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Examining non-invasive brain stimulation for the treatment of depression

Submission date
22/06/2022

Recruitment status
No longer recruiting

Registration date
26/07/2022

Overall study status
Ongoing

Last Edited
10/11/2023

Condition category
Mental and Behavioural Disorders

- [ ] Prospectively registered
- [ ] Protocol
- [ ] Statistical analysis plan
- [ ] Results
- [ ] Individual participant data
- [ ] 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 convetional 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

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
NU22-04-00192

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

Approved 16/06/2021, Ethics Committee of the National Institute of Mental Health Czech Republic (Topolová 748, 250 67 Klecany, Czech Republic; +420288003312; ek@nudz.cz), ref: 112 /21

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

Primary study design
Interventional

Study type(s)
Treatment

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

Key secondary outcome(s))
1. Response to treatment, defined as a reduction of total MADRS score ≥ 50%, after 6 weeks of treatment
2. Remission defined as an increase in MADRS ≥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

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 (≥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) ≥25
5. Aged 18-70 years old
6. Right-handedness
7. Duration of current episode of depression >1 but ≤ 12 months

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
70 years

Sex
All

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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Sponsor information

Organisation
Czech Health Research Agency

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

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes