Enhancing effect of dual interventions versus conventional TMS in the treatment of depression

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rTMS is an intensive but effective treatment that could benefit from further optimization. Cognitive control training (CCT) engages the same underlying neural circuitry as rTMS and has been shown to improve therapeutic response (Koster et al., 2017…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Depressed mood disorders and disturbances
Study type	Interventional research previously applied in human subjects

Summary

ID

NL-OMON57187

Source
ToetsingOnline

Brief title
DIRECT-TMS

Condition

- Depressed mood disorders and disturbances

Synonym
Depression Major Depressive Disorder

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: ZonMW

Intervention

- Psychosocial intervention

Keyword: Cognitive control training, Depression, Transcranial Magnetic Stimulation

Explanation

N.a.

Outcome measures

Primary outcome

Effectiveness of rTMS augmented with a CCT task as opposed to rTMS combined with a placebo task, as assessed by clinician-rated change in depressive symptom severity measured with the HDRS-17.

Secondary outcome

Cost-effectiveness of rTMS + CCT versus rTMS + placebo task.
Response, defined as >50% reduction in score on the HDRS-17.
Remission, defined as HDRS-17 <8.
Clinician-rated change in depressive symptom severity, assessed by change in HDRS-17 score over time during follow-up.
Subjective assessment of change in depression symptoms with the self-rated version of the IDS (IDS-SR) after 8 weeks of treatment and during follow-up.
Recurrence of depressive symptoms, assessed by change in remitter status between end of treatment and follow-up measurements.

Study description

Background summary

Repetitive transcranial magnetic stimulation (rTMS) is an effective treatment option for depression (level A evidence, definite efficacy; LeFaucheur et al., 2020). Unfortunately, not every patient responds (fully) to rTMS. Cognitive control training is proven effective as add-on treatment on top of treatment as usual, with less relapse during follow-up, and it can even induce synergistic effects. When simultaneously administering rTMS and a cognitive task, the *state-dependent* effects of rTMS are boosted might which results in an optimization of the therapeutic response. As rTMS is a time-consuming treatment, with patients receiving on average 25-30 30-minute treatment sessions, combining the two interventions leads to an efficient, pragmatic and cost-effective solution to increase effectiveness.

Study objective

rTMS is an intensive but effective treatment that could benefit from further optimization. Cognitive control training (CCT) engages the same underlying neural circuitry as rTMS and has been shown to improve therapeutic response (Koster et al., 2017; Motter et al., 2016; Legemaat et al., 2022). Simultaneous application of rTMS and a CCT task might further enhance treatment effectiveness in an efficient manner (Li et al., 2016). Our primary objective is therefore to assess the (cost-)effectiveness of rTMS augmented with CCT as opposed to rTMS combined with a placebo task.

Study design

A randomized multicenter clinical trial consisting of eight weeks of treatments and follow-up assessments up to twelve months.

Intervention

Treatment will consist of 30 rTMS sessions in an 8-week period. The rMT will be defined in each participant during the baseline assessment. Treatment will target the left dorsolateral prefrontal cortex (DLPFC). We will use BeamF3 (freely available software) to find the DLPFC, which is based on electrode position F3 from the EEG 10-20 system. The coil will be positioned over this location at an angle of 45° relative to the midline. rTMS will be conducted using a high-frequent protocol, applying 75 trains of 10Hz pulses with a duration of 4s and an inter-train interval of 11s over the left DLPFC (40 pulses per train, 3000 pulses per session), with an intensity of 120% of the rMT.

A progressive dual n-back task as described by Jaeggi et al. will be used as CCT task. Visuospatial and auditory stimuli will be presented simultaneously to the patient. The patient has to remember the location of stimuli and auditory sounds and is supposed to respond when either the location or sound is the same as n-turns back, starting at n=2. If the patient scores >=0.9 the level of the dual n-back is increased, to for instance n=3. If the score of the patient is <=0.9 the n-back level is lowered. One block consists of 20+n trials, each trial has a duration of 3000 ms. The visual spatial stimuli consist of blue squares projected on a computer screen at 9 different locations. The auditory stimuli consist of eight consonants presented through headphones. In the placebo condition patients will be passively view the visuospatial stimuli and passively listen to the auditory stimuli.

