Circuit-level mechanisms of cerebral compensation in Parkinson's disease

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

Summary

ID

NL-OMON40985

Source
ToetsingOnline

Brief title
Cerebral compensation in Parkinson's disease

Condition

- Movement disorders (incl parkinsonism)

Synonym
eye movements, Parkinson's disease

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universiteit Nijmegen
Source(s) of monetary or material Support: NWO-MaGW;ZonMW

Intervention

Keyword: eye movements, functional MRI, Parkinson's disease, Transcranial Magnetic Stimulation

Outcome measures

Primary outcome

The main behavioural parameters will be the differences in eye movement behaviours depending on cTBS condition (Arm 1) and cTBS and TMS single-pulse timing (early versus late with respect to an eye-movement) (Arm 2). The main neurobiological parameters will be differences in fMRI activation patterns in oculomotor regions depending on cTBS location (Arm 1), and changes in cerebral blood flow after cTBS (Arm 2).

Secondary outcome

In Arm 1, the secondary study parameters will be differences in fMRI activation patterns in a larger oculomotor circuit. Additionally, we will assess any changes in tremor-related activity following cTBS. In Arm 2, we will more precisely examine the TMS pulse timings on eye-movement behavior.

Study description

Background summary

The brain is adaptable, and numerous brain regions can change their neural signal patterns following neurodegeneration in Parkinson's disease (PD). However, it is not clear whether these changes are pathological, or, if they represent compensatory mechanisms to help maintain function. We will explore possible compensatory brain changes in the parietal-occipital cortex in Parkinson's disease, which we hypothesize could relate to patients utilizing visual information to guide movements. This hypothesis is grounded on clinical and neuroimaging evidence: first, Parkinson*s patients show increased use of visual cues when initiating movement, but also freeze their motion when the

visual environment changes (known as freezing of gait); second, in neuroimaging studies, visuo-motor portions of the parietal-occipital cortices show increased activity when Parkinson*s patients need to move. It is important to test whether this *hyperactivity* is actually beneficial to movement initiation, because, an over-reliance on visual information could also contribute to freezing of gait in PD. Knowledge from this experiment will be directly useful to clinicians and the scientific community in understanding the neural mechanism behind compensatory strategies used by people with Parkinson*s disease.

Study objective

Our objective is to perturb neural activity in the parietal-occipital cortex in PD patients (and age-matched control subjects) to determine if the activity contributes to better visually-guided behaviour, but at the same time, to diminished voluntary control. We will also perturb this activity in healthy young adult subjects to more precisely explore the nature of parietal-occipital hyperactivity.

Study design

This study has two arms, because it requires the participation of people with Parkinson*s disease and age-matched control subjects in a patient-control design, but in addition, the participation of healthy young adults who will undergo different experimental procedures. This is necessary because we have a specific hypothesis that cannot be addressed by only performing at patient-control study. In brief, one arm will directly test for compensatory changes in the brains of people with Parkinson*s disease by measuring behavior along with functional magnetic resonance imaging; the second arm will more precisely examine the functional relevance of this activity in a behavioral-only study where fMRI cannot be collected, and which would be an unnecessary extra burden on the patients to perform. In Arm 1 we will apply a form of repetitive Transcranial Magnetic Stimulation (rTMS), known as continuous theta-burst stimulation (cTBS) to the parietal-occipital cortex in Parkinson's patients and control subjects to see how this changes behaviour and neural activity measured with functional magnetic resonance imaging (fMRI). In Arm 2, we will apply cTBS to the frontal cortex in healthy young adults because we have previous evidence for parietal-occipital compensation following frontal cortex cTBS. We will then use single pulse TMS at different times to the parietal-occipital cortex, to test more precisely how the parietal-occipital cortex might compensate for motor system impairments by enhancing visual processing. (This will be a behavior-only study, as we do not possess the ability to perform single pulse TMS while scanning with fMRI).

Intervention

All participants will receive single-pulse transcranial magnetic stimulation (TMS), and continuous theta-burst transcranial magnetic stimulation (cTBS).

Study burden and risks

Each participant will receive no direct benefit from participating in the study, but will receive a compensatory (financial) incentive. Transcranial magnetic stimulation (TMS) is a widely used non-invasive brain stimulation technique, based on the principle of electromagnetic induction. During stimulation the participant will likely hear the clicks of the TMS pulses and experience stimulation of nerves and muscles of the head. The most common side effect is a light transient headache (2-4% occurrence). A severe headache is uncommon (0.3-0.5% occurrence). In TMS studies of patient populations (e.g. epilepsy) or that exceeded the standard protocols (e.g. in intensity or frequency) epileptic seizures have been reported in rare cases. In the current study all participants will be stimulated with protocols that fall within the safety guidelines. All subjects are screened for their relevant medical history and other TMS safety aspects (e.g. presence of metal parts in the head). 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.
The noise in the fMRI scanner, and lying in a small space, may lead to discomfort in some subjects. If all security measures are fulfilled, then there is no risk for the subjects. Parkinson*s patients will be asked to withhold dopaminergic medications for at least 12 hours to be in a practically defined off-state (Langston et al., Movement Disorders, 7(1) 2-13, 1992). When OFF-medication, their Parkinson symptoms may temporarily worsen, which can lead to discomfort. At the end of the measurement, they will resume their normal medication regime.

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

A person with Parkinson's disease must meet the following:
- Idiopathic Parkinson*s disease according to UK brain bank criteria.
- Mild to moderate disease severity (Hoehn and Yahr 1-3).
- Dopaminergic therapy with a clear clinical response of non-tremor symptoms (bradykinesia, rigidity).
- Right-handed
- Normal/corrected-to-normal vision;A control subject must meet the following:
- right handed
- normal / corrected to normal vision
- and be considered healthy

Exclusion criteria

- Epilepsy, convulsion or seizure (TMS)
- Serious head trauma or brain surgery
- Large or ferromagnetic metal parts in the head (except for a dental wire)
- Implanted cardiac pacemaker or neurostimulator
- Pregnancy
- Familial epilepsy
- Any other exclusion as per TMS screening form
- Neurological or psychiatric co-morbidity (e.g. stroke, depression).
- Severe head tremor or dyskinesias
- cognitive impairment (MMSE < 26)
- General MRI exclusion criteria (e.g. pacemaker, implanted metal parts, deep brain stimulation, claustrophobia).
- Skin diseases at intended electrode sites (EMG)
- Any prescribed medication that can alter cortical excitability (e.g. antiepileptics, tricyclic

anti-depressives or benzodiazepines) or can have an influence on the participant*s vigilance or cognitive performance within two weeks prior to participation
- disorders of vision

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-11-2014
Enrollment:	90
Type:	Actual

Ethics review

Approved WMO Date:	28-08-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-04-2015
Application type:	Amendment

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	NL47978.091.14

Study results

Date completed: 18-04-2016

Actual enrolment: 46

Summary results
Trial is onging in other countries