The effects of Transcranial Magnetic Stimulation on freezing in Parkinson's Disease patients with Freezing of Gait

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Movement disorders (incl parkinsonism)
Study type	Interventional

Summary

ID

NL-OMON35602

Source
ToetsingOnline

Brief title
TBS in Parkinson's Disease patients with freezing of gait

Condition

- Movement disorders (incl parkinsonism)

Synonym
freezing of gait, Parkinson's Disease

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: Smart Mix;Braingain

Intervention

Keyword: freezing of gait, Parkinson's Disease, TMS

Outcome measures

Primary outcome

The primary outcome for this study is the total time a patient freezes during the gait and upper limb task. This outcome will be rated by a blinded examinator who rates the videos of the different tasks off-line.

Secondary outcome

1. The stride length (amplitude) and velocity in the gait task.

2. The amplitude and velocity of the flexion-extension movement of the index fingers in the upper limb task.

3. The average duration and the frequency of freezing in the gait and the upper limb task.

4. MEP amplitude before and after TBS stimulation.

5. The performance on the pegboard test.

Study description

Background summary

Freezing of gait (FOG) is one of the most disabling features in Parkinson*s Disease (PD). It can be described as short involuntary stops during gait and a feeling of *being glued to the floor*. FOG has an episodic character that is usually experienced during step initiation or turning. It occurs in 20-80 % of the PD patients depending on the disease stage and treatment and it is one of the most common causes of falling and mobility problems in PD.

Nevertheless, the brain mechanism behind the occurrence of FOG is still not completely clear. The fronto-striatal circuitry is probably involved. Our recent study showed patients with FOG had a decreased Supplementary Motor Area

(SMA) activity and an increased activity in the mesencephalic locomotor region in the brainstem (CMO nr. 2004/150).
In addition, there may also be a role for the cerebello-cortical circuitry, although this has never been investigated extensively. In PD patients without FOG, hypoactivity in the putamen, SMA and pre-SMA and hyperactivity in the motor cortex and left and right cerebellum has been found during a hand task. It has been hypothesized that this hyperactivation in the ipsilateral cerebellum is a compensatory mechanism for the defective basal ganglia.

We now hypothesize that patients with FOG are less able to recruit the cerebellum to compensate for the dysfunction in frontro-striatal circuitry.

Study objective

For a possible (better) treatment of FOG a better understanding of the brainmechanism behind this phenomenon is needed. Previous studies showed some brain areas that are possibly involved in FOG.The aim of this study is to see whether we can induce a positive effect on freezing by stimulating the hypoactive Supplementary Motor Area (SMA) in the fronto-striatal or the compensatory cerebellum in the cerebello-cortical pathway in PD patients with FOG.

The primary research question is:

1. What is the effect of TBS over the SMA and the cerebellum on the total freezing time (duration of all freezing episodes combined) in PD patients with FOG?

The secondary research question's are:

1. What is the effect of TBS over the SMA and the cerebellum on the frequency and average duration of freezing in PD patients with FOG?

2. Is there a difference in effect between TBS over the SMA and cerebellum on freezing in PD patients?

3. Does TBS over the SMA and cerebellum have a similar effect on upper limb freezing and FOG in PD patients?

4. What stimulation protocol over the cerebellum has the most beneficial effect on freezing? Inhibitory (cTBS) or excitatory (iTBS)?

5. Does TBS over the SMA and cerebellum have an effect on the motor evoked potentials measured over the motor cortex?

Study design

The study is an intervention study consistsing of four sessions. During each of these sessions a different stimulation condition is used. The four possible conditions are iTBS over the SMA, cTBS over the cerebellum, iTBS over the cerebellum and cTBS over the SMA. The order of the stimulation conditions in time is randomized. Two consecutive sessions are separated by at least one week.

The protocol for session 1 consists of four major parts, which in total last approximately 3 hours. The four major parts are:
1. Instruction and clinical measures
2. Baseline measurements
3. Determination threshold and TMS intervention
4. Post-intervention measurements

Sessions 2, 3 and 4 are similar in set up to session 1. During these sessions the baseline measurements, an intervention and the outcome measurements are performed. The difference with session 1 is that less clinical measures are performed and the determination of the threshold are not repeated. This means that the total time needed is approximately between one and a half and two hours.

Intervention

The intervention used in this study is Theta Burst Stimulation (TBS), which is a repetitive form of Transcranial Magnetic Stimulation. In total four stimulions will be given seperated over four different days.
The Supplementary Motor Area (SMA) and the cerebellum will be stimulated with both Continuous Theta Burst stimulation (cTBS) and Intermittent Theta Burst Stimulation (iTBS).

CTBS consists of 3 pulses at 50 Hz repeated every 200 ms for 40 seconds (600 pulses). This kind of stimulation has a transitory inhibiting effect on the stimulated brain area. ITBS consists of 3 pulses at 50 Hz repeated every 200 ms in trains of 2 seconds. These trains are repeated every 10 seconds for a total of 190 seconds (600 pulses). This kind of stimulation has a transitory excitatory effect on the stimulated brain area. The stimulation intensity of the TBS will be 70 % of the resting motor threshold (RMT) found over the motor cortex. During TBS the subjects are instructed to relax their whole body as much as possible.

Study burden and risks

Concerning the risks two major points have to be addressed, namely
1. Withdrawal of morning medication till the end of the experiments
2. Application of TBS

We will not go into the safety aspects concerning MRI. For it has been well

established that this is a safe technique, which brings no disadvantageous effects to the patients.

1. To study the phenomenon of FOG the patients have to be in the *off* state concerning their medication. A widely accepted and used method to do this is to ask patients to postpone their morning medication uptake until after the experiments. This way the risk is minimal because the patients are allowed to take their medication directly after the experiments. However, there is a temporary increase of PD symptoms during the experiment. This is by no means harmful over a longer period of time. The responsible neurologist involved has a lot of experience with this method.
During the gait task, there are some additional risks of falling caused by the withdrawal of the patients morning drugs. Therefore a researcher will accompany the patient while performing the gait task.

2. Repetitive Transcranial Magnetic Stimulation is a non-invasive technique that is considered reasonably save. In the last couple of years thousands of papers with TMS and rTMS are produced with minimal reports of serious adverse events. These concern studies with healthy subjects and patients (e.g. parkinson). However, there are some potential risks involved that require some attention. The most important risk to take into account is unintended epileptic seizure, although even this risk is certainly very low. Concerning the specific application of TBS only 1 case with seizure is reported out of 741 participants that have undergone TBS till mid 2009. This specific case concerned a healthy man who underwent a 100 % resting motor threshold TBS stimulation. A physical exam, detailed neurological exam and mental status exam 45 minutes after the end of the stimulation showed normal results, and they stayed normal later on. In addition to the seizure risk, a small percentage of participants (10-30 %) experience some discomfort due to scalp or facial muscle twitches or headaches from rTMS. The headaches are transitory and can be treated with aspirin or acetaminophen (c.q. Paracetamol).

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Postbus 9101
6500 HB Nijmegen
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Postbus 9101

6500 HB Nijmegen
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Idiopathic Parkinson's Disease patients diagnosed according to the UK Brain Bank criteria.
- Hoehn and Yahr stage 2 or 3.
- Presence of freezing of gait.

Exclusion criteria

- Presence of neurological disease other than Parkinson's Disease.
- Presence of deep brain stimulator.
- MMSE score under 24
- Contra indications for administrating TMS

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Single blinded (masking used)
Control:	Uncontrolled

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-02-2012
Enrollment:	0
Type:	Actual

Ethics review

Approved WMO

Date:	26-01-2012
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	NL37627.091.11