ISRCTN17144095 https://doi.org/10.1186/ISRCTN17144095

Predictors of response to deep transcranial magnetic stimulation treatment in obsessive-compulsive disorder

Submission date
02/11/2023

Recruitment status
Recruiting

Registration date
16/11/2023

Overall study status
Ongoing

Last Edited
16/11/2023

Condition category
Mental and Behavioural Disorders

[ ] Prospectively registered
[ ] Protocol
[X] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Repetitive transcranial magnetic stimulation (rTMS) is a method used for non-invasive brain stimulation. It's employed both for research purposes and as a treatment for various neurological and psychiatric disorders. Furthermore, it has been explored as a potential therapy for Obsessive-Compulsive Disorder (OCD). Traditionally, rTMS targets the prefrontal cortex, particularly the left, right, and bilateral dorsolateral prefrontal cortex, using a figure-of-eight coil.

In recent times, rTMS for OCD has focused on the dorsomedial prefrontal cortex, such as the anterior cingulate cortex, employing specialized coils like the H7 or double-cone coil to reach deeper into the cerebral hemispheres. Based on the findings of previous deep TMS (dTMS) studies in treating OCD, a recent analysis supports considering the H7-coil dTMS as the primary approach for individuals with treatment-resistant OCD, particularly those resistant to serotonin reuptake inhibitors (SRI-R).

However, the effectiveness of dTMS in reducing OCD symptoms varies significantly among patients. Approximately 50% of patients experience a significant decrease in OCD symptoms based on data from published dTMS studies. The presence of a considerable number of non-responders creates challenges, such as subjecting individuals to a treatment that doesn't benefit them, missing the opportunity for alternative treatments, and increasing healthcare costs.

To address these challenges, a research project aims to understand why some OCD patients do not respond to deep rTMS. The primary objective of the project is to investigate the effects of dTMS on the medial prefrontal cortex (mPFC) in OCD patients and identify the specific brain factors that might cause a lack of response to mPFC-dTMS.

In individuals with OCD, structural brain characteristics typically involve smaller volumes in certain mPFC regions, increased volume in the basal ganglia, and decreased volume in specific white matter regions. There are also functional changes in OCD, including altered communication between the ventromedial prefrontal cortex and the striatum, increased brain

wave activity when errors occur, and heightened amplitudes of slow-frequency EEG rhythms when the brain is at rest.

The project will test the hypothesis that the size and structure of certain brain regions before treatment can predict whether a patient will respond to dTMS. Additionally, the project will investigate changes in both gray matter and white matter in the brain after a six-week dTMS treatment to determine if the absence of these changes plays a role in non-responsiveness to dTMS.

The research will also examine pre-treatment levels of brain activity when errors are made, brain wave amplitudes at rest, functional brain activity when OCD symptoms are provoked, and communication within the mPFC as potential predictors of the response to dTMS treatment. The expectation is that changes in functional brain activity before and after treatment will be observed in individuals who respond positively to dTMS but not in non-responders.

Who can participate?
Adults aged 18-75 years with OCD.

What does the study involve?
The study includes a 6-week dTMS treatment with ongoing assessment of clinical status and repeated MRI and EEG examinations before and after dTMS treatment.

What are the possible benefits and risks of participating?
Benefits
Relief of OCD symptoms after dTMS treatment.
Risks
Adverse effects (AE) during dTMS treatment are usually very low, with headache being the most common AE. This AE should not lead to withdrawal and can be managed with non-prescription pain medication.

