Is Transcranial Magnetic Stimulation a potential tool for cognitive therapy in Multiple Sclerosis?

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Autoimmune disorders
Study type	Interventional

Summary

ID

NL-OMON37898

Source
ToetsingOnline

Brief title
TMS as potential tool for cognitive therapy in MS

Condition

- Autoimmune disorders
- Demyelinating disorders

Synonym
MS, Multiple Sclerosis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: MS centrum Amsterdam

Intervention

Keyword: Cognitive therapy, Multiple Sclerosis, Neuroimaging, Transcranial magnetic stimulation

Outcome measures

Primary outcome

More insight will be given into the potential role for rTMS in cognitive therapy in MS patients. This will increase our knowledge on this topic and will hopefully give us insights on how to start future interventional longitudinal cognitive rehabilitation studies.

The primary study parameters of this study are:

1) Functional connectivity (resting state and task-specific fMRI): How do task-related (N-back task) and resting state functional connectivity patterns, as measured by functional MRI, change in response to high frequency rTMS in MS?

2) Working memory task performance (task-specific fMRI): How does the performance on the N-back task change in response to a single rTMS application?

Secondary outcome

As a secondary objective, we are interested in functional changes at the metabolic level of rTMS. To learn more about this, we will perform MR-spectroscopy. Also, we would like to establish that plasticity takes place in the motor cortex when our rTMS protocol is applied to this brain area (positive control).

The secondary study parameters of this study are:

3) Are there changes in brain metabolites, specifically in Glutamate/Glutamine

levels (as detected by MR spectroscopy) in the prefrontal cortex after

stimulation with rTMS?

4) Does rTMS of the motor cortex (M1) of MS patients induce synaptic

plasticity?

Study description

Background summary

Cognitive impairment, e.g. working memory impairment, is highly prevalent in multiple sclerosis (MS) and causes severe impairment of daily living activities. So far, just a few studies have been performed on cognitive rehabilitation in MS, mostly applying mental training schemes or pharmacological stimulation, and they showed only little improvement of cognitive function. Repetitive transcranial magnetic stimulation (rTMS) may be a suitable method to improve cognitive function in MS patients, as it is known to induce neural plasticity as well as improvement in working memory function in psychiatric patients. rTMS has been applied in MS patients to improve spasticity. However, it has not yet been used to improve working memory function. Within the scope of cognitive therapy and cognitive rehabilitation, rTMS seems to be a promising method, but more research is now needed to increase our understanding of the precise clinicocognitive effects of rTMS in MS patients. The current study is planned to provide necessary insights for future longitudinal studies using rTMS to treat cognitively impaired MS patients.

Study objective

The aim of the proposed pilot study is to explore the efficacy of rTMS in inducing a (transient) localized increase in brain activity of MS patients which is hypothesized to be beneficial for cognitive functioning. This is the first step that needs to be taken to validate the technique for further studies on compensatory brain mechanisms and cognitive rehabilitation in a future longitudinal research setting.

Study design

This is a cross-sectional, double-blind, sham-controlled, pre-post intervention study using different neuroimaging modalities, including conventional MRI and advanced MRI techniques (task specific functional MRI (fMRI), resting state fMRI, MR spectroscopy).

Neuropsychological testing will be used to differentiate between cognitively preserved and cognitively impaired MS patients. The scans will be post-processed and analyzed to obtain information on the differences in brain activity between rTMS stimulation and no stimulation/sham condition.

Intervention

Repetitive Transcranial Magnetic Stimulation (rTMS) will be used to temporarily (30 minutes) stimulate the dorsolateral prefrontal cortex in patients and in healthy controls.

Study burden and risks

Participants need to visit the outpatient clinic of the VUmc on three separate occasions, specified as follows:
Day 1: Baseline visit
- Neuropsychological testing (60 min),
- MRI-session (structural and functional, approximately 60 min)
- rTMS to study motor cortex plasticity (10 min; positive control)
- Blood sample

Day 2: Intervention/ placebo intervention
- rTMS treatment (or sham condition) (30 min)
- MRI-session (50 min)

Day 3: Intervention/placebo intervention
- rTMS treatment (or sham condition) (30 min)
- MRI-session (50 min)

MRI:
Earplugs will be provided to reduce the noise of the scanner. The scan will be made at 1.5T and is considered to have neglectable risks. Before every examination the subjects will be screened for metal objects in their bodies, risk of claustrophobia, or other MR dependent exclusion criteria. In between the different scans that will be made, the researcher will ask the subject after their condition. If necessary, the scan session can be stopped immediately by the researcher or by the participant (emergency button). To our knowledge, the MRI is not causing any damage as long as normal procedures are followed.

rTMS:
With regard to the rTMS intervention, the published safety guidelines will be followed sincerely. Since MS patients are more prone to epileptic activity compared to the general population, additional safety precautions will be taken, such as, exclusion of all subjects (both patient and control) with a (first degree family) history of epilepsy, and/or use of tricyclic

antidepressants, neuropleptic agents, Fampridine, and other drugs that lower the seizure threshold. Also, MS patients with extensive cortical pathology (based on Calabrese et al., 2008 and the baseline MR scan) will be excluded from participation to be conservative and on the safe side with regard to the induction of epileptic activity by rTMS. Following these precautions, there are hardly any risks for adverse events.

During the study, all participant do have the ability to withdraw from the study without a reason and without consequences for further treatment in our hospital.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age 18-55 years
- Clinically definite MS (based on Poser criteria, 1983)
- Need to meet the safety criteria to undergo an MRI examination
- Need to meet the safety criteria to undergo transcranial magnetic stimulation

Exclusion criteria

For all participants:
- History of drug abuse
- Psychiatric disorders
- Claustrophobia
- Visual impairment
- Foreign non MR compatible metal objects in the body
- Foreign metal objects in or close to the head
- (family)history of epilepsy, seizures
- Use of tricyclic anti-depressants, neuroleptic agents, fampridine and other drugs that lower the seizure threshold
- Cardiac rhythmic disorders;Additionally for healthy controls:
- Neurological disorders;Additionally for patients:
- Other neurological disorders besides MS
- Relapse or steroid treatment in the month prior to the investigation
- High number of cortical lesions (according to Calabrese et al., Journal of Neurology 2008)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2012
Enrollment:	45
Type:	Actual

Ethics review

Approved WMO Date:	29-03-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-07-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL39510.029.12