) after HF dTMS, which Carmi showed in his study (Carmi et al., 2018).

~~6.0.02.2.2~~ 2.2.2 Study 2 - a clinical population of patients with OCD

A single active ACDC TMS application in a patient population with OCD will lead to:

- 1) Enhancement of the inhibitory control performance as measured by the Stroop test - decrease in the interference (see above),
- 2) Lower reaction times to incongruent stimuli (as previous studies showed; see Introduction 1.7.4),
- 3) Lower error count,
- 4) Increase of the ERN amplitude and
- 5) In patients with high Y-BOCS scores, we expect post-stimulation changes (in the above hypotheses) to be more pronounced.

2.2.22.2.3 Study 3 – a compilation comparison study of healthy and clinical OCD populations

Given that the main functional changes in OCD involve increased ERN amplitude in response to errors, we hypothesize that:

- 1) ACDC TMS will have a more pronounced effect in the participants, where the inhibitory control circuit can be normalized, and OCD patients will significantly improve in Stroop test performance (there will be a significant decrease in interference effect, reaction times to incongruent stimuli, and error count) compared to healthy volunteers after a single dTMS application,
- 2) We also expect a more significant increase in ERN's amplitude in response to errors in the OCD population when measured electrophysiologically compared to healthy participants,
- 3) Behavioral and electrophysiological changes will be seen after active but not sham ACDC TMS.

3 Methodology

Below, we present the methodology of the three studies: with a healthy population, OCD patients, and a compilation study of those two.

The studies were conducted in the Neurostimulation Laboratory of the National Institute of Mental Health, Klecany. They were supported by a grant project of the UK grant agency (140223: The anterior cingulate double cone transcranial magnetic stimulation (ACDC TMS) as an instrument for the treatment and investigation of obsessive-compulsive disorder (OCD)).

3.1 Study 1 – healthy volunteers

3.1.1 Study design

A randomized, placebo-controlled, double-blind study.

3.1.2 Participants

This project included a group consisting of healthy individuals (n=30) with no history of mental illness, even among first-degree relatives. The exclusion criteria included organic brain damage, neurological or endocrinological disease, substance dependence, mental retardation, motor or sensory impairment, inability to provide informed consent, contraindications to rTMS (presence of any metallic or non-metallic objects in the cranial cavity (surgical material, cochlear implants, etc.), history of epilepsy), or inability to measure motor threshold. Participation in the study was conditional on signing an informed consent form approved by the Ethics Committee of the NUDZ and the 3rd Faculty of Medicine.

Demographic data (sex, age, education, marital status) were collected from this group.

3.1.3 Study scheme

Thirty healthy participants completed one session of ACDC TMS (active n=15 and sham n=15). Before and after the session, EEG activity was measured with simultaneous Stroop testing to register the electrophysiological and behavioral changes. During stimulation, participants did the PASAT task to activate the mPFC-ACC cognitive control circuit. Afterward, statistical analysis was performed using R software (psychometric measurement) and BESA and Python (EEG).

Visit 1 (day 0): meeting eligibility criteria, informed consent, EEG with Stroop task recording, and randomization. The participant was randomly allocated to one of the two groups: a) active 20Hz ACDC TMS, 100% of motor threshold, 40 trains, 50 pulses per train, 18 minutes duration; 2000 pulses per session; 1 session; b) sham ACDC TMS with a sham coil applied either to mPFC; 1 session. Right after the stimulation: EEG with Stroop task, side effect assessment.

Please see Figure 12.

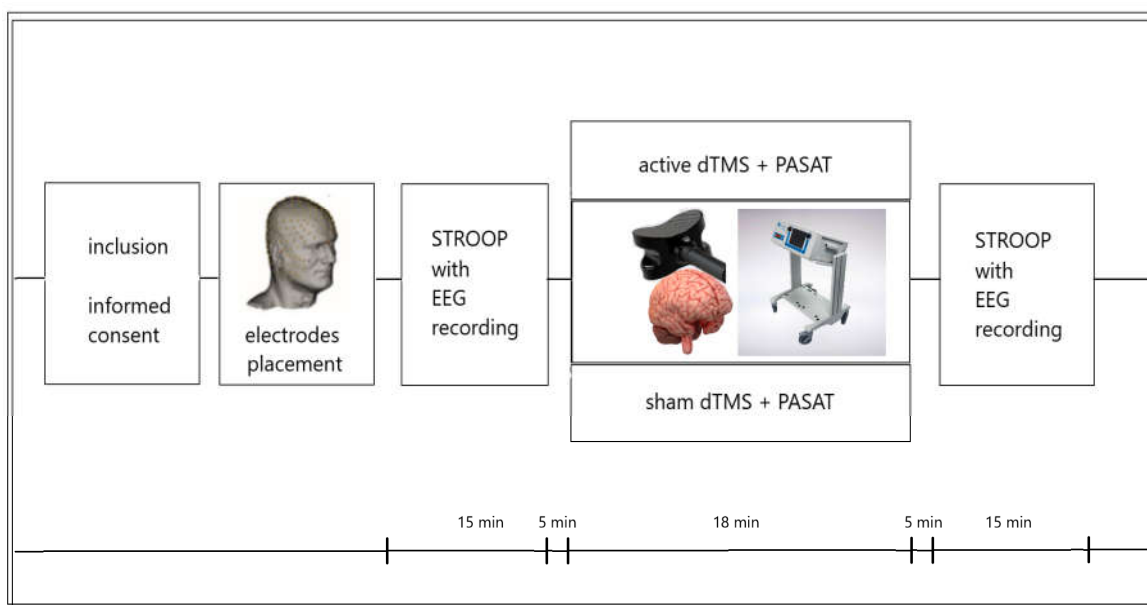


Figure 12. The scheme of study – one session of ACDC TMS (active or sham) healthy participants with EEG recording and Stroop task. dTMS deep transcranial magnetic stimulation; PASAT The Paced Auditory Serial Addition Task

Duration of the experimental session:

- Determination of the individual motor threshold – 10 min
- Pre-measurement with EEG recording during the Stroop task – approx. 20 min
- ACDC TMS sham or active with simultaneous PASAT – approx. 18 min
- Post-measurement with EEG recording during the Stroop task – approx. 20 min

Total duration: 1:10 h

The study included 30 participants, each of whom underwent 1 ACDC TMS session – 30 sessions. 60 EEG recordings were performed.

3.1.4 Study procedures and measurements

3.1.4.1 Psychometric evaluation

Healthy participants completed a computer Stroop task.

3.1.4.1.1 The Stroop Task (computer version)

The Stroop Task (computer version) measures interference and processing speed (for more information, please see Chapter 1.3.2.1). In this task, participants were instructed to press the button on the color of items presented on the screen. A few measures were used to analyze this task: the interference effect, measured as the reaction time to incongruent stimuli minus the reaction time to congruent stimuli, reaction times to congruent and incongruent trials, and error rate.

3.1.5 ACDC TMS procedure

3.1.5.1 ACDC TMS

Stimulation was administered using a MagPro R30 stimulator with a cool D-B80 A/P coil designed 1) to reach deeper cortical structures and 2) for double-blind research. Active ACDC TMS of 20 Hz was administered to the medial prefrontal cortex at 100% of the personal motor threshold (measured before the session), 2000 pulses/session. For sham ACDC TMS, the coil with a shielded magnetic field was applied to the same location as during the active ACDC TMS. The ACDC TMS applicators were blinded to stimulation conditions (the subject ID guided the stimulator for active or sham ACDC TMS according to a predetermined, saved randomization sequence) (Klířová et al., 2020).

3.1.5.2 PASAT

The Paced Auditory Serial Addition Task (PASAT) is a cognitive function test assessing auditory information processing speed and flexibility. Single digits were presented every 3 seconds, and the participants had to add each new digit to the one immediately before

it. The PASAT was applied during the ACDC TMS in healthy participants to activate the cognitive control circuit.

3.1.6 EEG acquisition and assessment

Recording of EEG was realized in subjects comfortably sitting in a sound-attenuated and electrically isolated room by 256-channel HCGSN 100, an evenly spaced network of Ag-AgCl electrodes. Subjects were asked to keep their eyes open and perform the Stroop task on a computer screen, during which congruent and incongruent trials with colored words appeared randomly on the screen. A fixation cross appeared after each trial. The resulting parameters of EEG were assessed in pre/post measurement in each condition with BESA 7.0 software and Python. Data were gathered according to conditions (congruent/incongruent), divided by response type (correct/mistake), and filtered to the theta band (4-8 Hz).

3.1.7 Statistical Analyses

All analyses were conducted using the R version 4.3.0 and BESA and Python software (for EEG).

The primary outcomes were:

- a) Behavioral “cognitive” effect – the interference effect, measured as the reaction time to incongruent minus the reaction time to congruent stimuli, reaction times to incongruent trials, and error rate in the Stroop task before and after the stimulation.
- b) Electrophysiological effect – change in error-related negativity (ERN) amplitude.

Demographic and clinical characteristics among groups were compared by one-way analysis of variance (ANOVA) and a chi-square test.

The behavioral outcomes were analyzed using:

- 1) Interference effect - A two-way ANOVA was performed to analyze the impact of stimulation (active/sham) and time (before/after the stimulation) on the difference between RTs to incongruent and congruent trials (delta).
- 2) Reaction times of answers to incongruent trials - To compare the reaction times of answers to incongruent trials between active and sham groups, we first calculate the difference between RTs before and after the stimulation (delta of incongruent RTs). The normality of these data was tested using the Shapiro-Wilk normality test. Then, the Welch Two

Sample t-test was applied. Then, analysis was conducted using extraction of percentiles (5, 25, 50, 75, 95) from the reaction times distribution. These were subjected to three-way ANOVA, with Percentiles x Time (pre/post-stimulation) x Stimulation (active/sham). When the condition (post correct or post error) was added to the analysis, a three-way mixed ANOVA was used to test a three-way Time x Condition x Treatment interaction.

3) Number of errors in incongruent trials—The number of mistakes in incongruent trials was analyzed as a difference (delta) between Stroop performance before and after the stimulation. First, the normality was checked using the Shapiro-Wilk test. Then, the Welch Two Sample t-test was applied, which tested the difference in delta errors by stimulation.

EEG analysis:

Continuous EEG data were preprocessed in BESA using FIR filtering at 1 - 100 Hz band-pass and 50 Hz notch. The data was segmented into trials that were time-locked to the participants' response (2 seconds epochs, 1 second before, and 1 second after the participant response). The segmented data were baseline corrected (at -300 ms to -70 ms before the event), and noisy segments were manually inspected and removed. Subsequently, the data were decomposed using Independent Component Analysis (ICA), excluding eye blinks and horizontal eye movements. A second manual inspection was then performed, and residual artifacts were removed. Excluded channels were replaced with spherical interpolation of the neighboring channel values. To analyze ERPs for the Stroop task, data were then gathered according to conditions (congruent/incongruent), divided by response type (correct/mistake), and filtered to the theta band (4-8 Hz). Since most errors (93%) were made within the incongruent trials, analysis was carried out solely for this condition. The ERN was computed as the amplitude difference between correct and mistake conditions, generally between 50-150 ms (Gehring et al., 2000). However, to determine the optimal time window of the ERN signal for our sample, we calculated a combined ERN of all participants; an analysis revealed a time window of 0-120 ms post-response. Within this time window, the amplitudes following correct and mistake responses were computed using an adaptive mean measure, a fixed time window (60 ms) surrounding the negative peak for each subject. In addition, we used a Morlet wavelet transform analysis with 5 cycles in the wavelet to convert the data from a time to a frequency domain. Thus, the mean theta power from the Cz electrode, ranging between 0 and 120 ms post-response, was converted to decibels (dB) (Tzur and Berger, 2007). The power spectral perturbation was expressed as a change from baseline (in dB). All EEG analyses were performed using the MNE toolbox in Python.

EEG amplitude and power were analyzed using a mixed-model measure ANOVA with Stimulation (active and sham), Time (Pre- and post-stimulation), and Response type (correct and mistake) as independent variables and with theta band mean power as the dependent variable.

3.2 Study 2 - a clinical population of patients with OCD

3.2.1 Study design

A randomized, placebo-controlled, double-blind study

3.2.2 Participants

The study group consisted of patients with OCD (n=30) according to the ICD-10 diagnostic criteria and were those falling under the diagnosis group F42.X Obsessive-compulsive disorder (F42.1-9). The group corresponded in age and sex distribution with the healthy volunteers group. The exclusion criteria included organic brain damage, neurological or endocrinological disease, substance dependence, mental retardation, motor or sensory impairment, inability to provide informed consent, contraindications to rTMS (presence of any metallic or non-metallic objects in the cranial cavity (surgical material, cochlear implants, etc.), history of epilepsy), or inability to measure motor threshold. Participation in the study was conditional on signing an informed consent form approved by the Ethics Committee of the NUDZ and the 3rd Faculty of Medicine.

Demographic data (sex, age, education, marital status) and anamnestic data on the total duration of the disease and the severity of OCD measured via the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), types, duration, and dosage of medication used were collected from the group of patients.

3.2.3 Study scheme

Thirty OCD patients underwent one session of the active ACDC TMS (n=15) or sham TMS (n=15). Before and after the session, EEG activity was measured with simultaneous Stroop testing to register the electrophysiological and behavioral changes. During stimulation, patients complete simultaneous mental “exposure” (symptom provocation) to activate the CSTC circuit. Afterward, statistical analysis was performed using R software (psychometric measurement) and BESA and Python (EEG).

