rTMS and cognitive control training in the context of depression

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Ethical review	Approved WMO
Status	Completed
Health condition type	Mood disorders and disturbances NEC
Study type	Interventional

Summary

ID

NL-OMON50907

Source
ToetsingOnline

Brief title
rTMS + CCT

Condition

- Mood disorders and disturbances NEC

Synonym
depression major depressive disorder

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Afdeling Psychiatrie Radboudumc

Intervention

Keyword: cognitive control training, mood, rTMS

Outcome measures

Primary outcome

Our primary outcome is change in PANAS score from pre- to post-intervention,

between conditions.

Secondary outcome

Our secondary outcome is change in Stroop performance from pre- to

post-intervention, between conditions.

Study description

Background summary

rTMS is increasingly used to treat depression at various stages of severity and has been shown to be effective, however, with response percentages of about 40% and remission percentages of about 30%, there is still room for improvement (Berlim, Van den Eynde, & Daskalakis, 2013a, 2013b; Berlim, van den Eynde, Tovar-Perdomo, & Daskalakis, 2014). One of the theories regarding the working mechanisms of rTMS concerns neural modulation of brain regions mediating cognitive control. Cognitive control is closely associated with affective disorders, as it plays a critical role in emotion regulation processes (Ochsner & Gross, 2005). Mood improvement after treatment with rTMS could be the result of improved cognitive control or emotion regulation processes. Indeed, studies have shown that rTMS over the left DLPFC increases the excitability of this region (Fitzgerald et al., 2006; Schutter, 2010), which has been implicated as the functional basis of cognitive control (Carter & van Veen, 2007; Miller, 2000). Additionally, cognitive control has been shown to improve in both healthy participants and depressed patients after stimulating the DLPFC with rTMS (Corlier et al., 2020; Pulopulos et al., 2020). Cognitive control training is another treatment strategy that has been used for depression. CCT has been shown to be effective in reducing depressive symptoms (Siegle, Ghinassi, & Thase, 2007; Siegle et al., 2014), and results in increased efficiency of the frontoparietal network and other brain regions implicated in affective and cognitive control, notably the anterior cingulate cortex (Kim, Chey, & Lee, 2017; Schweizer, Grahn, Hampshire, Mobbs, & Dalgleish, 2013). In addition, the

n-back task, which is often used in CCT, has been shown to robustly activate the DLPFC (Owen, McMillan, Laird, & Bullmore, 2005).
Both rTMS and CCT are effective treatment strategies for depression, and both target and activate the DLPFC, which is thought to play a hub function in the dynamic shift between the cognitive executive and salience network in particular (Peters, Dunlop, & Downar, 2016). In a previous experiment we have shown that active versus sham stimulation of the left DLPFC resulted in a different susceptibility to mood induction (Mobius et al., 2017), which in turn may affect cognitive control. Negative mood induction is a common experimental manipulation, aimed at momentarily changing the mood of a participant in a controlled manner.

Study objective

In this study, we want to combine rTMS and CCT to assess whether the combination of these two treatment would have synergistic effects and strengthen each other. We specifically want to assess the effect on mood and cognitive control, in a group of healthy participants. We hypothesize that the combination of active rTMS and CCT results in a smaller decrease in mood after negative mood induction as compared to either treatment alone. We also hypothesize that the combination of active rTMS and CCT will result in a smaller decrease in cognitive control, as a result of the negative mood induction, as compared to either treatment alone.

Primary Objective: Our primary objective is to assess the effect of the combination of active rTMS and CCT on mood after negative mood induction in healthy participants, compared to rTMS combined with a control task and sham rTMS combined with CCT.

Secondary Objective(s): Our secondary objective is to assess the effect of the combination of active rTMS and CCT on cognitive control after negative mood induction in healthy participants, rTMS combined with a control task and sham rTMS combined with CCT.

