

# The influence of stress on Parkinson's tremor

<b>Submission date</b> 18/11/2021	<b>Recruitment status</b> No longer recruiting	<input type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 10/12/2021	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 23/08/2023	<b>Condition category</b> Nervous System Diseases	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

### Background and study aims

Parkinson's disease is the second most common neurodegenerative (nervous system) disease worldwide. Clinically, Parkinson's disease is characterized by slow movement (bradykinesia), stiffness (rigidity) and resting tremor. A low level of dopamine is the main cause of Parkinson's, and this can be treated with medication (levodopa). However, for many people with Parkinson's levodopa has little or no effect on tremor. This suggests tremor is not only caused by low dopamine. The stress hormone noradrenaline seems to play a role in tremor, since tremor worsens in stressful situations. The aim of this study is to test how psychological stress causes tremors to get worse by measuring tremor activity in the brain using functional MRI scans. In addition, the study will look at whether the effects of stress can be reduced with a medicine called propranolol.

### Who can participate?

Patients aged 18-80 years with Parkinson's disease who have either a marked resting tremor of one arm (left, right, or both), or never experience a resting tremor.

### What does the study involve?

The study consists of two testing days of about 5 hours for tremor-dominant Parkinson's patients and one testing day of about 5 hours for Parkinson's patients who have no tremor. The tremor-dominant group will receive a single oral dose of propranolol on one day, and a placebo on the other. Researchers and participants do not know on what day the propranolol will be given. On both days, participants lie down in the scanner for 1 hour. Amongst others, they will do a mental calculation task. The researchers will measure the trembling of their hands with stickers and will continuously monitor heart rate, breathing and pupil size. Outside the scanner, the severity of Parkinson's symptoms is determined and participants fill out some questionnaires.

### What are the possible benefits and risks of participating?

There are no direct personal benefits from this study for patients. The researchers hope to gain more insight into the relationship between stress and tremor with this study. This could lead to new treatments for tremor in the future. The disadvantages are that it takes one or two half-days, that patients have to lie still for about 1 hour in the fMRI scanner, and patients cannot take their dopaminergic medication on the morning before the study days. Temporarily stopping medication may cause temporary worsening of Parkinson's symptoms. In addition, tremor-

dominant patients will be given a 40 mg propranolol tablet once. In the long-term, there are no ill effects.

Where is the study run from?

Donders Institute for Brain Cognition and Behaviour (Netherlands)

When is the study starting and how long is it expected to run for?

January 2016 to September 2021

Who is funding the study?

Netherlands Organization for Scientific Research (Netherlands)

Who is the main contact?

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## Contact information

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Scientific

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## **Additional identifiers**

### **EudraCT/CTIS number**

2016-004629-18

### **IRAS number**

### **ClinicalTrials.gov number**

Nil known

### **Secondary identifying numbers**

helmich-veni-2016

## **Study information**

### **Scientific Title**

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

### **Study objectives**

The researchers expect to see that attenuation of the noradrenergic system (with propranolol versus placebo) reduces tremor power (accelerometry), tremor-related activity in the thalamus (fMRI), and functional connectivity between the cerebello-thalamo-cortical tremor network and a cognitive control network (fMRI) (Dirkx et al., Brain 2020).

### **Ethics approval required**

Old ethics approval format

### **Ethics approval(s)**

Approved 13/04/2017, Commissie Mensgebonden Onderzoek, Region Arnhem-Nijmegen (Postbus 9101, 6500 HB, Nijmegen, Netherlands; +31 (0)24 3613154; commissiemensgebondenonderzoek@radboudumc.nl), ref: CMO2016-3101

### **Study design**

Double-blind counterbalanced cross-over randomized trial

### **Primary study design**

Interventional

### **Secondary study design**

Randomised cross over trial

### **Study setting(s)**

Hospital, Other

### **Study type(s)**

Quality of life, Treatment

## **Participant information sheet**

See additional files

## **Health condition(s) or problem(s) studied**

Parkinson's disease

## **Interventions**

The intervention concerns only tremor-dominant Parkinson's disease patients (n=30), who receive a single oral dose of propranolol 40 mg in one session and a placebo in the other (the order of the two medication conditions is counter-balanced and pseudo-randomized). The randomization list with the order of drugs is only accessible to independent researchers who are responsible for preparing either the drug or placebo. This way, the patients as well as the researchers involved are blinded for the given medication. To activate the noradrenergic system, patients undergo a cognitive-coactivation task with alternating blocks of mental calculations versus rest.

Parkinson's patients with a non-tremor phenotype (n=30) undergo one session without intervention and serve as a control group to compare structural integrity of the locus coeruleus.

## **Intervention Type**

Drug

## **Phase**

Phase II

## **Drug/device/biological/vaccine name(s)**

Propranolol

## **Primary outcome measure**

Tremor-related brain activity and connectivity (quantified using concurrent accelerometry and fMRI blood-oxygen-level-dependent [BOLD]) are measured as a function of behaviourally induced stress (cognitive-coactivation vs rest) and the pharmacological intervention (propranolol vs placebo) at 11:55 (175 min after the start of both testing days).