Please see Figure 13.

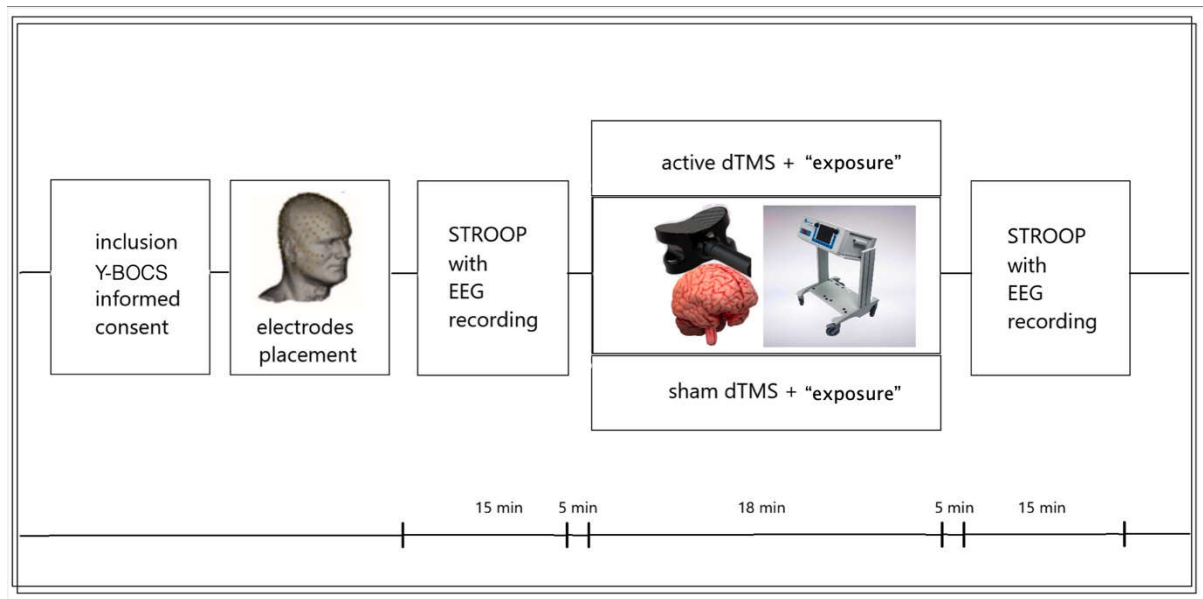


Figure 13. The scheme of study – one session of ACDC TMS (active or sham) in patients with EEG recording and Stroop task. dTMS deep transcranial magnetic stimulation; Y-BOCS Yale-Brown Obsessive-Compulsive Scale

Duration of the experimental session:

- Determination of the individual motor threshold – 10 min
- Pre-measurement with EEG recording during the Stroop task – approx. 20 min
- ACDC TMS sham or active with simultaneous mental symptom provocation – approx. 18 min
- Post-measurement with EEG recording during the Stroop task – approx. 20 min

Total duration: 1:10 h

The study included 30 participants, each of whom underwent 1 ACDC TMS session – 30 sessions. 60 EEG recordings were performed.

3.2.4 Study procedures and measurements

3.2.4.1 Psychometric and clinical evaluations

Patients were clinically assessed by clinical interview and by the Y-BOCS—Yale-Brown Obsessive-Compulsive Scale at baseline; Stroop task (computer version) during EEG recording was used during the experiment.

Raters were blind to patients' group assignments.

3.2.4.1.1 The Stroop Task (computer version)

The Stroop Task (computer version) was the same as in Study 1 (for detailed information, please see Chapter 3.1.4.1.1).

3.2.4.1.2 Y-BOCS

Y-BOCS - is a scale to rate the severity of obsessive-compulsive disorder symptoms. The scale is widely used in clinical settings and research to assess the severity of OCD and track therapeutic progress. Y-BOCS assesses obsessions independently of compulsions and measures the intensity of obsessive-compulsive disorder symptoms without favoring or disfavoring any particular sort of obsessional or compulsion content. The total score is calculated using the subscales of obsessions (items 1–5) and compulsions (items 6–10).

Clinical severity can be defined as Y-BOCS scores of (Storch et al., 2015):

0–13 – “mild symptoms”

14–25 – “moderate symptoms”

26–34 – “moderate-severe symptoms”

35–40 – “severe symptoms”

For the Czech version of the scale, please see Supplement 2.

3.2.5 ACDC TMS procedure

3.2.5.1 ACDC TMS

Stimulation was administered using a MagPro R30 stimulator with a cool D-B80 A/P coil. The stimulation protocols were the same as in Study 1 (for detailed information, please see Chapter 3.1.5.1).

3.2.5.2 Symptom provocation

The patients were asked to provoke OCD symptoms during the stimulation as recommended by European guidelines to enhance the effect of rTMS through the cortico-striato-thalamo-cortical circuitry activation.

3.2.6 EEG acquisition and assessment

EEG recording was realized in the same way as in Study 1 (for detailed information, please see Chapter 3.1.6).

3.2.7 Statistical Analyses

All analyses were conducted using the R version 4.3.0 and BESA and Python software (for EEG).

The primary outcomes were:

- a) Behavioral “cognitive” effect – the interference effect, measured as the reaction time to incongruent minus the reaction time to congruent stimuli, reaction times to incongruent trials, and error rate in the Stroop task before and after the stimulation.
- c) Electrophysiological effect – change in error-related negativity (ERN) amplitude.

Demographic and clinical characteristics among groups were compared by one-way analysis of variance (ANOVA) and a chi-square test.

We excluded patients who had more than 90% mistakes from the analysis (2 from the sham group), so 28 patients were included in the final analysis.

The behavioral outcomes were analyzed using:

Interference effect - A two-way ANOVA was performed to analyze the impact of stimulation (active/sham) and time (before/after the stimulation) on the difference between RTs to incongruent and congruent trials (delta).

Reaction times of answers to incongruent trials - To compare the reaction times of answers to incongruent trials between active and sham groups, we first calculate the difference between RTs before and after the stimulation (delta of incongruent RTs). The normality of these data was tested using the Shapiro-Wilk normality test. Then, the Welch Two Sample t-test was applied. Then, analysis was conducted using extraction of percentiles (5, 25, 50, 75, 95) from the reaction times distribution. These were subjected to three-way ANOVA, with Percentiles x Time (pre/post-stimulation) x Stimulation (active/sham). When the condition (post correct or post error) was added to the analysis, three-way mixed ANOVA was used to test a three-way Time x Condition x Stimulation interaction.

Number of errors in incongruent trials—The number of mistakes in incongruent trials was analyzed as a difference (delta) between Stroop performance before and after the stimulation. First, the normality was checked using the Shapiro-Wilk test. Then, the Welch Two Sample t-test was applied, which tested the difference in delta errors by stimulation.

The interaction between behavioral and clinical data:

For the RT of incongruent stimuli, we fitted a linear model to predict “RT_incon_pre” with “ybocs” (formula: $RT_incon_pre \sim ybocs$). Standardized parameters were obtained by fitting the model on a standardized dataset version. 95% Confidence Intervals (CIs) and p-values were computed using a Wald t-distribution approximation.

We also applied a linear model (estimated using OLS) (formula: $delta_pre \sim ybocs$) for the delta between incongruent and congruent stimuli.

Since the obtained data wasn't normal, we used Spearman's rank correlation for the number of errors.

For testing the impact of the Y-BOCS score on the stimulation effect, we used the “delta of delta” parameter ((RT of incongruent before – RT of congruent before) – (RT of incongruent after – RT of congruent after)). We fitted the two-way ANOVA (the data was tested previously for the normality) with the formula $delta_delta \sim stimulation * ybocs$.

EEG analysis:

Continuous EEG data were preprocessed in BESA using FIR filtering at 1 - 100 Hz band-pass and 50 Hz notch. The data was segmented into trials that were time-locked to the participants' response (2 seconds epochs, 1 second before, and 1 second after the participant

response). The segmented data were baseline corrected (at -300 ms to -70 ms before the event), and noisy segments were manually inspected and removed. Subsequently, the data were decomposed using Independent Component Analysis (ICA), excluding eye blinks and horizontal eye movements. A second manual inspection was then performed, and residual artifacts were removed. Excluded channels were replaced with spherical interpolation of the neighboring channel values. To analyze ERPs for the Stroop task, data were then gathered according to conditions (congruent/incongruent), divided by response type (correct/mistake), and filtered to the theta band (4-8 Hz). Since most errors (93%) were made within the incongruent trials, analysis was carried out solely for this condition. The ERN was computed as the amplitude difference between correct and mistake conditions, generally between 50-150 ms (Gehring et al., 2000). However, to determine the optimal time window of the ERN signal for our sample, we calculated a combined ERN of all participants; an analysis revealed a time window of 0-120 ms post-response. Within this time window, the amplitudes following correct and mistake responses were computed using an adaptive mean measure, a fixed time window (60 ms) surrounding the negative peak for each subject. In addition, we used a Morlet wavelet transform analysis with 5 cycles in the wavelet to convert the data from a time to a frequency domain. Thus, the mean theta power from the Cz electrode, ranging between 0 and 120 ms post-response, was converted to decibels (dB) (Tzur and Berger, 2007). The power spectral perturbation was expressed as a change from baseline (in dB). All EEG analyses were performed using the MNE toolbox in Python.

EEG amplitude and power were analyzed using a mixed-model measure ANOVA with Stimulation (active and sham), Time (Pre- and post-stimulation), and Response type (correct and mistake) as independent variables and with theta band mean power as the dependent variable.

3.3 Study 3 – a compilation comparison study of healthy and clinical OCD populations

The study's main aim was to compare the healthy participants from Study 1 and the patient population in Study 2.

We compare both – the behavioral and electrophysiological parameters between those two groups.

For such analyses, we used R software version 4.3.0.

3.3.1 Demographic data

Demographic characteristics among groups were compared by two-way analysis of variance (ANOVA).

3.3.2 Behavioural outcomes

Interference effect - A two-way ANOVA was performed to analyze the effect of stimulation (active/sham) and group (healthy/patient) on the difference between RTs to incongruent and congruent trials (delta).

Reaction times of answers to incongruent trials - To compare the reaction times of answers to incongruent trials between active and sham groups within patients and healthy participants, we first calculate the difference between RTs before and after the stimulation (delta of incongruent RTs). The normality of these data was tested using the Shapiro-Wilk normality test. Then, the two-way ANOVA was applied. Then, analysis was conducted using extraction of percentiles (5, 25, 50, 75, 95) from the reaction times distribution. A linear model was fitted to predict RT based on type, stimulation, time, and percentile (formula: $RT \sim \text{type} + \text{stimulation} + \text{time} + \text{percentile} + \text{time} * \text{stimulation} + \text{time} * \text{type} + \text{time} * \text{type} * \text{stimulation} * \text{percentile}$). Standardized parameters were derived from a standardized dataset, and 95% Confidence Intervals (CIs) and p-values were computed using a Wald t-distribution approximation.

When the condition (post correct or post error) was added to the analysis, we fitted a linear mixed model (estimated using REML and nlminb optimizer) to predict RT with time, group (HC or OCD), stimulation and condition (formula: $\text{mean} \sim \text{time} * \text{group} * \text{stimulation} * \text{condition}$). The model included the subject as a random effect (formula: $\sim 1 | \text{subject}$).

Number of errors in incongruent trials - A linear mixed model (estimated using REML and the nlminb optimizer) was fitted to predict the delta of errors (number of errors after the stimulation – before the stimulation), with group and stimulation as fixed effects and subject as a random effect (delta_err ~ group + stimulation + group * stimulation; random effect: $\sim 1 | \text{subject}$).

3.3.3 Electrophysiological outcomes

Differences in the ERN response expressed in the theta band at the baseline were checked for normality via the Shapiro-Wilk test, and then the Welch Two Sample t-test was applied to test the difference of theta power by group (healthy vs patient).

Then, since the difference was more pronounced when incorrect answers were given, we analyzed only them. The three-way mixed ANOVA was applied with the formula Stimulation x Group X Time.

4 Results

4.1 Study 1 – healthy volunteers

4.1.1 Demographic data – gender, age

A total of 30 subjects were enrolled in the study (15 had active and 15 had sham stimulation).

We found no significant difference in gender representation (Pearson's Chi-squared test: $p > .999$; Adjusted Cramer's $v = 0.00$) or age (Welch Two Sample t-test: $t_{27,47} = 0.02$, $p = .983$). Details are given in Table 3.

		Active (n=15)	Sham (n=15)
Gender	Male (%)	6 (40)	6 (40)
	Female (%)	9 (60)	9 (60)
Age	Mean $\pm$ SD	29.13 $\pm$ 7.94	29.07 $\pm$ 9.13
	Median	27	27

Table 3. Demographic data of healthy volunteers. Group mean ($\pm$ SD) and median are reported. SD standard deviation

4.1.2 Results of cognitive testing – Stroop test

Thirty healthy volunteers were randomized to complete one treatment condition—active or sham. Twenty-eight completed the trial, and their data obtained from the Stroop test with EEG recording were then analyzed. Two participants from the active group didn't finish the trial due to headaches and nausea.

Values of means and SD of analyzed reaction times and error count are summarized in Table 4.

