Neuro-Cardiac-Guided Transcranial Magnetic Stimulation: a method to probe the depression network. Replication and dose-response.

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To explore whether influence on parasympathetic activity can be used as a functional outcome measure reflecting adequate targeting of the DLPFC-sgACC network and, secondary: 1) to explore the dose-response to the intensity of the TMS output and 2)…

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

Summary

ID

NL-OMON48765

Source
ToetsingOnline

Brief title
NCG-TMS: replication and dose-response

Condition

- Mood disorders and disturbances NEC

Synonym
depression, MDD

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W,Onderzoeksinstituut Brainclinics

Intervention

Keyword: Depression, Heart-brain network, TMS

Outcome measures

Primary outcome

Heart rate converted to RR intervals. The troughs of these intervals are used

as input in analysis.

Secondary outcome

Gender, head size, age and motor threshold.

Study description

Background summary

Autonomic regulation is disturbed in patients with major depressive disorder (MDD), indicated by a higher heart rate (HR) and lower heart rate variability (HRV). Moreover, the heart seems to be functionally connected via the vagus nerve (VN) to other brain structures that are dysregulated in depression, such as the subgenual anterior cingulate cortex (sgACC), and the dorsolateral prefrontal cortex (DLPFC), suggesting dysregulated network function in MDD. In line with this network dysregulation hypothesis of MDD, optimal transcranial magnetic stimulation (TMS) sites are currently thought to be those that show functional connectivity to the sgACC such as the DLPFC and multiple studies have shown that stimulation of the DLPFC, sgACC and nervus vagus decreased heart rate, suggestive of parasymphatetic action. We hypothesized that this influence on parasympathetic activity can be used as a functional outcome measure reflecting adequate targeting of the DLPFC-sgACC network, similar to the motor evoked potential (MEP) as functional key measure for primary motor cortex stimulation. Recently, we have conducted a pilot study proposing a new functional neuronavigation method for localizing the frontal area representation of DLPFC-sgACC connectivity using HR, called: Neuro-Cardiac-Guided TMS (NCG-TMS), which we aim to replicate.

Study objective

To explore whether influence on parasympathetic activity can be used as a functional outcome measure reflecting adequate targeting of the DLPFC-sgACC network and, secondary: 1) to explore the dose-response to the intensity of the TMS output and 2) whether differences can be attributed to age, gender or head size

Study design

Randomized controlled intervention study

Intervention

All participants receive the same intervention. Session 1: 1 minute of iTBS on 7 different cortical brain locations. Session 2: 1 minute of iTBS spread over 2 different cortical brain locations, with 5 different intensities. In session 2, for the first 29 participants also deep TMS will be applied, and thus this part has finished. Results will be analysed. Deep TMS is not randomised to one hemisphere and is thus the same location for all subjects, resulting in sufficient power for statistical analysis.

The intervention is not lasting outside the session. There are no specific rules to follow in between the two sessions.

10 subjects will be tested twice due to a protocol change.

Study burden and risks

The participants burden is minimal. The main burden is time consummation. There will be two session, of which each maximal 1 hour. The exact stimulation time is in the first session just over 1 minute, and in the second session 2 minutes. For the first 29 subjects, deep TMS is applied as well, consisting of another 750 pulses.

During a session, the participant does not to conduct any tasks, but should only sit relaxed in the TMS chair. There will be magnetic pulsed applied to the skull, which is a non-invasive method. The TMS trains can give an uncomfortable feeling, sometimes lightly painful, but this does not persist after the train. After a session, there might arise a headache due to stimulation of the muscles in the face, but this is not dangerous, and will, if applicable, disappear on itself within a few hours. (Fitzgerald et al., 2009; Machii et al., 2006; Rusjan et al., 2010). If needed, pain medication can be taken. The risks of this research are like the risks of the approved treatment TMS. The technique of TMS in safe and FDA approved, and has no negative consequences on the health (Rossi et al., 2009). However, TMS will not be applied if epilepsy is common in the first grade of the participant*s family, or the participant experienced epilepsy him/herself. Also, no metal is allowed in the participant*s head.

The maximal allowed number of pulses and the maximal allowed intensity are not violated in this protocol. In the first session, 7 minutes of iTBS will be applied, spread over 7 different locations, comparable to 1470 pulses, on 100% of the MT. In session 2, this will be 10 minutes of iTBS, spread over two cortical areas, comparable to 2100 pulses, on different intensities (70, 80, 890, 100, 110% MT). 10Hz TMS has already numerously been applied for, amongst others, the treatment of depression, in where the amount of pulses can be as much as 2500 pulses or even more. Furthermore, stimulation usually is applied at 110% or 120% of the MT, while our protocol is in a range of 70-110% of the MT. For the first 29 subjects, also deep TMS will be applied in session two, consisting of 750 pulses.

The chosen location are locations that surround F3 or F4: FC3, F1, AF3, F5, FC5 en FC4, F2, AF4, F6 en FC6. This means that they are, in fact, all aimed at the DLPFC. Furthermore, stimulation is applied on or around the motor cortex (C3 and C4). These locations have been stimulated many times now as well, in various research populations, without negative effects (Fitzgerald et al., 2009; Machii et al., 2006; Rusjan et al., 2010).

First, heart related effects were studies for safety issues, and later for a better understanding of the parasympathetic system (Rossi et al., 2016). The effect of neuromodulation on the heartbeat has been studied extensively and the lowering of the heart beat has not led to adverse events (Sampaio et al., 2012). In theory, this effect on the heart rhythm is because an effect on the parasympathetic system, and not on the basal heart rhythm. Thus, the heart rate cannot become lower than the basal heart rate.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Healthy, between the ages of 18-60.

Exclusion criteria

Similar to TMS exclusion criteria: no prior experience with epilepsy, no pregnancy or wish for pregnancy within the period of the research. No metal in the head or cochlear implants.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	16-03-2018
Enrollment:	50

Type:	Actual

Medical products/devices used

Generic name:	Transcranial magnetic stimulation
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	04-01-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-08-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL63092.041.17

Study results

Date completed:	02-05-2019
Results posted:	21-05-2019
Actual enrolment:	50

First publication
01-01-1900