Co-primary outcome measure: Tremor intensity (quantified using accelerometry) is measured as a function of behaviourally induced stress (cognitive-coactivation vs rest) and the pharmacological intervention (propranolol vs placebo) at 11:55 (175 min after the start of both testing days).

## **Secondary outcome measures**

1. Structural integrity of the locus coeruleus, measured using neuromelanin sensitive MRI at 12:16 (196 minutes after the start of testing day 1)
2. Intensity of rest tremor, postural tremor, and kinetic tremor, measured with accelerometry and EMG in a separate measurement before MRI scanning at 11:00 (120 minutes after the start of both testing days)
3. Resting-state network connectivity, especially in the default mode network, salience network, and frontal executive network, measured with fMRI BOLD Independent Component Analysis (ICA) at 11:40 (160 minutes after the start of both testing days)
4. Clinical parameters measured using the Movement Disorder Society-Sponsored Revision of

the Unified Parkinson's Disease Rating Scale (MDS-UPDRS)-III, measured before MRI scanning at 10:10 (70 minutes after start of both testing days)

5. Autonomous stress markers, measured as salivary cortisol (at 11:00 and 11:30; 120 and 150 minutes after the start of both testing days and before MRI scanning), heart rate, pupil diameter and skin conductance (11:40-12:10 continuously during fMRI scanning 160 minutes after the start of both testing days)

**Overall study start date**

04/01/2016

**Completion date**

06/09/2021

## **Eligibility**

**Key inclusion criteria**

1. Idiopathic Parkinson's disease according to UK brain bank criteria
2. Age range: 18-80 years
3. Tremor-dominant group: the presence of clear resting tremor for at least one arm (defined as a resting tremor score of  $\geq 2$  MDS-UPDRS points)
4. Non-tremor group: absence of clear resting and postural tremor

**Participant type(s)**

Patient

**Age group**

Mixed

**Lower age limit**

18 Years

**Upper age limit**

80 Years

**Sex**

Both

**Target number of participants**

Tremor-dominant phenotype: 30; non-tremor phenotype: 30

**Total final enrolment**

64

**Key exclusion criteria**

1. Neuropsychiatric co-morbidity
2. Contraindications for MRI scanning (e.g. pacemaker, implanted metal parts, deep brain stimulation, claustrophobia)
3. Cardiac arrhythmias (in patient history or visible on ECG)
4. Contraindications for beta-blockers (e.g. bradycardia, peripheral circulation disturbances, asthma or obstructive lung disease, hypotension)

5. Use of medication that may interact with propranolol
6. Use of medication that inhibits relevant CYP enzymes that are involved in metabolizing propranolol
7. Severe head tremor or dyskinesias
8. Cognitive impairment (Mini-Mental State Exam [MMSE] <26)
9. Parkinson disease duration >10 years, severe ON/OFF medication fluctuations, or daily Levodopa-equivalent dose >1200 mg

**Date of first enrolment**

01/09/2019

**Date of final enrolment**

06/09/2021

## **Locations**

**Countries of recruitment**

Netherlands

**Study participating centre**

**Donders Institute for Brain, Cognition and Behaviour**

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## **Sponsor information**

**Organisation**

Radboud University Nijmegen

**Sponsor details**

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**Sponsor type**

University/education

**Website**

<http://www.ru.nl/english/>

**ROR**

<https://ror.org/016xsfp80>

## **Funder(s)**

**Funder type**

Government

**Funder Name**

Nederlandse Organisatie voor Wetenschappelijk Onderzoek

**Alternative Name(s)**

Netherlands Organisation for Scientific Research, Dutch National Scientific Foundation, Dutch National Science Foundation, Dutch Research Council (Nederlandse Organisatie voor Wetenschappelijk Onderzoek), NWO:Nederlandse Organisatie voor Wetenschappelijk Onderzoek, Nederlandse Organisatie voor Wetenschappelijk Onderzoek (NWO), Dutch Research Council, Dutch Research Council, Netherlands, NWO

**Funding Body Type**

Government organisation

**Funding Body Subtype**

National government

**Location**

Netherlands

## **Results and Publications**

**Publication and dissemination plan**

Planned publication in a high-impact peer-reviewed journal

**Intention to publish date**

01/07/2023

**Individual participant data (IPD) sharing plan**

All datasets generated during the current study will be stored in the Donders Institute for Brain Cognition and Behaviour Repository. Everyone can request access to the published data sharing collections. Anonymized raw data is stored in the Data Acquisition Collection (DAC) directly after collection at di.dccn.DAC\_3024005.02\_884. A Data Sharing Collection containing data on which

published results are based will be added to the Donders Repository as soon as an article is published. All participants gave consent for sharing of data for scientific purposes.

### IPD sharing plan summary

Stored in publicly available repository

### Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">Participant information sheet</a>	Non-tremor		01/12/2021	No	Yes
<a href="#">Participant information sheet</a>	Tremor		01/12/2021	No	Yes
<a href="#">Protocol file</a>	version 6	16/04/2021	01/12/2021	No	No
<a href="#">Basic results</a>			23/08/2023	No	No