			Active (n=13)		Sham (n=15)	
			Before	After	Before	After
RT of incongruent	Total		823.182 ±	723.772 ±	837.374 ±	755.256 ±
			99.821	94.508	149.214	102.396
	Post error		967.616 ±	777.335 ±	1050.177 ±	950.275 ±
			311.752	239.595	313.785	295.908
	Post correct		812.936 ±	721.626 ±	818.735 ±	745.752 ±
			252.395	221.407	267.746	227.008
Delta (RT of incongruent – RT of congruent)			112.972 ±	84.659 ±	110.154 ±	107.604 ±
			70.181	52.617	69.011	62.169
Errors in incongruent			8.692 ±	4.923 ±	11.067 ±	6.467 ±
			4.590	3.546	10.918	7.864

Table 4. Mean ± SD of reaction times of answers in incongruent trials (after all answers, after mistakes, and after correct answers), the difference (delta) between reaction time of answers in incongruent and congruent trials, and number of errors made in incongruent trials. RT reaction time in ms

4.1.2.1 Interference effect - Difference between reaction times to incongruent and congruent trials

A two-way ANOVA was performed to analyze the effect of stimulation (active/sham) and time (before/after the stimulation) on the difference between RTs to incongruent and congruent trials (delta). The test revealed no statistically significant interaction between the effects of stimulation and time ($F_{1, 52} = 0.56$, $p = .46$). Please see Fig. 14.

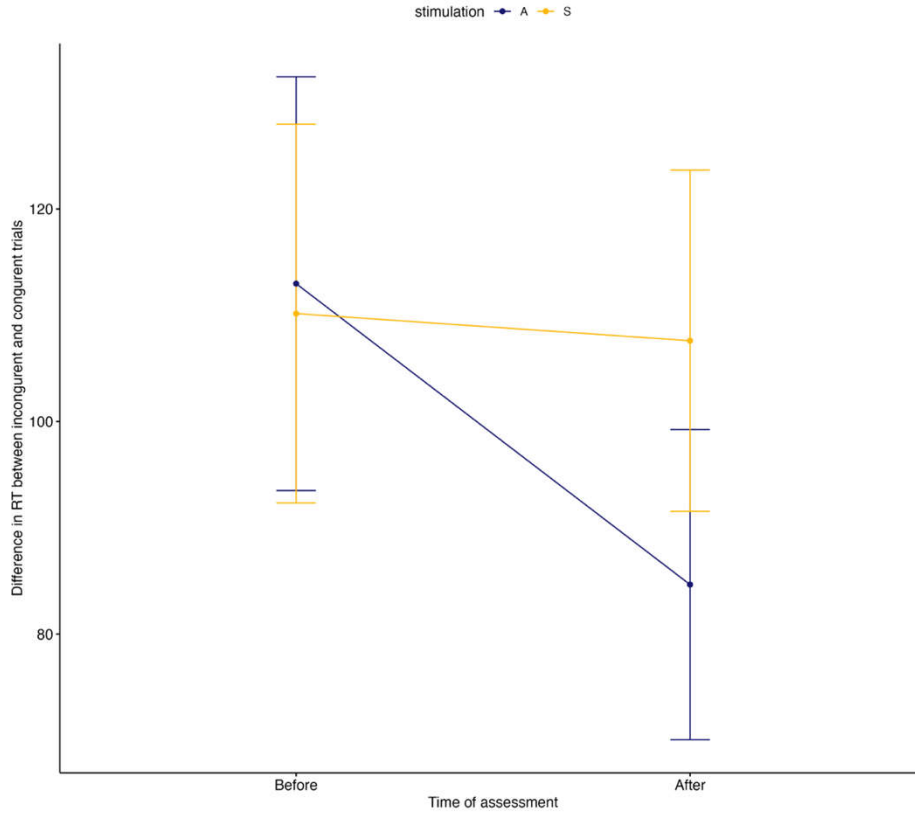


Figure 14. Difference in reaction times between incongruent and congruent trials. Data are presented as Mean $\pm$ SD. A active group; RT reaction time in ms; S sham group

4.1.2.2 Reaction times of answers to incongruent trials

To compare the reaction times of answers to incongruent trials between active and sham groups, we first calculate the difference between RTs before and after the stimulation (delta of incongruent RTs). The normality of these data was tested using the Shapiro-Wilk normality test. From the output, the p-value was greater than the significance level of 0.05 ($p = .18$), implying that the distribution of the differences is not significantly different from a normal distribution. In other words, we can assume the normality.

Then, the Welch Two Sample t-test was applied. The t-test testing the difference of RT_incon_delta by stimulation (mean in group Active = 99.41, mean in group Sham = 82.12) suggests that the effect was statistically not significant (difference = 17.29, 95% CI [-27.62, 62.20], $t_{24.05} = 0.79$, $p = .435$).

The results as boxplots for each time point and stimulation condition are depicted in Figure 15.

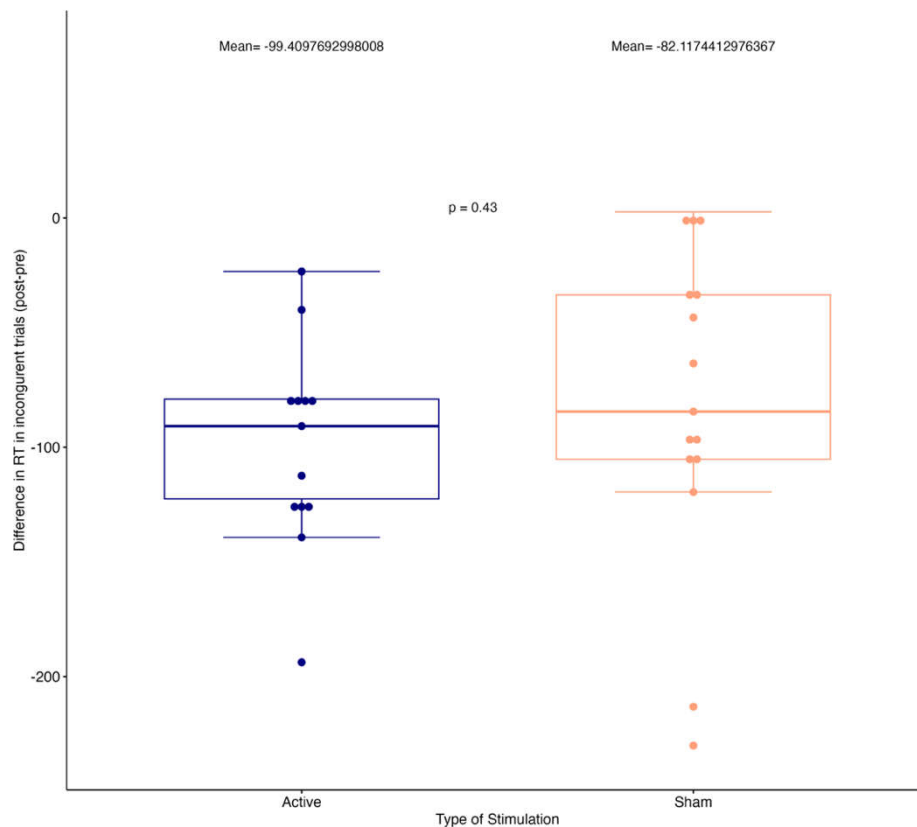


Figure 15. Boxplot of the Stroop test results – the difference in reaction time (incongruent trials). RT reaction time in ms. The boxplot displays the first and third quartiles and the outliers.

By percentiles:

Total RT distribution was analyzed using extraction of percentiles (5, 25, 50, 75, 95) from the RT distribution during incongruent trials. These were subjected to three-way ANOVA, which showed that the interaction between time, percentile, and stimulation is statistically insignificant and very small ($F_{1, 12} = 0.04$, $p = .84$). Please see Fig. 16.

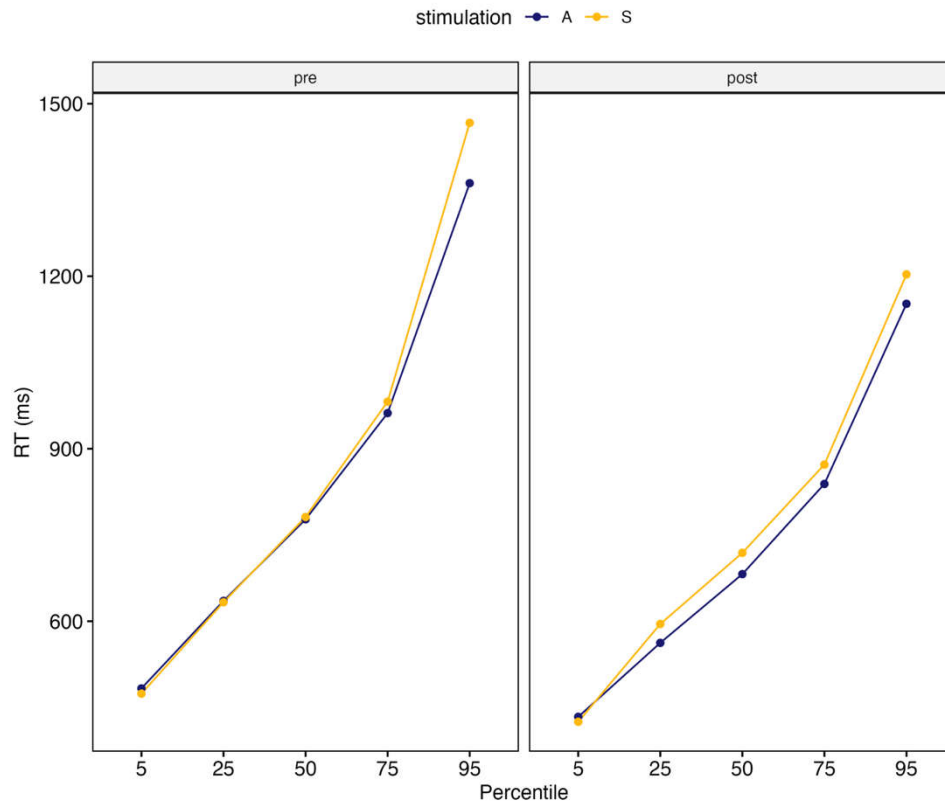


Figure 16. Percentiles distribution of RTs before and after the stimulation. Data are presented as Mean. A active; RT reaction time; S sham

After mistakes vs. after correct answers:

When the condition (post correct or post error) was added to the analysis, mixed three-way ANOVA with stimulation as between factor and time and type of response as within factors showed that a three-way Time x Condition x Stimulation interaction is not statistically significant ($F_{1,20} = 0.008, p > .05$). Please see Fig. 19.

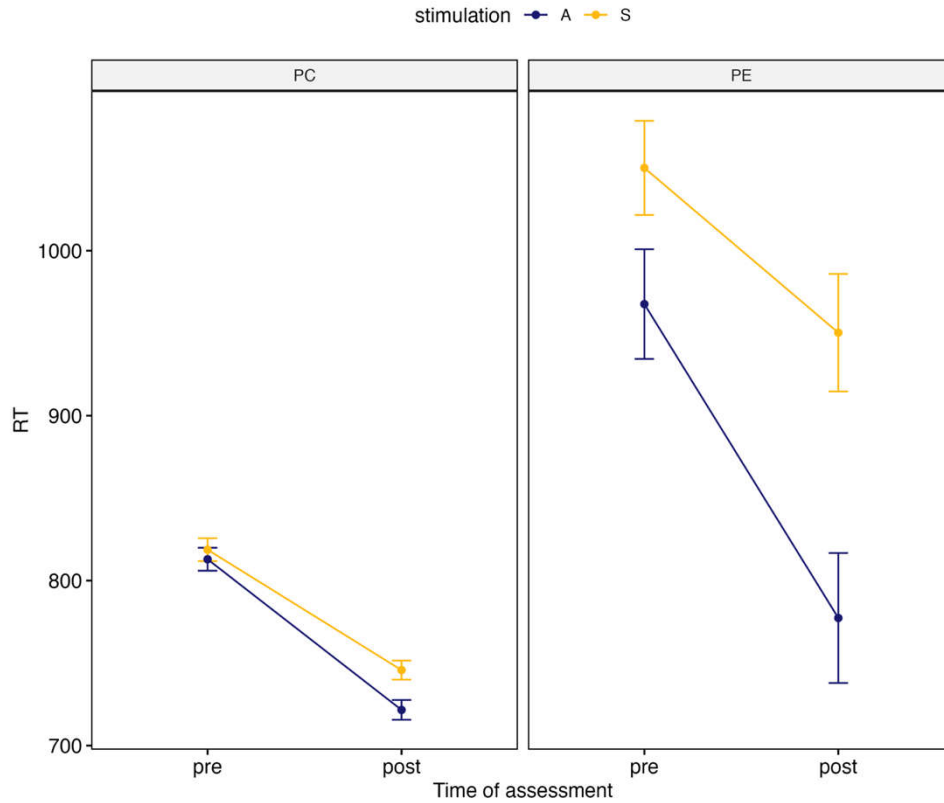


Figure 17. Average RTs following correct (PC) and erroneous responses (PE). Data are presented as Mean $\pm$ SD. A active group; PC post correct; PE post error; RT reaction times in ms; S sham group

4.1.2.3 Number of errors in incongruent trials

The number of errors in incongruent trials was analyzed as a difference (delta) between Stroop performance before and after the stimulation. Firstly, the normality was checked by the Shapiro-Wilk test; there is $p = .02$. From the output, we can assume the normality.

Then, the Welch Two Sample t-test was applied, testing the difference of delta of errors by stimulation (mean in group A = -3.77, mean in group S = -4.60). It suggests the effect is statistically insignificant (difference = 0.83, 95% CI [-2.72, 4.38], $t_{25,02} = 0.48$, $p = .634$). Please see Fig. 18.