Study design

We want to include 40 participants in this randomized single-blind cross-over study. Participants will be seen thrice in the lab, with a one-week interval. The estimated total time is 3 hours and 45 minutes. Session one has an estimated duration of 45 minutes, whereas the estimated time for session 2 and 3 is 1,5 hours each. See figure 1 for an overview of the study design.

The first 20 participants will receive the control condition consisting of active rTMS combined with a control task. The order of the control and experimental condition will be counterbalanced. After 20 participants, we will perform an interim analysis to assess the results thus far. If the results are

in line with our hypotheses, we will include the next 20 participants, which will receive the experimental condition and the other control condition, consisting of sham rTMS combined with CCT. The order will again be counterbalanced. If we do not find a difference between the experimental condition and control condition 1 based on the interim analysis, we will terminate the study. With this cost-effective design we hope to first establish whether the combination of rTMS and CCT adds something to the current situation, which is rTMS alone. In our study, this is represented as rTMS combined with a control task. After we have established this, we can further examine the effects of the treatment by also looking into sham rTMS combined with CCT.

Intervention

Transcranial Magnetic Stimulation (TMS)
TMS will be performed in line with the DCCN Standard Operating Procedure for non-invasive brain stimulation. Transcranial magnetic stimulation (TMS) is a widely used non-invasive brain stimulation technique, based on the principle of electromagnetic induction (Rossi et al., 2020). During stimulation, the participant will likely hear the clicks of the TMS pulses and experience stimulation of nerves and muscles in the scalp. All known side-effects of TMS are transient and occur during or immediately after the stimulation session. Importantly there is no evidence for long-lasting side-effects of TMS. The stimulation parameters relevant for the assessment of the safety, risk and burden of online and short-term TMS studies are the intensity, quantity, frequency, and duration of stimulation (with higher doses elevating the risks), and the site of stimulation (with stimulation over facial muscles and nerves being less comfortable than stimulation elsewhere). In addition, for long-term TMS studies the repetition rate and number of stimulation sessions is also relevant.
The most common side-effect of online and short-term TMS protocols 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 have been several reports of reflexive syncope occurring in relation to TMS stimulation, but it is unclear if the stimulation itself or the context of study participation is causative of this side-effect (Rossi et al., 2020). In rare cases an epileptic seizure has been unintentionally induced by TMS before international consensus guidelines were established. Importantly, there is no report of TMS causing a severe adverse event (including epileptic seizures) 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 otherwise higher doses 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 is still minimal. Please note that all parameters of online and short-term TMS protocols are within the range considered safe according to the

latest published safety guidelines (Rossi et al., 2020). For example, to assess whether the risk of a TMS study protocol is considered minimal, we follow (Rossi et al., 2020) which refers to table 4 of (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). This table lists guidelines for stimulation frequency, intensity, and number of pulses.

Different tasks can be used for cognitive control training, the n-back task is one of them (Koster, Hoorelbeke, Onraedt, Owens, & Derakshan, 2017). In this study, we will use the version of the task that has been described elsewhere (Jaeggi et al., 2007; Jaeggi, Buschkuehl, Jonides, & Perrig, 2008). In this dual n-back task, squares are presented at eight different locations sequentially on a computer screen. The stimulus is presented for 500 ms, the inter-stimulus interval is 2500 ms. Simultaneous with the presentation of the squares, one of eight consonants will be presented sequentially through headphones. A response is required when one of the presented stimuli, either auditory or visually, matches one of the stimuli presented n positions back in the sequence. The value of n is the same for both auditory and visual stimuli. There will be six auditory and six visual targets per block (four appearing in only one modality, and two appearing in both modalities simultaneously), and their positions will be determined randomly. Participants respond by pressing on the letter *A* for visual targets, and on the letter *L* for auditory targets. No responses are required for non-targets. The level of difficulty will be varied by changing the level of n. After each block, the performance of a participant is analysed, and in the following block, the level of n is adapted accordingly. If the participants makes fewer than three mistakes per modality, n is increased by one. If more than five mistakes are made, n is decreased by 1. In all other cases, n remains unchanged. The task consists of 20 blocks, each consisting of 20 + n trials, resulting in a total of ~ 25 minutes.
As a control task, the single n-back task will be used. In this version, only visual stimuli are presented. Furthermore, n will remain constant at 1, to make this an easier version of the n-back task used for CCT that is still very similar.

Study burden and risks

Considering the extensive exclusion criteria, the screening procedure, constant monitoring of the subjects we do not expect (S)AE side effects. MRI measurements themselves do not pose any risk, if appropriate precautions are made. However, the noise and the relative confined space of the MRI scanner may cause discomfort to some subjects.
As described in the Donders non-invasive brain stimulation SOP: transcranial magnetic stimulation (TMS) is a widely used non-invasive brain stimulation technique, based on the principle of electromagnetic induction (Rossi et al., 2020). During stimulation, the partici-pant will likely hear the clicks of the TMS pulses and experience stimulation of nerves and muscles in the scalp. The most common side-effect of online and short-term TMS proto-cols is a light

transient headache. A severe transient headache is uncommon. In TMS stud-ies of patient populations (e.g. epilepsy) or those exceeding the standard TMS protocols (e.g. long-term TMS protocols) epileptic seizures have been reported in rare cases. Online and short-term TMS protocols are considered safe according to the latest published inter-national safety guidelines. All subjects are screened for their relevant medical history and other TMS safety aspects (e.g. metal parts in the head). In summary, the risk and burden associated with participation can be considered minimal and no serious adverse events are expected during online and short-term TMS studies.
The consent discussion starts sufficiently in advance of the initiation of study-related pro-cedures to allow potential subjects time to reflect on the potential benefits and risks and possible discomforts. Participants are informed about our standard studies when they are screened (usually days before inclusion) and the risk associated with participation in this study can be regarded as minimal.
Further discomfort might be caused by procedures such as filling out questionnaires and the time spend on the study.
The results of this study will provide us with better insight into two treatments for depres-sion and how we can combine them to increase efficacy and better help patients with de-pression.
In case of an incidental finding concerning a deviation in the MRI scan, step 1, the re-searcher will immediately contact the MRI lab manager:
a. If it concerns a healthy subject the MRI lab manager will send the images out for as-sessment by a radiologist. At this stage the participant is not informed, but the incidental finding will be documented (proceed to step 2).
b. If it concerns a patient and/or minor the researcher is required to consult the responsible study MD.
- The responsible MD is trained to judge the images adequately proceed step 3.
- The responsible MD is not trained to judge the images proceed step 1a.
Step 2, if, according to a written report of the radiologist,
a. No clinically relevant finding is obtained, the participant will not be informed, but the documentation updated.
b. A clinical relevant finding is obtained; the home physician will receive a letter. Also the participant will receive a letter, which, however, does not reveal any diagnosis but which asks the participant to contact his/ her home physician.
c. The incidental finding will be centrally documented at the DCCN.
Step 3, if the responsible MD considers the abnormality as clinically relevant the home physician or the treating specialist will be personally contacted by the responsible MD. (for details see K6b).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Age 18-65 years

Exclusion criteria

Metal in cranium
A history of severe neurological problems (e.g. epilepsy, head surgery or severe head injury)
A history of mood disorders (e.g. depression, bipolar disorder, anxiety disorder)
Severe physical illness
Pregnancy
A score of >=13 on the Beck Depression Inventory (BDI-II)

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Single blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	02-02-2022
Enrollment:	40
Type:	Actual

Medical products/devices used

Generic name:	repetitive transcranial magnetic stimulation (rTMS)
Registration:	Yes - CE intended use

Ethics review

Approved WMO

Date:	10-11-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL77177.091.21

Study results

Date completed:	31-05-2022
Results posted:	05-08-2022
Actual enrolment:	20

First publication
01-01-1900