Study burden and risks

Benefits: Decrease in depressive symptoms

Risks: Transcranial magnetic stimulation (TMS) is a non-invasive brain stimulation technique, based on the principle of electromagnetic induction. The discharge of the TMS coil generates a hearable noise (*click*) and the participant might experience sensations originating from the potential stimulation of peripheral nerves outside the skull and the potential contraction of facial or neck muscles. The most common side effect is a transient light headache (2-4%

occurrence) which is usually short lasting and can be sufficiently treated with light painkillers like paracetamol. A severe headache is uncommon (0.3-0.5% occurrence). There is no report of TMS causing a severe adverse event (such as an epileptic seizure) in healthy participants when using TMS protocols that accord to the published safety guidelines (Rossi et al., 2020). When stimulation parameters significantly exceed these guidelines (e.g., a higher intensity, frequency, or amount of stimulation), or when patients with a lowered cortical excitability threshold (e.g., as a consequence of epilepsy or drug treatment) are stimulated, the risk of inducing a seizure are increased from negligible to minimal. Please note that that all TMS parameters are within the range considered safe according to the latest published safety guidelines. The magnetic field of TMS can affect metal and electrical devices close to the coil. Therefore, large or ferromagnetic metal parts in the head (except for a dental wire behind the teeth), or the presence of a cardiac pacemaker or neurostimulator are strict exclusion criteria. All subjects are screened for their relevant medical history and other aspects concerning the safety of TMS application. All investigators involved in the study are well trained and qualified, and the used equipment adheres to the required international safety standards. In summary, because the risk and burden associated with participation can be considered negligible-to-minimal, we do not expect serious adverse events during the project.

Contacts

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Trial sites

Trial sites in the Netherlands

Maastricht Universitair Medisch Centrum +
Target size: 12

Radboud Universitair Medisch Centrum
Target size: 36

GGZ inGeest in samenwerking met Amsterdam UMC
Target size: 24

Listed location countries

Belgium, Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Age 18 years and older
- Current depressive episode with moderate or severe depression (HDRS-17 >16)
- Indicated for treatment with rTMS, i.e. inadequate response to >=2 adequate treatment trials
- Ability to perform CCT task
- Stable treatment for at least 6 weeks

Exclusion criteria

- Lifetime diagnosis of bipolar disorder, schizophrenia or schizoaffective disorder
- Current psychotic depressive episode
- Meeting criteria of stimulant use disorder in the last 6 months or opioid use disorder in
the last 12 months
- Organic brain syndrome
- Substance*induced psychiatric conditions or substance-related medical conditions
(e.g. delirium tremens)
- Presence of a concurrent significant medical condition impeding the ability to participate
- Seizure disorders
- Serious head trauma or brain surgery
- Large or ferromagnetic parts in the head (except for a dental wire)
- Implanted neurostimulator

- Pregnancy

Study design

Design

Study phase:	N/A
Study type:	Interventional research previously applied in human subjects
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Other type of control
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-02-2025
Enrollment:	72
Duration:	12 months (per patient)
Type:	Actual

WORLD

Recruitment status:	Recruiting
Start date (anticipated):	01-01-2025
Enrollment:	132
Type:	Actual

Medical products/devices used

Product type:	N.a.
Registration:	Yes - CE intended use

IPD sharing statement

Plan to share IPD: Yes

Plan description

De data worden 'upon reasonable request' beschikbaar gesteld in een data repository

Ethics review

Approved WMO Date:	18-12-2024
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-01-2025
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-05-2025
Application type:	Amendment
Review commission:	METC Oost-Nederland

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL87510.091.24
Research portal	NL-005301