Where is the study run from?
National Institute of Mental Health (Czechia)

When is the study starting, and how long is it expected to run for?
May 2023 to February 2028

Who is funding the study?
National Institute of Mental Health (Czechia)

Who is the main contact?
Assoc. Prof. Monika Klírová M.D., Ph.D., monika.klirova@nudz.cz

Contact information

Type(s)
Public, Scientific, Principal Investigator

Contact name
Prof Monika Klírová

ORCID ID

http://orcid.org/0000-0002-8092-9586

Contact details
National Institute of Mental Health
Topolová 748
Klecany
Czech Republic
250 67
+420 774325110
monika.klirova@nudz.cz

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
AZV-2024-1-0002 (RZPRO)

Study information

Scientific Title
Neural Predictors of Treatment Response to Deep Transcranial MAgnetic Stimulation (dTMS) of Medial Prefrontal Cortex in Obsessive-COmpulsive Disorder

Acronym
MASCOD

Study objectives
1. The volume of the striatum and medial frontal cortex (mPFC) prior to a course of a 6-week deep transcranial magnetic stimulation (dTMS) therapy will differentiate responders (>35 % drop in obsessive-compulsive disorder (OCD) symptoms) and non-responders.
2. The volume of the mPFC will increase following a course of dTMS therapy, especially in responders.
3. The structure of white matter (WM) in the sagittal stratum and cingulate bundle prior to treatment will differentiate responders and non-responders.
4. Functional connectivity (FC) of the striatum with (mPFC) and the orbitofrontal cortex (OFC) prior to treatment will differentiate dTMS non-responders from responders, and the FC will change following treatment in responders but not in non-responders.
5. Hyperactivation in different brain regions during symptom provocation prior to treatment will differentiate responders from non-responders, and activations in involved brain regions will decrease following treatment in responders but not in non-responders.
6. Amplitudes of delta and theta oscillations prior to treatment will differentiate dTMS responders and non-responders; amplitudes of delta and theta oscillations will decrease following treatment in responders but not in non-responders.

7. The amplitude of the error-related negativity (ERN) in the arrowed flanker task prior to treatment will differentiate dTMS responders and non-responders; ERN will decrease following a course of dTMS more in responders than in non-responders.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 18/05/2023, National Institute of Mental Health Ethics Committee (Topolova 748, Klecany, 25067, Czech Republic; +420 (0)283 088 312; ek@nudz.cz), ref: 102/23

Study design
Randomized parallel-group double-blind placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Other

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Obsessive-compulsive disorder

Interventions
Patients diagnosed with OCD will be included in the study.

Visit -1 (-20 - 0 days):
Anamnesis, including demographic data and medical history, checking the adequate maintenance treatment.
Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), Hamilton Depression Rating Scale (HAM-D), and Clinical Global Impression Scale (CGI).
Assessment of whether the subject can be included in the study, including determination of the motor threshold.
Informed consent.

Next, subjects will be randomly assigned to one of the groups (active n=60, sham n=15).

Visit MRI (-7 – 0 days).

Visit EEG (-7 – 0 days).

Visit 0 (-2 – 0 days): Y-BOCS, HAM-D, CGI, checking medications, if used.

dTMS:
Active stimulation: 20Hz mPFC-dTMS, 100% of motor threshold, 40 trains, 50 pulses per train, 18 minutes duration; 2000 pulses per session; 28 sessions in 6 weeks. Placebo: sham-dTMS applied to mPFC; 28 sessions in 6 weeks.
All mPFC-dTMS applications will be preceded by OCD symptoms provocation for five minutes before the start of the mPFC-rTMS/sham session (according to FDA protocol for rTMS in OCD).

Subjects will be on stable medication during the acute phase of the study (deep TMS treatment) if taken and on maintenance psychotherapy if attending.

Visit 1 (14 ± 2 days): Y-BOCS, HAM-D, CGI, and side effect TMS assessment, checking medications, if used.

Visit 2 (28 ± 2 days): Y-BOCS, HAM-D, CGI, and side effect TMS assessment, checking medications, if used.

Visit 3 (42±2 days): Y-BOCS, HAM-D, CGI, and side effect TMS assessment, checking medications, if used.

Visit MRI II (42 + 7 days).

Visit EEG II (42 + 7 days).

Follow-up visit 4W (70 ± 5 days): Y-BOCS, HAM-D, CGI, checking medications, if used.

Follow-up visit 12W (126 + 5 days): Y-BOCS, HAM-D, CGI, checking medications, if used.