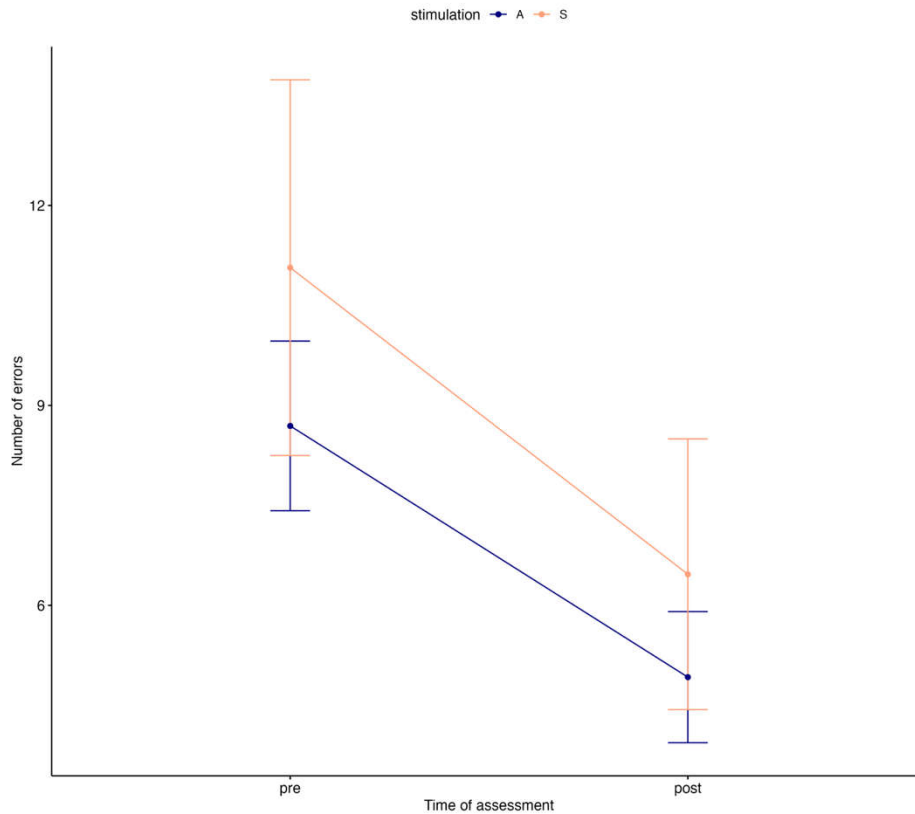


Figure 18. The difference in the number of errors (mistakes) in incongruent trials between before (pre) and after (post) the stimulation time points. Data are presented as Mean $\pm$ SD. A active; S sham

4.1.3 Results of neurophysiological measurement – EEG

The ERN response expressed in the theta band (0–120 ms post response) was similar in both groups at baseline (mean in active group = 0.08, mean in sham group = 0.33; $t_{39.89} = -1.52$, $p = .136$), but there was a shift towards increased ERN in the active group, and decreased ERN in the sham group following stimulation (Fig. 19). However, analysis of the theta power didn't reveal a significant Group X Time X Response interaction ($F_{1, 19} = 1.009$, $p > .05$).

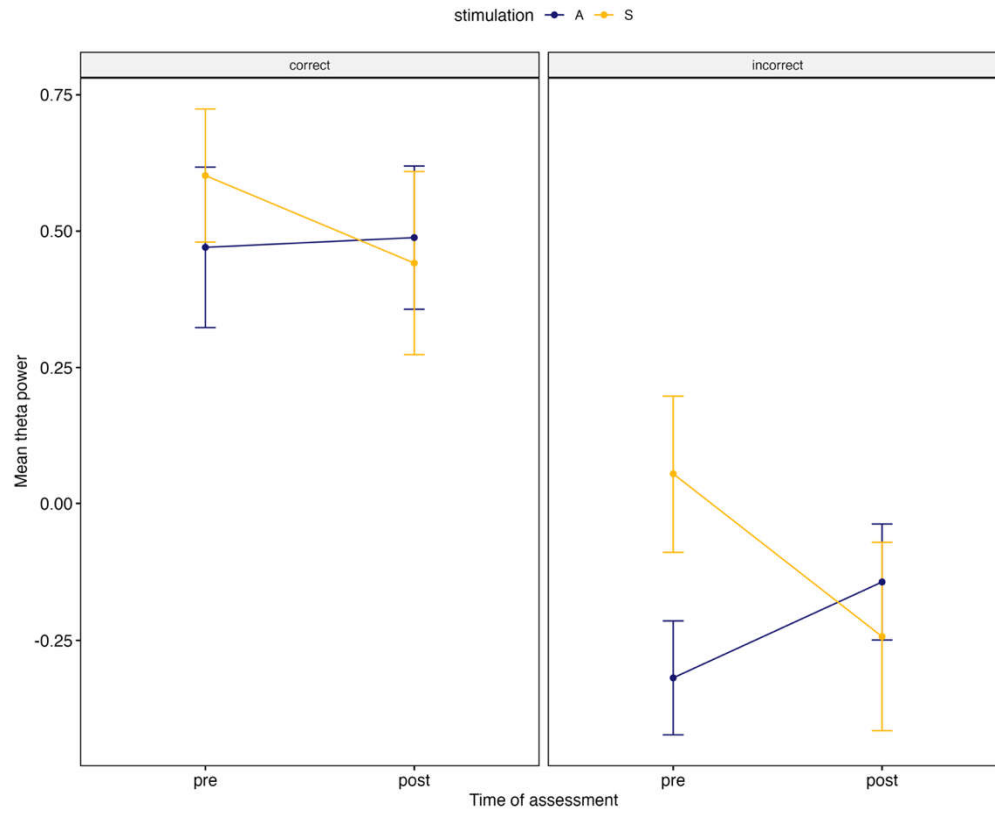


Figure 19. Mean theta power measured in μV during incongruent trials – in correct and mistaken answers. A active; S sham

4.2 Study 2 - a clinical population of patients with OCD

4.2.1 Demographic, anamnestic, and clinical data

In the next experiment with the patients with OCD, a total of 30 subjects were enrolled (15 had active and 15 had sham stimulation).

We found no significant difference in gender representation (Pearson's Chi-squared test: $p = .715$; Adjusted Cramer's $v = 0.00$) or age (Welch Two Sample t-test: $t_{22,54} = -1.13$, $p = .27$). Details are given in Table 5.

		Active (n=15)	Sham (n=15)
Gender	Male (%)	8 (53)	7 (47)
	Female (%)	7 (47)	8 (53)
Age	Mean $\pm$ SD	29.6 $\pm$ 10.52	34.85 $\pm$ 13.55
	Median	29	36
Y-BOCS		23,1 $\pm$ 6,44	22,5 $\pm$ 3,71

Table 5. Demographic data of patients with OCD. Group mean ($\pm$ SD) and median are reported. Y-BOCS Yale-Brown Obsessive Compulsive Scale

Data on the patient's psychiatric history (duration of illness, type, and dose of medication used, and Y-BOCS results) are detailed in Table 6. All but one patient was treated with medication; 5 were on monotherapy (3 taking escitalopram 10-35 mg pro die; 1 sertraline 250 mg pro die; 1 vortioxetine 10 mg pro die). 13 patients received dual-combination therapy, with the majority receiving a combination of antidepressant and antipsychotic medication or combination of two antidepressants (escitalopram 20 mg + pregabalin 75 mg, sertraline 200 mg + aripiprazole 10 mg, clomipramine 200 mg + risperidone 3 mg, clomipramine 150 mg + amitriptyline 75 mg, clomipramine 150 mg + mirtazapine 15 mg, escitalopram 30 mg + quetiapine 50 mg, sertraline 150 mg + alprazolam, risperidone 1 mg + fluoxetine 60 mg, clomipramine 225 mg + chlorprothixene 45 mg, venlafaxine 150 mg + trazodone 75 mg,

escitalopram 20 mg + quetiapine 100 mg, aripiprazole 10 mg + sertraline 300 mg, sertraline 200 mg + trazodone 50 mg). Five subjects were medicated with a combination of three drugs (sertraline 200 mg, lamotrigine 200 mg, and mirtazapine 30mg; escitalopram 20 mg, risperidone 2 mg, and mirtazapine 7,5 mg; venlafaxine 150mg, trazodone 250 mg, and quetiapine 150 mg; clomipramine 225mg, aripiprazole 10 mg, and trazodone 75 mg; paroxetine 60 mg, venlafaxine 75mg, and trazodone 50 mg). Another 5 with four-combination (venlafaxine 150 mg, risperidone 2mg, lamotrigine 300 mg, pregabalin 75 mg; paroxetine 60 mg, tiapride 300 mg, pregabalin 450 mg, olanzapine 5 mg; clomipramine 150 mg, diazepam 5 mg, quetiapine 250 mg, pregabalin 525 mg; clomipramine 150 mg, escitalopram 25 mg, risperidone 3mg, clonazepam 1 mg; quetiapine 300 mg, risperidone 2 mg, clonazepam 1 mg, sertraline 400 mg). 1 patient was on five-combination – venlafaxine 300 mg, aripiprazole 15 mg, clonazepam 0,5 mg, mianserin 60 mg, and quetiapine 25 mg.

	Mean ± SD
Duration of illness	8,93 ± 7,97

	Number of patients	%
Severity of illness (measured by Y-BOCS)		
0-13; Mild symptoms or less; CGI-Severity = 0 to 2	1	3,3
14-25; Moderate symptoms (Functions with effort); CGI-Severity = 3	21	70
26-34; Moderate-severe symptom (Limited functioning); CGI-Severity = 4	7	23,3

35-40; Severe or greater symptoms (Functions with assistance or completely non-functional); CGI-Severity = 5 to 6	1	3,3
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	Name	Type	Number of patients	Dose, mg (Mean)
Medication (3 most used)	Escitalopram	AD (SSRI)	8	24,38
	Sertraline	AD (SSRI)	7	242,86
	Clomipramine	AD (TCA)	7	178,57

Table 6. Patients' psychiatric history data. AD antidepressants; CGI clinical global impression; SSRI selective serotonin reuptake inhibitors; TCA tricyclic antidepressants; Y-BOCS Yale-Brown obsessive compulsive scale

4.2.2 Results of cognitive testing – Stroop test

Thirty patients with diagnosed OCD were randomized to complete one treatment condition—active or sham. All patients completed the trial, and their data obtained from the Stroop test with EEG recording were then analyzed. Before the analysis, the outliers (n=2) were deleted by the Tukey rules on quartiles ± 1.5 IQR. Values of means and SD of analyzed reaction times and error count are summarized in Table 7.

			Active (n=15)		Sham (n=13)	
			Before	After	Before	After
RT of incongruent	Total		1021.069 $\pm$	918.441 $\pm$	1015.572 $\pm$	868.035 $\pm$
			165.414	155.345	136.516	120.802

	Post error	1183.426 ±	1020.146 ±	1088.020 ±	1009.608 ±
		297.352	379.865	383.167	357.348
	Post correct	993.598 ±	906.907 ±	994.977 ±	855.939 ±
		303.040	297.746	309.854	274.259
Delta	(RT of	154.729 ±	142.946 ±	120.677 ±	107.428 ±
incongruent	– RT of	45.881	80.889	70.490	39.479
congruent)					
Errors in incongruent		23.6 ±	15.0 ±	28.538 ±	10.308 ±
		19.493	15.62	18.086	9.196

Table 7. Mean ± SD of reaction times of answers in incongruent trials (after all answers, after mistakes, and after correct answers), the difference (delta) between reaction time of answers in incongruent and congruent trials, and number of errors made in incongruent trials. RT reaction time in ms

4.2.2.1 Interference effect – Difference between reaction times to incongruent and congruent trials

We performed a two-way ANOVA to analyze the effect of stimulation (active/sham) and time (before/after the stimulation) on the difference between RTs to incongruent and congruent trials (delta). The test revealed no statistically significant interaction between the effects of stimulation and time ($F_{1, 52} = 0.002$, $p > .05$). Please see Fig. 20.

