The noradrenergic basis of Parkinson*s tremor: a systems-level fMRI approach

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I will test the hypothesis that the noradrenergic system amplifies tremulous activity in the cerebello-thalamo-cortical circuit. More specifically, I will test how this modulation takes place (i.e. through which brain regions and connections).

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

Summary

ID

NL-OMON55729

Source
ToetsingOnline

Brief title
Noradrenergic basis of Parkinson tremor

Condition

- Movement disorders (incl parkinsonism)

Synonym
Parkinson's disease, tremor

Research involving
Human

Sponsors and support

Primary sponsor: Neurologie
Source(s) of monetary or material Support: VENI beurs

Intervention

Keyword: fMRI, Noradrenaline, Parkinson's disease, Tremor

Outcome measures

Primary outcome

Tremor-related activity and connectivity (quantified using concurrent

EMG-fMRI).

Secondary outcome

Structural integrity of the locus coeruleus (quantified using neuromelanin

sensitive MRI).

Functional integrity of the locus coeruleus (quantified using task fMRI).

Clinical parameters

Study description

Background summary

Parkinson*s disease is the second most common neurodegenerative disease worldwide. Clinically, Parkinson*s disease is characterized by motor slowing (bradykinesia), stiffness (rigidity) and resting tremor. The pathological hallmark of Parkinson*s disease is striatal dopamine depletion, but the dopaminergic basis of resting tremor is disputed. For instance, striatal dopamine depletion correlates with all motor symptoms except resting tremor. Furthermore, resting tremor is often resistant to dopaminergic medication. Instead, resting tremor worsens consistently during psychological stress, and recent findings suggest that the noradrenergic (stress) system is hyperactive in Parkinson*s disease. Based on empirical (fMRI) data, I have recently proposed a new systems-level model of Parkinson*s tremor. According to this model, tremor is initiated in the basal ganglia and amplified in the cerebello-thalamo-cortical circuit. In this study, I will use this model as the basis for understanding how the noradrenergic (stress) system amplifies Parkinson tremor.

Study objective

I will test the hypothesis that the noradrenergic system amplifies tremulous activity in the cerebello-thalamo-cortical circuit. More specifically, I will test how this modulation takes place (i.e. through which brain regions and connections).

Study design

Cross-over intervention study.

Intervention

The intervention only concerns the Parkinson patients with a tremor-dominant phenotype (n=40). Parkinson patients with a non-tremor phenotype (n=30) will undergo one session (without an intervention). They will serve as a control for the tremor-dominant group, where we will compare the structural integrity of the locus coeruleus between groups, and we will localize the locus coeruleus in this group (using task fMRI).

To activate the noradrenergic system, I will use a validated and controlled stress-induction task (cognitive-coactivation: alternating blocks of mental arithmetic versus rest). This tasks consists of performing difficult arithmetics under time pressure and under social pressure. The control task will consist of performing easy arithmetics without any time pressure or social pressure. Furthermore, I will test whether a pharmacological intervention (propranolol 40 mg single dose) can counteract the effects of psychological stress on the tremor circuitry. Propranolol is commonly used in clinical practice to treat tremor. The control condition will be a placebo.

Study burden and risks

The burden of this study will be different for the two groups.

1. For the tremor-dominant Parkinson group (n=40):
The experimental protocol will consist of clinical measurements, and performance of a simple cognitive task in the fMRI scanner. These measurements will be performed on two 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 session, patients will receive a single dose of propranolol (40 mg). Propranolol is commonly used in clinical practice to treat tremor. This may sometimes lead to temporary side effects such as dizziness, bradycardia, and cold hands/feet. Patients will be extensively monitored during the measurements (blood pressure, heart rate) to avoid any health risks. In addition, our task is designed to induce psychological stress, and this may lead to some

discomfort. 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.

2. For the non-tremor group (n=30):
The experimental protocol will consist of clinical measurements, and performance of a simple cognitive task in the fMRI scanner. These measurements will be performed on one morning (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. 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.

Tremor is a common and debilitating symptom of Parkinson's disease. If tremor does not respond to dopaminergic treatment, then there are only few therapeutic options. Better pathophysiological insights are needed to provide a rational basis for improved treatment strategies. This study aims at better understanding the pathophysiology of Parkinson*s tremor, by focusing on the noradrenergic system. Identifying the respective neural substrates could potentially have great clinical and therapeutic implications and will also help to better understand why tremor increases dramatically during stressful circumstances. As such, this research may provide clues to target new therapies in tremor-dominant Parkinson patients.

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

- idiopathic Parkinson*s disease according to UK Brain Bank criteriaPatients will fall in one of two groups (Parkinson phenotypes); either:
- tremor-dominant phenotype (defined as a resting tremor score of ><= 2 UPDRS points for at least one arm) or:
- non-tremor phenotype (defined as a resting tremore score of 0 points on the UPDRS).

Exclusion criteria

- use of beta-blockers
- neuropsychiatric co-morbidity
- contraindications for MRI scanning (e.g. pacemaker, implanted metal parts, deep brain stimulation, claustrophobia)
- Cardiac arrhythmias (in patient history or visible on ECG)
- contraindications for beta blockers (e.g. bradycardia, peripheral circulation disturbances, asthma or obstructive lung disease, hypotension)
- Use of medication that may interact with propranolol, e.g. other bèta-blockers, calcium antagonists, digoxine, cimetidine, hydralazine, fluvoxamine, rifampicine, barbiturates, amiodaron, flecainide, kinidine, propafenon, disopyramide, chlorpromazine, and clonidine
- Use of medication that inhibits relevant CYP enzymes that are involved in metabolizing propranolol (CYP2D6, CYP1A2, and CYP2C19): fluoxetine, paroxetine, sertraline, duloxetine, terbinafine, cinacalcet, bupropion, and ciprofloxacine
- Severe head tremor or dyskinesias
- Cognitive impairment (MMSE < 26)
- Severe PD: disease duration > 10 years, severe ON/OFF fluctuations, or levodopa equivalent dose >1200 mg

Study design

Design

Study phase:	4
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):	31-10-2019
Enrollment:	70
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Propranolol (40 mg)
Generic name:	Propranolol (40 mg)
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	17-01-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-04-2017
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-07-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2021
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
EudraCT	EUCTR2016-004629-18-NL
CCMO	NL59724.091.16