Explorations into the structural and molecular cerebral differences between tremor dominant and non-tremor 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-OMON42970

Source
ToetsingOnline

Brief title
Tremor and non-tremor Parkinson's Disease.

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease, tremor

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universiteit Nijmegen

Source(s) of monetary or material Support: Internal grant of Donders;Dutch Brain Foundation (Hersenstichting)

Intervention

Keyword: Molecular, Parkinson's Disease, Structural, Tremor

Outcome measures

Primary outcome

(1) Structural integrity of brain stem nuclei (substantia nigra pars compacta, retrorubral area, locus coeruleus and raphe nuclei) using DTI and SWI; (2) GABA concentrations in the thalamus both OFF and ON dopaminergic therapy; (3) Cognitive performance on dopamine-dependent (go/nogo) and dopamine-independent (paired associative learning) behavioural task. (4) functional connectivity at rest, both OFF and ON dopaminergic therapy;

Secondary outcome

- Result of clinical assessment of cognitive function (MMSE, FAB).

- Result of clinical assessment of parkinsonian symptom severity (TRS, UPDRS) before and after medication.

Study description

Background summary

Resting tremor is a core symptom of Parkinson*s disease (PD), which is seen in about 75% of patients. Aside from the appearance of tremor, these patients also show a difference in disease progression than non-tremor PD patients: they have less cognitive decline and a slower overall disease progression. The reason for this variability is unclear, preventing treatment and development of new therapies. Post-mortem studies suggest different patterns of (dopaminergic) cell loss in the midbrain of tremor-dominant and non-tremor PD patients, but in vivo evidence is lacking. These structural differences may in turn produce downstream functional changes in the basal ganglia and thalamus. Here we test

this hypothesis in patients with PD, using both structural and functional MRI scanning. Our structural scans will look at the structural integrity of deep brain (dopaminergic) nuclei, and our functional scans will be focused on thalamic GABA, which is the most important inhibitory neurotransmitter in the human brain and strongly linked to the expression of tremor. Finally, we will test the consequences of these underlying structural and functional changes for behavioural performance using cognitive testing.

Study objective

We hypothesize that PD patients with and without tremor have different patterns of midbrain structural integrity in (dopaminergic) nuclei, different patterns of functional connectivity from midbrain to basal ganglia, differences in GABA-ergic tone in the thalamus, and differences in dopamine-specific behavioural performance.

Study design

This research will combined with a previous study (CMO: NL47614.091.14 /2014-014), where we measured two groups of tremor-dominant PD patients (dopamine-resistant and dopamine-responsive) and one group of matched controls. The non-tremor group will undergo a very similar procedure, making them fully comparable with the previous groups. This entails: testing all patients twice, i.e. without their normal medication and after a single dose of Levodopa-Benserazide 250 mg. The participants will undergo the following MR scans: (1) diffusion tensor imaging (DTI; 15 min) and a high-resolution localizer scan (SWI; 5 min) to quantify the structural integrity of deep brain regions; (2) magnetic resonance spectroscopy (MRS; 30 min) to measure GABA concentrations in the thalamus (and control regions) (3) fMRI resting state (10 min) to measure functional connectivity;. Outside the scanner, we will measure cognitive performance on 2 behavioural tasks (40 min) measuring dopamine-dependent and dopamine-independent cognitive performance.

Intervention

The intervention includes two fMRI sessions per subject. The patients are measured both OFF their own dopaminergic drugs, and ON 250 mg Levodopa-Benserazide + 10 mg Domperidone. During the OFF condition, patients will receive a placebo with the same physical appearance. Patients (but not researchers) will be blinded to the intervention.

Study burden and risks

The experimental protocol will consist of clinical and behavioural measurements plus anatomical and functional scans in the MRI scanner. These measurements will be performed on 2 mornings (duration: 4 hours per session). Patients will

arrive in a practically defined OFF state, i.e. at least 12 hours after having taken their last dopaminergic medication. At the end of the measurement, they will resume their normal medication regime. When OFF-medication, their Parkinson symptoms may temporarily worsen, which can lead to discomfort. On one out of two sessions, patients will receive a dose of Levodopa-Benserazide (250 mg) that may be higher than the patient's usual dose. This may sometimes lead to side effects such as nausea or dizziness. For this reason, patients will receive 10 mg Domperidone, which is a standard clinical treatment to avoid such side effects. Finally, the noise in the fMRI scanner, and lying in a small space, may lead to discomfort. If all security measures are fulfilled, then there is not risk for the patients.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Idiopathic Parkinson*s disease according to UK brain bank criteria.
- Absence of a clear resting tremor of at least one arm (UPDRS tremor-score <= 0).
- Mild to moderate disease severity (Hoehn and Yahr 1-3).

Exclusion criteria

- 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).
- Co-medication associated with elongated QT-time.
- Pregnancy.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-12-2016
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO Date:	27-09-2016
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	NL56811.091.16