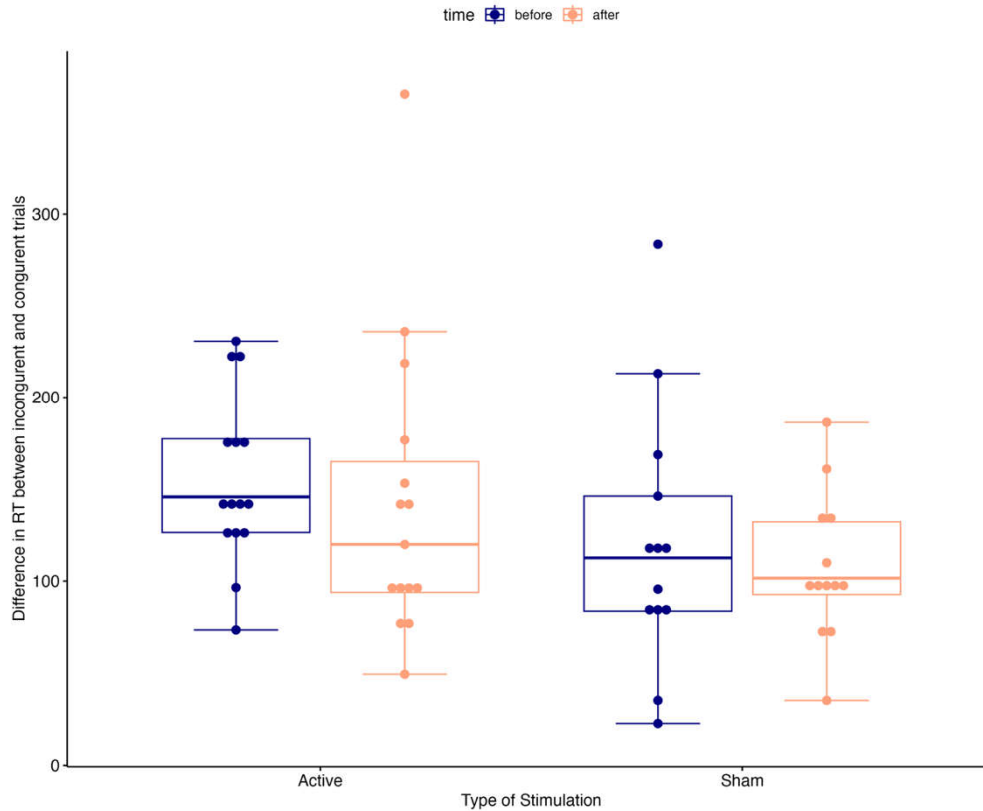


Figure 20. Difference in RTs between incongruent and congruent trials. Data are presented as Mean $\pm$ SD. RT reaction time in ms

4.2.2.2 Reaction times of answers to incongruent trials

We first analyzed reaction times of answers to incongruent trials by two-way mixed ANOVA with stimulation as between factor and time as within factor. The ANOVA suggests that the interaction between time and type of stimulation was statistically insignificant ($F_{1,26} = 1.91, p > .05$).

The results as boxplots for each time point and stimulation condition are depicted in Figure 21.

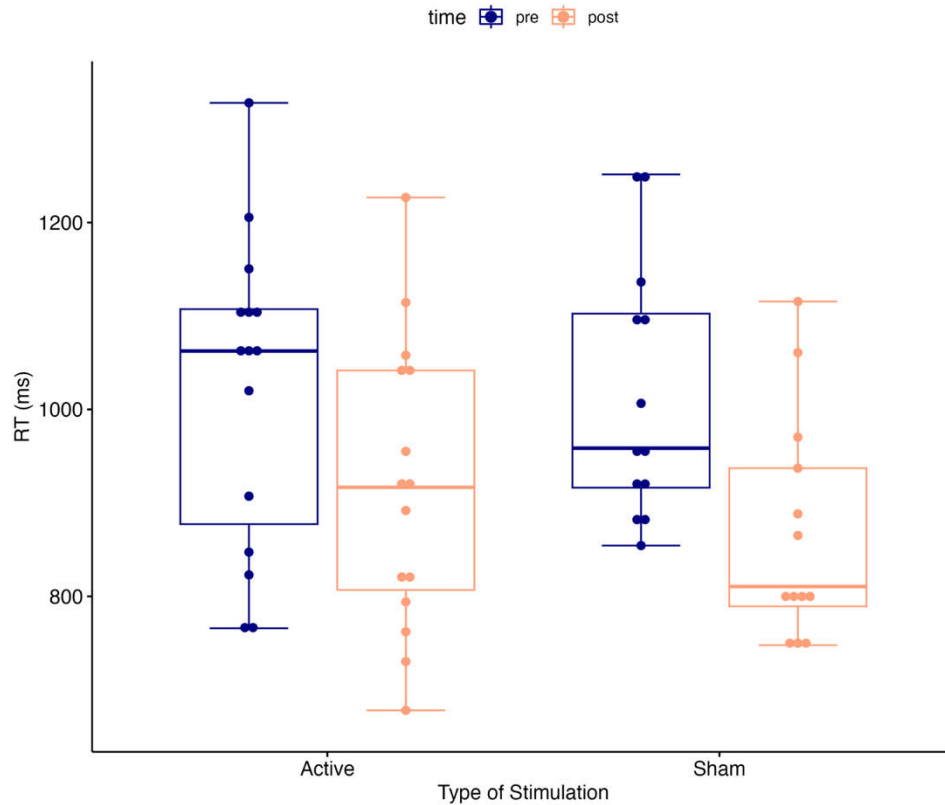


Figure 21. Boxplot of the Stroop test results – difference in RT (incongruent trials). RT reaction time in ms. The boxplot displays the first and third quartiles.

By percentiles:

Total RT distribution was analyzed using extraction of percentiles (5, 25, 50, 75, 95) from the RT distribution of each individual during incongruent trials. These were subjected to three-way ANOVA (formula: $RT \sim \text{time} * \text{percentile} * \text{stimulation}$), which showed that the main effect of time ($F_{1,12} = 9.77, p = .009$) and of the percentile ($F_{1,12} = 482.63, p < .001$) were statistically significant. No other significant effects or interactions were found. The interaction between time, percentile, and stimulation was also insignificant ($F_{1,12} = 0.11, p = .742$). Please see Fig. 22.

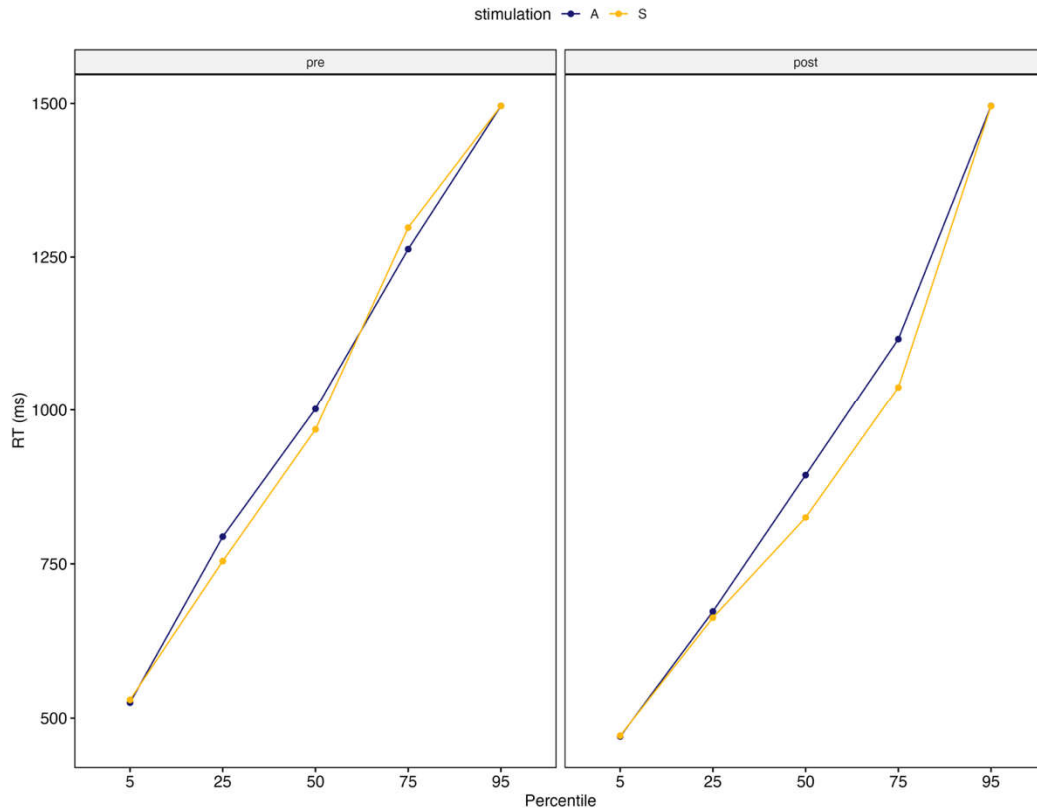


Figure 22. Percentiles distribution of RTs before and after the stimulation. Data are presented as Mean. A active; RT reaction time; S sham

After mistakes vs. after correct answers:

When the condition (post correct or post error) was added to the analysis, three-way mixed ANOVA with time and condition (PE or PC) as within factors and stimulation as between factors showed that the interaction between time, type of response (PC or PE), and kind of stimulation was statistically insignificant ($F_{1,24} = 0.155$, $p > .05$). Please see Fig. 23.

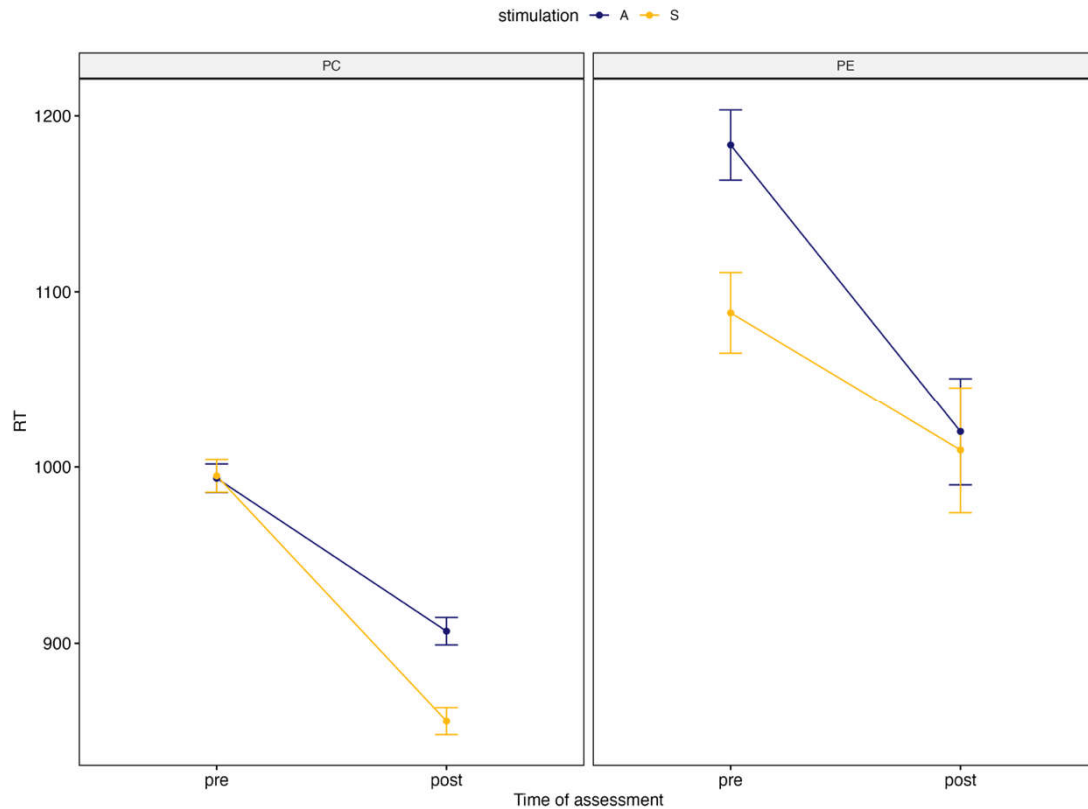


Figure 23. Average RTs following correct (PC) and erroneous responses (PE). Data are presented as Mean $\pm$ SD. A active; PC post correct; PE post error; RT reaction time; S sham

4.2.2.3 Number of errors in incongruent trials

The number of errors in incongruent trials was analyzed as the delta of mistakes (see above). Firstly, the normality was checked by the Shapiro-Wilk test; there is $p = .22$. From the output, we can assume the normality.

Then, the Welch Two Sample t-test was applied, testing the difference of delta of errors by stimulation (mean in group A = -8.60, mean in group S = -18.23). It suggests the effect is statistically significant (difference = 9.63, 95% CI [0.36, 18.90], $t_{21.92} = 2.16$, $p = .042$). However, the sham group showed “better” results than the active group. Please see Fig. 24.

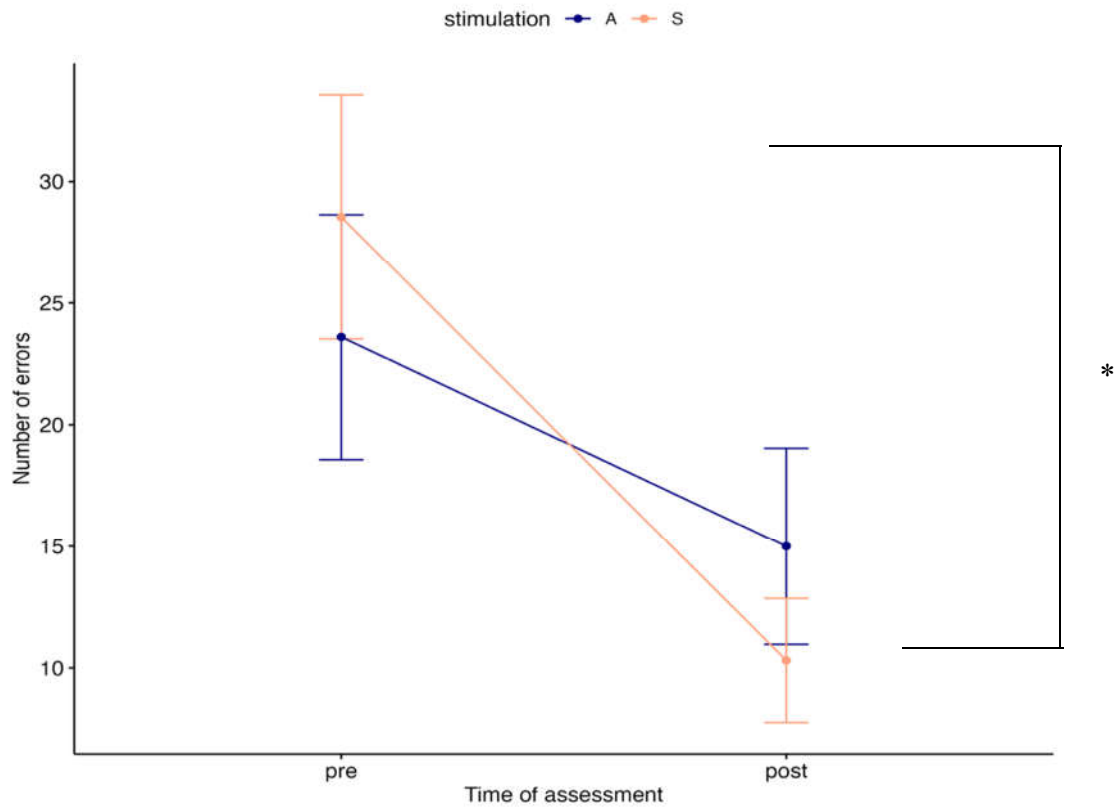


Figure 24. The difference in the number of errors in incongruent trials between before (pre) and after (post) the stimulation time points. Data are presented as Mean $\pm$ SD. A active; S sham. * $p < .05$

4.2.2.4 The interaction between cognitive testing results and clinical data

No correlation was found between the Y-BOCS score and Stroop test measurements before the stimulation (we used the reaction times of incongruent stimuli, delta between incongruent and congruent, and number of errors).

