

# Examining non-invasive brain stimulation for the treatment of depression

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		<input type="checkbox"/> Protocol
<b>Registration date</b> 26/07/2022	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan
		<input type="checkbox"/> Results
<b>Last Edited</b> 10/11/2023	<b>Condition category</b> Mental and Behavioural Disorders	<input type="checkbox"/> Individual participant data
		<input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Major depressive disorder (MDD), often referred to as depression, is one of the most common mental health conditions in the world. The symptoms of MDD can vary greatly from person to person, but they generally include low mood, problems with sleeping and/or eating, and a general loss of interest in life. Treatment often relies heavily on antidepressant medications, which work by increasing the activity and levels of a group of chemicals in the brain (neurotransmitters). Although many people benefit from antidepressant treatment, it does not work for everyone and so other treatment options are essential.

Over the last decades, a type of brain stimulation that uses magnetic fields to stimulate brain cells called repetitive transcranial magnetic stimulation (rTMS) has received increasing attention as a treatment for MDD. The treatment is considered to be a safe way to change brain function with limited and short-term side effects.

This study looks at the stimulation (TMS) of deeper located brain structures that have been shown to be involved in the development of MDD. The study aims to compare the effects of a deep stimulation with convention stimulation and a dummy (sham) procedure as an additional treatment to standard antidepressant treatment.

### Who can participate?

Adult right-handed outpatients and inpatients suffering from MDD who have not responded to previous treatment

### What does the study involve?

Participants are randomly allocated into one of three groups. After several days of not receiving any treatment for depression, participants are started on a six-week treatment plan. Those in group one are treated with antidepressant and deep stimulation, those in group two are treated with antidepressant and conventional stimulation, and the last group is treated with antidepressant and sham stimulation. Stimulation treatment is designed to 4-week period. Antidepressant will be applied for six weeks. The participants have their brain activity measured by electroencephalography (a method of recording brain activity) three times during the six weeks treatment period.

What are the possible benefits and risks of participating?

A possible benefit is the improvement of depressive symptoms. There is no substantial risk of participating, other than the possibility of medication side effects or side effects of stimulation methods. Both rTMS methods are generally well-tolerated, the main side effects are transient headache, scalp discomfort at the site of stimulation, tingling, spasms or twitching of facial muscles itching, tingling or burning sensation.

Where is the study run from?

National Institute of Mental Health (Czech Republic)

When is the study starting and how long is it expected to run for?

June 2021 to December 2025

Who is funding the study?

Ministry of Health (Czech Republic)

Who is the main contact?

Dr Martin Bares

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## Contact information

### Type(s)

Principal Investigator

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## Additional identifiers

### EudraCT/CTIS number

Nil known

### IRAS number

### ClinicalTrials.gov number

Nil known

### Secondary identifying numbers

## Study information

### Scientific Title

Dorsomedial prefrontal cortex repetitive transcranial magnetic stimulation in the augmentation of antidepressants (DOPRERA study). Efficacy, tolerability and neurophysiological changes

### Acronym

DOPRERA

### Study objectives

1. Compare efficacy/tolerability of dorsomedial prefrontal cortex-repetitive transcranial magnetic stimulation (dmPFC-rTMS) and high-frequency repetitive transcranial magnetic stimulation (HF-rTMS) over the left dorsolateral prefrontal cortex (DLPFC) with sham rTMS in the augmentation of standard antidepressant treatment (selective serotonin reuptake inhibitors; SSRI)
2. Identify the electrophysiological sequelae of dmPFC-rTMS, HF-rTMS of left DLPFC and sham rTMS in the augmentation of SSRI in the a priori defined ROI (current density, connectivity)
3. Identify clinical and electrophysiological predictors of treatment response

### Ethics approval required

Ethics approval required

### Ethics approval(s)

Approved 16/06/2021, Ethics committee of National Institute of Mental Health Czech Republic (Topolova 748, Klecany, 25067, Czech Republic; +420283088200; ek@nudz.cz), ref: 112/21

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### Study design

Six-week double-blind three-arm randomized sham-comparator-controlled active-comparator-controlled study

### Primary study design

Interventional

### Secondary study design

Randomised controlled trial

### Study setting(s)

Hospital

### Study type(s)

Treatment

### Participant information sheet

No participant information sheet available

## **Health condition(s) or problem(s) studied**

Depressive disorder

## **Interventions**

Following an initial wash-out period (2-5 days), eligible subjects will receive a 6-week treatment. They will be randomly allocated in a 1:1:1 ratio (no stratification) to either dmPFC-rTMS +SSRI, HF-rTMS left DLPFC + SSRI and sham stimulation+SSRI groups. RTMS will be delivered using the MagPro R30 stimulator (MagVenture, Denmark) and Cool D-B80 A/P (dmPFC-rTMS)/Cool-B65 A/P (conventional rTMS) with both an active and a placebo side that enables the rTMS operator to stay blinded. To empower the masking process, surface electrodes connected to the electric stimulator will be used for all treatments to mimic scalp sensation accompanying active rTMS. Patients in all three groups will undergo 20 sessions of rTMS (active ones or sham) each weekday (Mon-Fri) within the four weeks. The rTMS parameters (number of stimuli and trains, stimulation frequency, intensity etc. are derived from Kreuzer study except for the higher number of sessions. The resting motor threshold (RMT) that will be determined for the right abductor digiti minimi muscle.