Intervention Type
Device

Pharmaceutical study type(s)
treatment prediction (neural prediction of deep TMS efficacy in OCD treatment)

Phase
Phase III

Drug/device/biological/vaccine name(s)
MagPro R30 with a double-cone coil (Magventure) and deep TMS (DTMS) System with H7 coil (Brainsway). The first ten patients will be stimulated with MagPro R30 using a double-cone coil device, and the remaining 65 with a deep TMS system using an H7 coil.

Primary outcome measure
Neuronal predictors of therapeutic success of mPFC-dTMS in OCD patients using MRI by evaluating pre- and post-treatment dTMS-mPFC changes in grey matter (GM) in the anterior cingulate cortex (ACC), mPFC, OFC, and striatum, and WM in selected tracts and bundles using fMRI.

Secondary outcome measures

Neuronal predictors of therapeutic success of mPFC-dTMS in OCD patients using EEG and MRI by evaluating pre- and post-treatment dTMS-mPFC changes in:
1. EEG resting state oscillations;
2. ERN during the Flanker task;
3. Resting-state FC of the ACC, striatum, and the prefrontal cortex (PFC)/OFC
4. Blood oxygenation level-dependent (BOLD) - functional MRI (fMRI) activations during the exposure to individual OCD symptoms-related visual stimuli.

Overall study start date
18/05/2023

Completion date
28/02/2028

Eligibility

Key inclusion criteria
1. Male and female outpatients aged 18-70 years;
2. Meeting DSM-V criteria for OCD;
3. Patients having completed at least one unsuccessful but adequate antidepressant treatment according to criteria for treatment-resistant OCD (treatment history is sufficient);
4. Being able to understand and sign the Informed Consent Form;
5. Being on a stable and adequate dose of antidepressants and/or antipsychotics (monotherapy or combination) for at least eight weeks before the commencement of dTMS, if used.
6. Y-BOCS score ≥20 corresponding to the Severity scale ≥ three on Clinical Global Impression on the initial visit.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
70 Years

Sex
Both

Target number of participants
75

Key exclusion criteria
1. Psychiatric comorbidity on axis I and II according to DSM V six months before enrollment to the study except for depressive, anxiety, and obsessive-compulsive related disorders;
2. Personality disorder that makes participation in the trial difficult;

3. History of substance dependence in the last year except for nicotine;
4. Contraindications of rTMS/dTMS treatment;
5. Pregnancy or breast-feeding;
6. Patients with severe somatic disorders (cardiovascular disease, neoplasms, endocrinology disorders, etc.);
7. Patients treated with electroconvulsive therapy less than three months before enrollment or suffering from neurologic disorder (e.g., epilepsy, head trauma with loss of consciousness) and patients using any treatment that can strongly affect EEG;
8. Substantial suicidal risk as judged by the treating psychiatrist;
9. Sensory and motor impairment precluding the participation in computer tests.

Date of first enrolment
20/07/2023

Date of final enrolment
31/12/2027

Locations

Countries of recruitment
Czech Republic

Study participating centre
National Institute of Mental Health
Topolova 748
Klecany
Czech Republic
250 67

Sponsor information

Organisation
3rd Medical Faculty, Charles University

Sponsor details
Ruská 87
Prague
Czech Republic
100 00
+420 774325110
pavlina.gembicky@lf3.cuni.cz

Sponsor type
University/education

Website

https://www.lf3.cuni.cz

Funder(s)

Funder type
Government

Funder Name
National Institute of Mental Health, Czechia

Results and Publications

Publication and dissemination plan
Data will be published in peer-reviewed journals with IF (Q1, Q2) after completion of the study. Preliminary and final results will also be communicated at scientific international conferences and to the public at educational public lectures.

Intention to publish date
31/12/2028

Individual participant data (IPD) sharing plan
After the article's publication, de-anonymized data will be made available for non-commercial academic projects. Data can be obtained by request to the corresponding author (Monika Klírová, monika.klirova@nudz.cz). The de-anonymized data files with a dictionary will be provided via a secure data transfer service.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Statistical Analysis Plan			06/11/2023	No	No