For the RT of incongruent stimuli, we fitted a linear model to predict “RT_incon_pre” with “ybocs” (formula: $RT_incon_pre \sim ybocs$). The model explains a statistically not significant and very weak proportion of variance ($R^2 = 0.01$, $F_{1,26} = 0.31$, $p = .580$, adj. $R^2 = -0.03$). The model's intercept, corresponding to $ybocs = 0$, is at 947.57 (95% CI [680.50, 1214.64], $t_{26} = 7.29$, $p < .001$). Within this model:

- The effect of “ybocs” is statistically non-significant (beta = 3.11, 95% CI [-8.30, 14.52], $t_{26} = 0.56$, $p = .580$; Std. beta = 0.11, 95% CI [-0.29, 0.51])

We also applied a linear model (estimated using OLS) (formula: $\delta_pre \sim ybocs$) for the delta between incongruent and congruent. The model also explains a statistically not

significant and very weak proportion of variance ($R^2 = 6.34e-03$, $F_{1,26} = 0.17$, $p = 0.687$, adj. $R^2 = -0.03$). The model's intercept, corresponding to $y_{BOCS} = 0$, is at 159.63 (95% CI [52.46, 266.79], $t(26) = 3.06$, $p = 0.005$). Within this model:

- The effect of y_{BOCS} is statistically non-significant ($\beta = -0.91$, 95% CI [-5.49, 3.67], $t_{26} = -0.41$, $p = 0.687$; Std. $\beta = -0.08$, 95% CI [-0.48, 0.32])

Since the obtained data wasn't normal, we used Spearman's rank correlation for the number of errors, which was negative and statistically insignificant ($\rho = -0.19$, $S = 4362.91$, $p = .323$).

For testing the impact of the Y-BOCS score on the stimulation effect, we used the “delta of delta” parameter ((RT of incongruent before – RT of congruent before) – (RT of incongruent after – RT of congruent after)). We fitted the two-way ANOVA (the data was tested previously for the normality) with the formula $\text{delta_delta} \sim \text{stimulation} * y_{BOCS}$. The test suggested that:

- The main effect of “stimulation” was statistically not significant ($F_{1,24} = 4.46e-03$, $p = .947$)
- The main effect of “ y_{BOCS} ” was statistically not significant ($F_{1,24} = 0.25$, $p = .621$)
- The interaction between “stimulation” and “ y_{BOCS} ” was statistically not significant ($F_{1,24} = 1.01$, $p = .325$)

4.2.3 Results of neurophysiological measurement – EEG

After stimulation during mistakes in incongruent trials, there was a shift towards increased ERN in the active group and decreased ERN in the sham group (Fig. 25). The ERN response expressed in the theta band (0–120 ms post response) was similar in both groups at baseline (mean in active group = 0.25, mean in sham group = 0.45; $t_{39.65} = -1.61$, $p = .116$). According to the theta power analysis, the Group X Time X Response interaction was significant ($F_{1,19} = 5.57$, $p = .029$). A Bonferroni adjustment was applied for the simple two-way interactions and simple main effects. There was a statistically significant simple two-way interaction between response and time for stimulation: Sham group, $F_{1,10} = 13.5$, $p = .004$, but not for stimulation: Active group, $F_{1,9} = 0.121$, $p = .74$.

The simple main effect of time on theta power was statistically significant only for the incorrect responses ($F_{1,10} = 6.41$, $p = .03$).

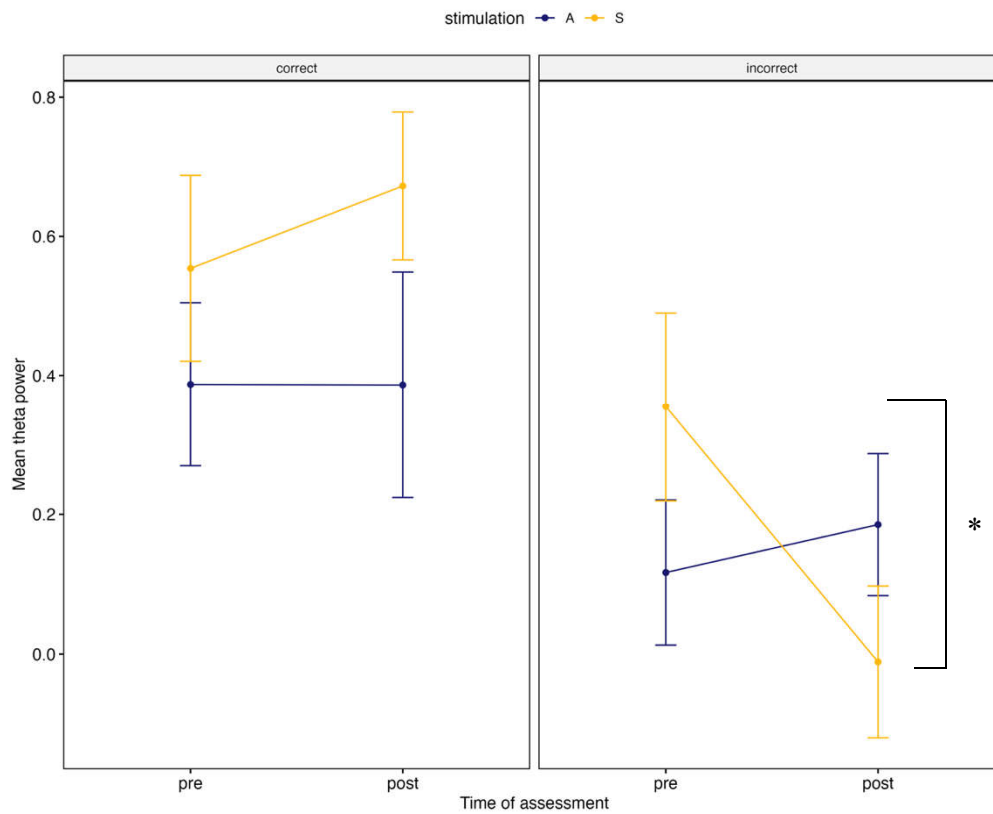


Figure 25. Mean theta power measured in μV during incongruent trials – in correct and incorrect answers. A active; S sham. * $p < .05$

4.3 Study 3 – a compilation comparison study of healthy and clinical OCD populations

4.3.1 Comparison of demographic data

No statistically significant effect on age was found for stimulation ($F_{1, 52} = 0.95$, $p = .333$) or group (healthy or patient) ($F_{1, 52} = 1.58$, $p = .215$). Or neither interaction between stimulation and group wasn't significant ($F_{1, 52} = 0.67$, $p = .416$).

4.3.2 Comparison of cognitive results

4.3.2.1 Interference effect - Difference between reaction times to incongruent and congruent trials

Analysis of the difference between reaction times to incongruent and congruent trials revealed no significant Stimulation x Group interaction ($F_{1, 52} = 1.06$, $p = .308$). Additionally, there was no significant main effect of stimulation ($F_{1, 52} = 0.82$, $p = .370$) or group ($F_{1, 52} = 0.05$, $p = .827$).

4.3.2.2 Reaction times of answers to incongruent trials

Reaction times of answers to incongruent trials:

The analysis of variance (ANOVA) revealed the following results: the main effect of stimulation was non-significant ($F_{1, 52} = 0.33$, $p = .567$), the main effect of the group was also non-significant ($F_{1, 52} = 3.02$, $p = .088$). The interaction between stimulation and group was found to be non-significant, too ($F_{1, 52} = 2.48$, $p = .121$).

By percentiles:

A linear model was fitted to predict RT based on type, stimulation, time, and percentile (formula: $RT \sim \text{type} + \text{stimulation} + \text{time} + \text{percentile} + \text{time} * \text{stimulation} + \text{time} * \text{type} + \text{time} * \text{type} * \text{stimulation} * \text{percentile}$). The model accounted for a substantial proportion of variance ($R^2 = 0.96$, $F_{15, 24} = 39.24$, $p < .001$, adjusted $R^2 = 0.94$). The intercept of the model, corresponding to type = HC, stimulation = A, time = post, and percentile = 0, was significant (363.63, 95% CI [218.15, 509.12], $t_{24} = 5.16$, $p < .001$).

Within this model, the effects were as follows:

Type [OCD]: $F_{1, 24} = 0.26$, $p = .794$

Stimulation [S]: $F_{1,24} = 0.04, p = .971$

Time [pre]: $F_{1,24} = 0.30, p = .764$

Percentile: $F_{1,24} = 39.25, p < .001$

Stimulation [S] $\times$ Time [pre]: $F_{1,24} = 0.24, p = .813$

Type [OCD] $\times$ Time [pre]: $F_{1,24} = 0.52, p = .609$

Type [OCD] $\times$ Stimulation [S]: $F_{1,24} = 0.13, p = .899$

Time [pre] $\times$ Percentile: $F_{1,24} = 0.96, p = .348$

Type [OCD] $\times$ Percentile: $F_{1,24} = 2.03, p = .053$

Stimulation [S] $\times$ Percentile: $F_{1,24} = 0.31, p = .762$

(Type [OCD] $\times$ Stimulation [S]) $\times$ Time [pre]: $F_{1,24} = 0.13, p = .898$

(Type [OCD] $\times$ Time [pre]) $\times$ Percentile: $F_{1,24} = 0.82, p = .419$

(Stimulation [S] $\times$ Time [pre]) $\times$ Percentile: $F_{1,24} = 0.24, p = .814$

(Type [OCD] $\times$ Stimulation [S]) $\times$ Percentile: $F_{1,24} = 0.36, p = .722$

(Type [OCD] $\times$ Stimulation [S] $\times$ Time [pre]) $\times$ Percentile: $F_{1,24} = 0.03, p = .979$

After mistakes vs. after correct answers:

We fitted a linear mixed model (estimated using REML and nlminb optimizer) to predict

RT with time, group (HC or OCD), stimulation, and condition (formula: $\text{mean} \sim \text{time} * \text{group} * \text{stimulation} * \text{condition}$). The model included the subject as a random effect (formula: $\sim 1 | \text{subject}$). The model's explanatory power related to the fixed effects alone (marginal R^2) is 0.59. The model's intercept, corresponding to time = post, group = HC, stimulation = A, and condition = PC, is at 914.91 (95% CI [882.17, 947.66], $t(144) = 55.23, p < .001$).

Within this model, the effect of time $\times$ group $\times$ stimulation $\times$ condition is statistically non-significant and negative (beta = -1.14, 95% CI [-15.79, 13.51], $t_{144} = -0.15, p = .88$).

4.3.2.3 Number of errors in incongruent trials

A linear mixed model (estimated using REML and the nlminb optimizer) was fitted to predict the delta of errors (number of errors after the stimulation – before the stimulation), with group and stimulation as fixed effects and subject as a random effect ($\text{delta_err} \sim \text{group} + \text{stimulation} + \text{group} * \text{stimulation}$; random effect: $\sim 1 \mid \text{subject}$). The model explained 77% of the variance in the fixed effects (marginal $R^2 = 0.77$). The intercept, representing group = healthy and stimulation = A, was estimated at -3.77 (95% CI [-8.67, 1.13], $t_{52} = -1.54$, $p = .129$).

Within the model:

The effect of the group (patient) was negative and not statistically significant ($\beta = -4.83$, 95% CI [-11.52, 1.86], $t_{52} = -1.45$, $p = .153$; standardized $\beta = -0.47$, 95% CI [-1.12, 0.18]).

The effect of stimulation (S) was also negative and not statistically significant ($\beta = -0.83$, 95% CI [-7.52, 5.86], $t_{52} = -0.25$, $p = .804$; standardized $\beta = -0.08$, 95% CI [-0.73, 0.57]).

The interaction between group (patient) and stimulation (S) was negative but did not reach statistical significance ($\beta = -8.80$, 95% CI [-18.26, 0.66], $t_{52} = -1.87$, $p = .068$; standardized $\beta = -0.86$, 95% CI [-1.78, 0.06]).

Standardized parameters were derived from a standardized dataset version, with 95% Confidence Intervals (CIs) and p-values computed using a Wald t-distribution approximation.