1. DmPFC-rTMS +SSRI group (Group 1): Patients assigned to group 1 will take standard antidepressants from the SSRI class (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram) in flexible doses within the range cited in the Summary of Product (SPC) for six weeks. The new SSRI will be chosen according to clinical judgment of the attending psychiatrists and with respect to the history of previous treatments, clinical status (anxiety, insomnia, psychomotor retardation etc.). The SSRI that has been ineffective in the treatment of the current episode will be excluded. DMPFC-rTMS will be delivered at 110% of RMT) at 10 Hz, for a total of 2000 pulses in 40 trains of 50 stimuli and an intertrain interval of 25 s). Coil positioning will follow the protocol described by Hayward et al. positioning the coil 1.5 cm anterior to one third of the distance from the nasion to theinion with the handle of the coil oriented in sagittal direction along the midline 22.

2. HF rTMS left DLPFC + SSRI (Group 2): Patients will be treated with SSRI's in the same manner as in Group 1. Coil will be positioned over DLPFC using F3 Beam algorithm and be held tangentially to the scalp with its handle pointing back and away from the midline at 45°.

3. Sham stimulation +SSRI (Group 3): There are the same principles and limits for SSRI treatment as in Group 1. Sham rTMS/dmPFC-rTMS with sham coils will be applied to left DLPFC or dmPFC (randomly per ten subjects).

Randomization: block random with random block size (6) with either dmPFC-rTMS treatment or HF rTMS and placebo sham HF rTMS and sham dmPFC-rTMS a P2 in ratio 2:2:1:1

## **Intervention Type**

Mixed

## **Primary outcome measure**

Change in the severity of depressive episodes measured using the Montgomery and Åsberg depression rating scale (MADRS) score from baseline to week 6

## **Secondary outcome measures**

1. Response to treatment, defined as a reduction of total MADRS score  $\geq 50\%$ , after 6 weeks of treatment
2. Remission defined as an increase in MADRS  $\geq 10$  points at the end of the study

3. Number of drop-outs from the study for any reason measured using the number of subjects who do not finish the study treatment from baseline to week 6

**Overall study start date**

01/06/2021

**Completion date**

31/12/2025

## **Eligibility**

**Key inclusion criteria**

1. Patients (outpatients or inpatients) suffering from MDD (recurrent or single episode) diagnosed according to Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V), confirmed using The Mini-International Neuropsychiatric Interview - M.I.N.I., Czech Translation version 7.0.2 33,34
2. Patients fulfilling at least Stage I ( $\geq 1$  previous, unsuccessful, adequate, antidepressant treatment) criteria for resistant depression according to Thase and Rush
3. The mental ability to understand and sign the Informed Consent Form
4. The score on the Montgomery and Åsberg Rating Scale (MADRS)  $\geq 25$
5. Aged 18-70 years old
6. Right-handedness
7. Duration of current episode of depression  $>1$  but  $\leq 12$  months

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

18 Years

**Upper age limit**

70 Years

**Sex**

Both

**Target number of participants**

group dmPFC-rTMS - 20 participants; group HF rTMS - 20 participants; group sham Hf rTMS /dmPFC rTMS - 20 participants, total number of participants - 60

**Key exclusion criteria**

1. History of any other DSM-V diagnosis other than MDD, except anxiety disorders in the last year
2. Personality disorder that makes participation in the trial difficult
3. History of substance dependence in the last year except nicotine
4. Contraindications of SSRI's treatment according to SPC
5. Contraindications of rTMS:
  - 5.1. History of epilepsy or any neurologic condition likely to increase risk of seizure

- 5.2. Mass brain lesions
- 5.3. Cerebrovascular accident
- 5.4. Metal in the head
- 5.5. History of major head trauma with unconsciousness
6. Pregnancy or breastfeeding
7. Patients with severe somatic disorders (cardiovascular disease, neoplasms, endocrinology disorders, etc) that could be associated with depression due to somatic diseases
8. Patients treated with electroconvulsive therapy less than 3 months before enrollment or suffering from neurologic disorder (e.g., epilepsy, head trauma with loss of consciousness) and patients using any treatment which can strongly affect EEG
9. Application of other concomitant medication that is not allowed in protocol (e.g. antipsychotics, mood stabilizers, etc.)
10. Unsuccessful treatment with more than one SSRI antidepressants or rTMS treatment in the current episode of MDD
11. Fluoxetine treatment before the enrollment in the study

**Date of first enrolment**

13/04/2022

**Date of final enrolment**

01/09/2025

## **Locations**

**Countries of recruitment**

Czech Republic

**Study participating centre**

**National Institute of Mental Health Czech Republic**

Topolova 748

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Czech Republic

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## **Sponsor information**

**Organisation**

Czech Health Research Agency

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**Sponsor type**

Research council

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## **Funder(s)**

**Funder type**

Research council

**Funder Name**

Agentura Pro Zdravotnický Výzkum České Republiky

**Alternative Name(s)**

Czech Health Research Council, AZV ČR

**Funding Body Type**

Government organisation

**Funding Body Subtype**

Local government

**Location**

Czech Republic

## **Results and Publications**

**Publication and dissemination plan**

Planned publication in a high-impact peer-reviewed journal

**Intention to publish date**

30/06/2026

**Individual participant data (IPD) sharing plan**

The data sharing plans for the current study are unknown and will be made available at a later date

**IPD sharing plan summary**

Data sharing statement to be made available at a later date