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The influence of stress on Parkinson's tremor

Submission date	Recruitment status	[_] Prospectively registered
18/11/2021	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
10/12/2021	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
20/04/2026	Nervous System Diseases	

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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Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2016-004629-18

Protocol serial number
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

Primary study design
Interventional

Study design
Double-blind counterbalanced cross-over randomized trial

Study type(s)
Quality of life, Treatment

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(s)
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).

Key secondary outcome(s)
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)

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 ≥2 MDS-UPDRS points)
4. Non-tremor group: absence of clear resting and postural tremor

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
80 Years

Sex
All

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

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Sponsor information

Organisation
Radboud University Nijmegen

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, The Dutch Research Council (NWO), Dutch Research Council, Netherlands, NWO

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location

Netherlands

Results and Publications

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?
Results article		21/12/2024	20/04/2026	Yes	No
Basic results			23/08/2023	No	No
Participant information sheet	Non-tremor		01/12/2021	No	Yes
Participant information sheet	Tremor		01/12/2021	No	Yes
Protocol file	version 6	16/04/2021	01/12/2021	No	No