4.3.3 Comparison of neurophysiological outcomes

Since the difference was more pronounced during incorrect answers, we analyzed only them.

At baseline, significant differences in the ERN response expressed in the theta band were observed between groups (mean in group “healthy” = -0.14, mean in group “OCD” = 0.24, $t_{39.81} = -2.95$, $p < .005$).

According to the theta power analysis, the Stimulation x Group x Time interaction was insignificant ($F_{1, 38} = 0.015$, $p > .05$). Please see Fig. 26.

The ANOVA results indicated a statistically significant main effect of group (mean in patient group = 0.334, mean in healthy group = 0.167; $F_{1, 38} = 11.26$, $p = .002$). Furthermore, the stimulation and time interaction was also statistically significant ($F_{1, 38} = 8.66$, $p = .006$).

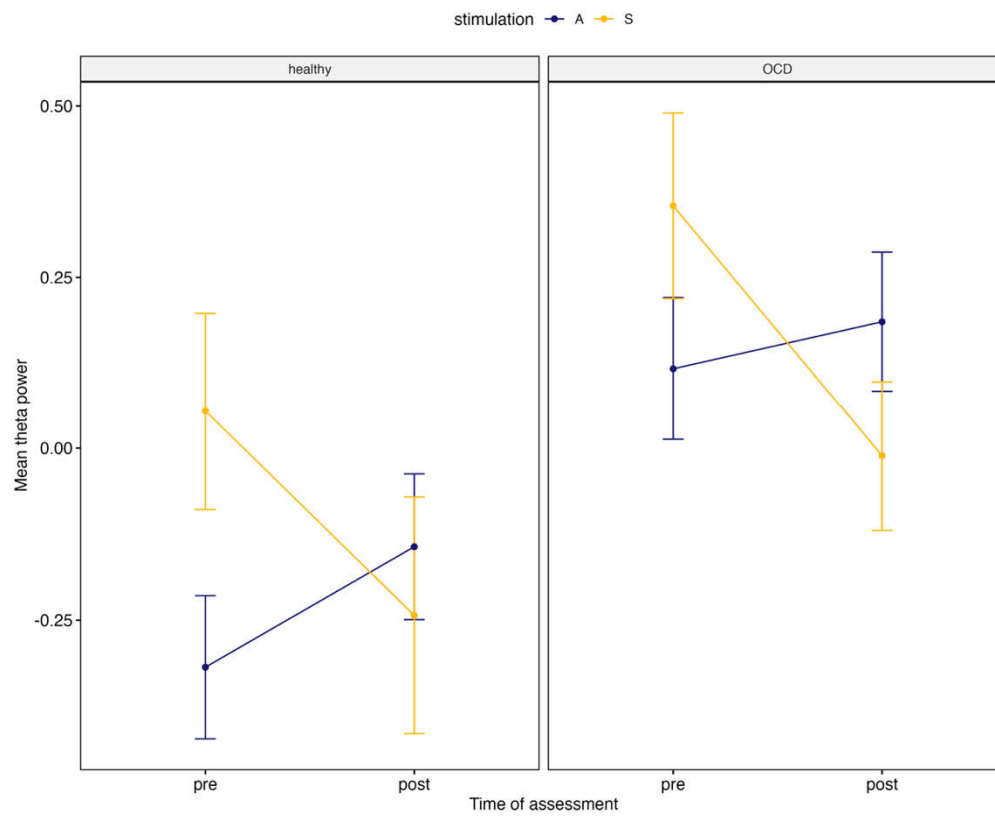


Figure 26. Mean theta power measured in μV during incorrect trials – in both groups: healthy volunteers and patients with OCD. A active group; S sham group

5 Discussion

5.1 Summary of findings: effects of ACDC TMS on inhibitory control

Our study aimed to answer whether it's possible to affect inhibitory control by ACDC TMS. We chose two groups and performed two divided studies with similar designs—one with 30 healthy volunteers and one with a clinical population—of patients with OCD. In these studies, we focused not only on the behavioral manifestation of inhibitory control, such as the Stroop task, but also tried to “catch” the effect by neurophysiological measurement.

In summary, no significant behavioral or neurophysiological effects were observed in healthy participants. In contrast, the study on OCD patients showed that ACDC TMS could surprisingly worsen inhibitory control measured as error rate in the Stroop task inpatient population. This goes against the known, albeit few, studies and does not meet our hypothesis. On the other hand, significant findings in event-related neural response are consistent with other studies to date (such as Carmi et al.) and suggest that ACDC TMS may influence inhibitory control in patients with OCD.

No significant findings were found in healthy participants, neither in the Stroop test nor in EEG. The only exciting finding was the trend, which can be seen in theta power during incorrect incongruent trials—the active stimulation increased the theta power, while the sham stimulation reduced it. Unfortunately, the two groups weren't the same as the baseline in this parameter, which probably led to insignificant results.

However, the findings in OCD patients were more noteworthy. In the Stroop task, the trend toward normalization of the reaction times to post-error answers was more pronounced after the active stimulation. However, we again didn't reach the level of significance. Interestingly, the significant difference between active and sham stimulation was found in the most rough parameter – error rate. To our surprise, however, the sham group here showed better results, and the number of errors was significantly reduced than in the active group.

The main result can be seen in electrophysiological measurement. The ERN analysis reveals the significant three-way interaction between response, time, and type of stimulation. Here again, we saw the same trend as in healthy participants – active stimulation led to an increase in theta, sham to decrease. However, this time, the sham group showed a statistically significant drop in theta power, which was not only a trend.

The third compilation study comparing the results from the two studies performed showed a significant difference in ERN baseline amplitude between healthy participants and patients with OCD. In both groups, the active stimulation led to an increase in amplitude and sham to decrease. No difference was shown here. No significant differences between Stroop task results were found between those two groups.

5.2 Comparing to previous studies

Although more studies are available using conventional TMS, we believe that dTMS should be considered separately since it has a deeper effect. As previously mentioned, only two studies were conducted using deep TMS and evaluating inhibitory control.

1) Carmi et al. in the year 2018 with adding a letter to the editor by Uri Alyagon et al. 2021 – this study was conducted with OCD patients; the final analysis included 13 participants from the active and 9 participants from the sham group, with no differences in behavior mistake percentage at baseline. The H7 coil was used, and the primary outcome was clinical improvement. Also, we must mention that the results were compared not after one stimulation but after a five-week (!) treatment. The ERN response was similar in both groups at baseline, but there was a shift towards increased ERN in the active group and decreased ERN in the sham group following treatment (Carmi et al., 2018). The finding was also seen in our Study 2. As for Stroop task results – Alygon, in his letter, recaps that there was a significant difference in Stroop task measured via reaction times (analyzed the same way – via percentiles, via post correct/post error dividing) before and after the treatment (Alyagon et al., 2021). We didn't see such results in Study 2, which, in our opinion, was plausibly connected with not enough stimulation.

2) The second available study is closer in methodology to our research. We are talking about a survey conducted in 2015 by Modirrousta et al. (Modirrousta et al., 2015a). One session of ACDC TMS was used; however, the stimulation was low-frequency (1 Hz), and there wasn't a sham group. The sample size was relatively small – 10 patients with OCD and 10 healthy controls. Also, it was not the Stroop task; instead, the Erikson Flanker task was performed. The authors didn't perform any objective (for example, EEG) measurement. Interestingly, the authors found no baseline difference between patients and healthy controls in reaction times. The error rate assessment showed a significant difference between patients and healthy controls, a finding we didn't see in Study 3.

To summarize, we should accept that our findings didn't entirely coincide with the results of previous studies. But of course, we cannot fail to consider the colossal difference in methodology that exists even in these two most closely related experiments.

5.3 Comparing inhibitory control between healthy participants and OCD patients

As we predicted, we saw a baseline difference in inhibitory control between healthy participants and patients with OCD. Patients presented with higher reaction times and more errors. Also, a statistically significant difference in mean theta power of ERN was shown, where patients performed higher amplitude during incongruent trials. These findings are consistent with the broader body of literature on executive dysfunction in OCD and with previous EEG findings (please see Introduction 6.2) (Endrass and Ullsperger, 2014; Gillan et al., 2017; Mathews et al., 2012; Norman et al., 2019; Stern et al., 2011).

Healthy participants in this study demonstrated more effective inhibitory control, as measured by task performance metrics such as error rates and reaction times. This suggests that individuals without psychiatric disorders typically exhibit robust inhibitory control, supported by the efficient functioning of regions like the DLPFC and ACC, areas involved in top-down cognitive control.

In contrast, patients with OCD showed impaired inhibitory control across the same measures. This is consistent with the documented cognitive rigidity and difficulties in response inhibition often observed in OCD. In the latest fMRI meta-analyses, patients' brains displayed hyperactivity during error processing in the bilateral dorsal ACC, SMA, pre-SMA, and the right anterior insula/frontal operculum and anterior lateral prefrontal cortex. Hypoactivity during inhibitory control was found in the rostral and ventral ACC, bilateral thalamus/caudate, the right anterior insula/frontal operculum, supramarginal cortex, and medial orbitofrontal cortex (Funch Uhre et al., 2022; Li et al., 2024). These dysfunctions likely contribute to the difficulty OCD patients face in suppressing repetitive, intrusive thoughts and compulsive actions, hallmark symptoms of the disorder.

Interestingly, the different effects of ACDC TMS on inhibitory control (such as the more pronounced trends in RTs or ERN mean power in EEG) across the two groups suggest that TMS may interact with these inhibitory deficits in OCD patients. While healthy participants exhibited relatively minor improvements in inhibitory control post-TMS, OCD

patients showed more substantial changes, such as an increase in ERN amplitude and, surprisingly, a higher number of errors compared to placebo. This suggests that TMS may be more effective in populations with existing inhibitory control impairments, potentially by modulating the CSTC circuit that is typically dysregulated in OCD.

5.4 Neural mechanisms underlying ACDC TMS effects

Understanding the neural mechanisms through which ACDC TMS influences inhibitory control is essential for advancing theoretical knowledge and clinical applications of TMS.

The ACC is a critical hub in cognitive control networks, and its dysfunction is frequently observed in psychiatric disorders. ACDC TMS is designed to stimulate this region directly. We believe that ACDC TMS may modulate activity in the ACC, which in turn influences downstream structures in the CSTC pathway, leading to rebalancing neural activity in this circuit. Does the ACDC TMS really stimulate the ACC? Only a few studies focused on the ACDC TMS mechanism using EEG, fMRI, or other “objective” effect measurements. To our knowledge, only one paper addressed this issue with a positive answer, unfortunately with only a limited number of participants ($n=7$) (Hayward et al., 2007), so more studies will be needed to prove this concept objectively. For now, we can only hypothesize. Our study, however, adds to the picture – for now, only with the trend in the ENR mean theta amplitude. Fortunately, more literature addressing this topic was published in the last few years for other types of coils for deep TMS, such as H-coils. Since both these types of coils were designed and presented with similar purposes (targeting the deeper cortical structures), we will risk combining our knowledge of these coils below.

In contrast to figure-of-eight coil-based rTMS, dTMS activated a larger brain volume in healthy participants, produced longer motor evoked potential (MEP) latencies at the threshold, and reached the threshold for motor activation at larger distances from the scalp. Following high-frequency dTMS with an H1-coil, fMRI studies (demonstrated activation linked to improved episodic and working memory. Brain-derived neurotrophic factor (BDNF), cortisol, and prolactin levels decreased following high-frequency dTMS with H-coil ($k=2$; $n=13$ healthy and $n=9$ alcohol-dependent individuals) compared to sham settings (Schmittwilken et al., 2017). Based on indirect data, dTMS may stimulate less focal but potentially deeper regions outside the cortical areas than rTMS.

5.5 Limitations of the study

Even though our study sheds light on how ACDC TMS affects (or doesn't) inhibitory control in healthy volunteers and OCD patients, there are a few limitations to be aware of. These limitations may influence the interpretation and generalizability of the findings.

- Sample Size

The primary limitation is the small sample size. However, we must admit that our studies will find a place between studies with dTMS. The two most extensive and, for now, most important studies that inspired us to conduct these experiments included $n=20$ and $n=41$ participants (Carmi et al., 2018; Modirrousta et al., 2015a). Studies with TMS are usually very labor-intensive and especially difficult with healthy participants since the TMS usually and ACDC TMS especially is quite unpleasant. However, considering the high ceiling effect of cognitive testing, we still have to admit that the total number of participants may not have been sufficient to detect subtle effects, particularly in healthy participants. A larger sample would lead to more robust findings on the impacts of ACDC TMS on inhibitory control.

The sample itself could be another potential limitation, especially in the OCD study. Medication use and comorbidities could modify inhibitory control and TMS responsiveness. However, since the clinical response wasn't our goal, we decided to limit ourselves only to the established diagnosis during patient recruitment.

- Methodological Considerations

Several methodological aspects of the study could also have influenced the findings:

1. TMS Parameters: The stimulation parameters used in the ACDC TMS protocol (e.g., frequency, intensity, duration) might not have been optimized for the specific neurocognitive outcomes measured in this study. Future studies would benefit from exploring different stimulation parameters to determine the most effective protocols for modulating inhibitory control.

2. Task Design: The Stroop task may not be enough to measure the complex nature of inhibitory control, particularly in OCD patients. Furthermore, this study only partially evaluated other components of executive functioning, like working memory or cognitive flexibility, despite their connections to inhibitory control. Another limitation connected with

the Stroop task is the analysis method of PC and PE reaction times, which may be subject to potential drift bias (although alternative methods suffer from other drawbacks) (Dutilh et al., 2012).

3. Temporal Effects of TMS: The study primarily assessed the immediate effects of ACDC TMS on inhibitory control. However, the long-term effects of TMS were not investigated. We don't know if the effects seen in OCD patients were transient or whether repeated TMS sessions could lead to sustained or even cumulative benefits. In the future, we plan to include follow-up assessments to evaluate the durability of TMS-induced changes in inhibitory control and concentrate on repeated stimulations in a clinical population.

- Technological and Practical Limitations

Trying to generalize the practical application of ACDC TMS, we, of course, will face challenges. The use of rTMS in general in the real world remains in the early stages, for example, the treatment protocols for OCD. There are logistical considerations, such as accessibility to TMS equipment, the cost of treatment, and the need for trained personnel to administer the sessions, all of which could limit clinical use and make it difficult to conduct scientific experiments.

5.6 Contributions and novelty of the study

Our study offers several significant contributions to the field of neuroscience, particularly in understanding the effects of ACDC TMS on inhibitory control in healthy individuals and patients with OCD. The findings introduce new insights into TMS's clinical and theoretical aspects and its role in modulating executive functions.

An essential contribution of our study is the use of ACDC TMS. It is among the first to apply ACDC TMS precisely to modulate ACC function and affect inhibitory control in OCD patients and healthy participants. Only one study has used this method to influence inhibitory control with a much smaller sample size (Modirrousta et al., 2015a).

By showing that ACDC TMS can influence inhibitory control in patients with OCD, our research strengthens the link between neural dysfunction in the ACC and cognitive symptoms in OCD, offering a targeted approach to remedy these impairments and supporting the hypothesis that ACC dysfunction contributes to the compulsive behaviors seen in OCD.

These findings contribute to a better understanding of how specific brain regions can be modulated to address executive dysfunction.

Not least of all, the studies target the specific cognitive domain and link it to ACC modulation. Thus, they provide novel information that helps us understand how non-invasive brain stimulation can affect key executive functions.

The findings also highlight the potential of ACDC TMS to serve as a personalized treatment tool for individuals with OCD. The observed effects suggest that targeting the ACC with double-cone TMS could offer a more specific intervention. This allows further exploration of dTMS interventions, which could be tailored to individual patient profiles based on the severity of cognitive dysfunction or ACC dysregulation. Finally, the study expands the potential therapeutic use of ACDC TMS to treat not only OCD but potentially other disorders characterized by executive function deficits. By demonstrating effect in inhibitory control, we suggest that ACDC TMS could be applied to other conditions such as ADHD, addiction, or binge eating disorder. However, finding an effective protocol that will improve inhibitory control will be necessary. This can lead to the application of ACDC TMS as a flexible tool for targeting specific cognitive impairments across various psychiatric conditions.

5.7 Clinical and theoretical implications

Our findings hold clinical and theoretical implications for using ACDC TMS in preclinical and clinical cognitive neuroscience. Targeted stimulation of the ACC presents new possibilities for therapeutic interventions and advances our understanding of the neural mechanisms underlying inhibitory control and executive dysfunction.

One of the most promising clinical implications of this study is the potential for ACDC TMS to be developed as a targeted intervention for cognitive impairment in patients with obsessive-compulsive disorder. The results demonstrated that stimulation of the ACC using ACDC TMS can modify inhibitory control in OCD patients. Of course, we must admit that our study does not fully confirm this, but the treatment of patients cannot and will not consist of one TMS session. So, more studies with more sessions will be needed to prove this concept. However, for now, we see that ACC-targeted stimulation could help address the core symptoms of OCD related to cognitive rigidity, especially for individuals who do not respond well to traditional therapies, such as pharmacological or cognitive-behavioral therapy.

Our study again showed that the TMS studies with healthy participants addressing cognitive functioning mostly led to no significant effects. This can be related to the ineffectiveness of TMS (as the most critical point of view) or the problematic use of cognitive tasks in healthy populations looking at the ceiling effect. However, we would like to say it out loud: maybe TMS can only affect the dysfunctional brain circuits? Perhaps a healthy brain just “resisted” the stimulation, and that’s why we didn’t see even “objective” significant EEG results in our study with healthy participants. Unfortunately, we are still unable to answer this question with confidence, and further research should lead us to greater certainty. However, our previous studies with other neurostimulation techniques combined with the present one led us precisely to this thought (Klírová et al., 2021; Laskov et al., 2023; Laskov and Klírová, 2021).

5.8 Future directions in research on TMS and inhibitory control

We can see several avenues for future research to deepen our understanding and expand the clinical applicability of ACDC TMS:

- investigating the long-term effects of ACDC TMS on inhibitory control, preferably with multiple TMS sessions in a clinical population. So, longitudinal studies that incorporate follow-up assessments weeks or months after TMS treatment are needed to determine the duration of its effects and whether maintenance sessions could prolong or enhance cognitive improvements in patients with OCD and other disorders.

- determining the optimal frequency, intensity, and duration of stimulation sessions for enhancing inhibitory control. Given that different individuals may respond differently to stimulation, personalized TMS protocols that adjust parameters based on patient-specific characteristics (e.g., baseline inhibitory control and neural activity patterns) could enhance treatment efficacy. Additionally, investigating how varying the number of sessions or intervals between treatments affects outcomes could provide insight into the most effective therapeutic protocols for long-term improvements. Perhaps the future lies in the accelerated TMS protocols (Ozer et al., 2024). We still don’t know that.

Exploring the neurobiological mechanisms of ACDS TMS using neuroimaging, such as fMRI and EEG, could provide valuable insights into how TMS alters neural activity in the ACC and related brain regions in real time. Imaging studies could help confirm that ACDC

TMS modulates the CSTC circuit and identify how these changes correlate with behavioral improvements. This would strengthen the link between neural modulation and cognitive outcomes and contribute to developing more targeted interventions.

- using ACDC TMS in diverse clinical populations beyond OCD. As stated before, inhibitory control deficits are present in a wide range of psychiatric and neurological disorders. Examining how ACDC TMS affects inhibitory control in these populations would broaden its clinical utility and help establish it as a tool for cognitive enhancement. Additionally, comparative studies could investigate whether the efficacy of ACDC TMS differs across conditions and patient groups, offering insights into how specific neural dysfunctions may influence treatment response.

- personalization of the ACDC TMS application, which can lead to more precise treatment. For example, neuroimaging or genetic markers could help identify patients most likely to benefit from ACC-targeted stimulation. This could offer more effective TMS protocols, ensuring treatments are tailored to each patient's unique neurocognitive profile.

- real-world application. Finally, future research should focus on the real-world applicability of ACDC TMS. While laboratory-based tasks, such as the Stroop task, help measure inhibitory control in controlled settings, assessing whether TMS-induced improvements generalize to everyday situations is essential. Studies that examine the effects of TMS on real-world decision-making, emotional regulation, and impulse control in daily life could provide more valid measures of its effectiveness and would help bridge the gap between laboratory findings and clinical practice, ensuring that TMS interventions lead to meaningful improvements in patient's quality of life.

6 Conclusion

This thesis explored the effects of ACDC TMS on inhibitory control in healthy individuals and patients with OCD, aiming to deepen our understanding of cognitive impact. The findings present a mixed but intriguing picture of ACDC TMS's capacity to modulate inhibitory control, particularly in clinical populations. No significant behavioral or neurophysiological effects were observed in healthy participants, suggesting that ACDC TMS may not be as effective in modulating well-functioning inhibitory control networks. The lack of significant changes in the Stroop task and EEG measures, apart from a trend in theta power, underscores the potential resistance of a healthy brain to such interventions.

In contrast, the study on OCD patients yielded more interesting results, indicating that ACDC TMS could surprisingly worsen inhibitory control in populations with pre-existing cognitive impairments, which goes against the known, albeit few, studies and does not meet our hypothesis. Significant findings in error rates and event-related neural responses suggest that ACDC TMS may influence inhibitory control in patients with OCD. However, the nature of this effect remains complex. The unexpected result that sham stimulation led to more significant reductions in error rates highlights the need for further investigation into the mechanisms underlying high-frequency ACDC TMS.

From a broader perspective, this research aligns with previous studies on deep TMS but also introduces unique insights into how ACDC TMS could target specific executive dysfunctions, particularly in OCD. The study's novelty lies in its application of ACDC TMS and in examining its ability to influence inhibitory control. The findings suggest that while ACDC TMS may not significantly affect healthy cognitive functioning, it has the potential to be used in clinical populations with inhibitory control deficits. However, it will be necessary to find an effective protocol that can help patients with OCD and potentially other disorders with similar cognitive impairments.

Future research will be essential to confirm these results and further investigate optimal TMS protocols, long-term effects, and potential applications across a broader range of psychiatric and neurological conditions. By contributing to the growing body of literature on TMS and inhibitory control, this thesis lays the groundwork for developing more refined, patient-specific neurostimulation treatments that could improve cognitive outcomes in clinical practice.

7 Summary

The present thesis investigates the effects of anterior cingulate double cone (ACDC) transcranial magnetic stimulation (TMS) on inhibitory control in both healthy participants and patients with obsessive-compulsive disorder (OCD). Research suggests that impaired inhibitory control, a crucial executive function, plays a central role in OCD, marked by overactivity in the anterior cingulate cortex (ACC) and other parts of cortical-striatal-thalamic circuit. Traditional interventions for OCD have shown variable effectiveness, leading to exploration of alternative methods such as neuromodulation techniques. Among these, repetitive transcranial magnetic stimulation (rTMS), particularly deep TMS (dTMS) over the ACC, shows promise for targeting neural pathways involved in inhibitory control.

Thirty healthy participants and thirty OCD patients underwent active ACDC TMS or sham stimulation in a double-blind design. Pre- and post-stimulation performance on the Stroop task with simultaneous EEG was measured, with particular attention to reaction times, error rates, and ERN amplitude. Comparisons were made between the effects in healthy participants and OCD patients.

Across a sample of 58 subjects (28 healthy and 30 OCD patients), results showed that ACDC TMS led to increased ERN amplitudes in both groups; however only in patients with OCD the stimulation led to significant difference. Interestingly, the application of ACDC TMS in OCD patients also influenced error rates in the Stroop task, leading to higher number of errors after active stimulation. However, no significant behavioral effects were observed in the healthy participants, indicating a potentially selective impact of ACDC TMS in clinical populations.

In the discussion, the study addresses limitations such as sample size, the single-session protocol, and the influence of factors like symptom severity, medication, and task choice, which may account for variations in results across the literature. This thesis underscores the need for further investigation with optimized TMS protocols and larger samples to better delineate the therapeutic and research applications of ACDC TMS in cognitive modulation and OCD treatment.

8 Souhrn

Tato práce zkoumá účinky transkraniální magnetické stimulace (TMS) pomocí double cone cívky nad předním cingulem (ACDC TMS) na inhibiční kontrolu u zdravých dobrovolníků a pacientů s obsedantně-kompulzivní poruchou (OCD). Výzkumy naznačují, že narušení inhibiční kontroly, jedné z klíčových exekutivních funkcí, hraje v OCD ústřední roli a je spojena s hyperaktivitou v oblasti předního cingulárního kortexu (ACC) a dalších částích kortiko-striato-thalamického okruhu. Tradiční intervence pro OCD vykazují proměnlivou účinnost, což vedlo k hledání alternativních metod léčby, jako jsou například neuromodulační techniky. Mezi nimi se opakovaná transkraniální magnetická stimulace (rTMS), zejména hluboká TMS (dTMS) nad ACC, jeví jako slibná pro cílenou modulaci nervových drah.

Třicet zdravých účastníků a třicet pacientů s OCD podstoupilo aktivní ACDC TMS nebo sham stimulaci ve dvojité zaslepené studii. Před a po stimulaci byla měřena jejich výkonnost ve Stroopově testu za současného EEG záznamu, přičemž byla věnována zvláštní pozornost reakčním časům, počtu chyb a amplitudě ERN. Bylo provedeno srovnání účinků stimulace mezi zdravými účastníky a pacienty s OCD.

Na vzorku 58 osob (28 zdravých a 30 s OCD) výsledky ukázaly, že ACDC TMS vedla ke zvýšení amplitud ERN v obou skupinách; významné rozdíly však byly pozorovány pouze u pacientů s OCD. Zajímavé je, že aplikace ACDC TMS u pacientů s OCD také ovlivnila počet chyb ve Stroopově testu, kde po aktivní stimulaci došlo k většímu počtu chyb v porovnání se sham stimulací. U zdravých účastníků nebyly pozorovány žádné významné behaviorální účinky, což naznačuje možný selektivní efekt ACDC TMS u klinické populace.

V diskusi se zabýváme limity studií, jako je velikost vzorku, protokol s jednou stimulační aplikací a vliv faktorů, jako je závažnost příznaků, medikace a volba úkolu, které mohou vysvětlit rozdíly v publikovaných výsledcích. Tato práce zdůrazňuje potřebu dalšího výzkumu s optimalizovanými protokoly TMS a většími vzorky, aby byly lépe definovány terapeutické a výzkumné možnosti aplikace ACDC TMS v modulaci kognitivních funkcí a léčbě OCD.

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10 List of author's publications

Original scientific papers related to the dissertation topic:

Laskov, O., Biačková, N., Stuchlíková, Z., Kostýlková, L., Klírová, M., 2023. Inhibitory Control in Young Healthy Adults – a tDCS Study. *Physiological Research* 72, 633–644. <https://doi.org/10.33549/physiolres.935066>; IF 1.94

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