# The Cerebral Mechanisms of Reemergent Tremor in Parkinson's Disease

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To unravel the cerebral mechanisms of re-emergent postural tremor in PD and understand to what extent these mechanisms overlap with those involved in resting tremor. A secondary objective is to understand how cerebral tremor-related mechanisms...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Movement disorders (incl parkinsonism)
Study type	Observational non invasive

# Summary

# ID

**NL-OMON57007** 

**Source** ToetsingOnline

Brief title RET-PD

# Condition

• Movement disorders (incl parkinsonism)

**Synonym** Parkinson's disease

**Research involving** Human

# **Sponsors and support**

Primary sponsor: Radboud Universitair Medisch Centrum Source(s) of monetary or material Support: Ministerie van OC&W

### Intervention

Keyword: fMRI, Parkinson, Postural tremor, Resting tremor

### **Outcome measures**

### **Primary outcome**

Re-emergent postural tremor-related cerebral activity, as measured by combined electrophysiology-fMRI. This robust technique has already been widely applied to several different tremor syndromes, including Parkinsonian resting tremor, essential tremor, and dystonic tremor.

### Secondary outcome

Clinical assessments: disease severity using MDS-UPDRS Part III (motor examination), most-affected side, most-tremulous side, handedness (Edinburgh Handedness Inventory), and cognitive function (MoCA).

Structural MRI: T1 and T2-weighted structural images, diffusion-tensor imaging (DTI) scan, and neuromelanin scan. The anatomical T1-image will be used for registration of the fMRI-scans and the T2-image for improved cerebellar segmentation. The DTI and neuromelanin scans will be used to look for the integrity of the substantia nigra and locus coeruleus (LC). These measures are then correlated to clinical and electrophysiological tremor characteristics, as well as cerebral tremor-related activity (see below).

Functional MRI: the fMRI experiment will be used to investigate and localize cerebral tremor-related activity. Moreover, within-subject differences in cerebral activity patterns and connectivity strengths between resting tremor 2 - The Cerebral Mechanisms of Re-emergent Tremor in Parkinson's Disease 7-06-2025 and re-emergent postural tremor will be investigated. The extent of activity and effective connectivity parameters of the tremor-circuit will be correlated with electrophysiological tremor characteristics (e.g., tremor amplitude, the duration of the latency, etc).

Electrophysiology: tremor will be measured from surface-electromyography (EMG) and accelerometery. Surface EMG electrodes will be placed on the first dorsal interosseus, abductor pollicis brevis, extensor carpi radialis, flexor carpi radialis, biceps, and triceps on the most-tremulous side. In case of clear leg tremor, surface EMG-electrode may be placed on the gastrocnemius and/or tibialis anterior muscles. A tri-axial accelerometer will be placed on both the most and least-tremulous side (dorsum of the hand). These peripheral tremor measures will be used to characterize tremor, assess tremor-specific eligibility for the fMRI session, and during scanning to compute scan-by-scan fluctuations of tremor power, which will be used to obtain cerebral tremor-related activity, as done before.

Behavioural assessments: subjects will perform a mental arithmetic task during part of the trials (e.g., 100-3, 100-6, 100-7, 100-9). Such a cognitive co-activation task is known to induce tremor, increase its (variations in) amplitude and shorten the latency duration. This task is added to increase the odds of capturing clear tremor episodes before the trial ends. Pupil diameter and heart rate will be recorded as a proxy of cognitive effort during scanning, similar to previous studies.

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Participant characteristics: date of birth, biological sex, disease duration

since diagnosis, disease duration since subjective symptom onset, relevant

comorbidities, and medication use.

# **Study description**

### **Background summary**

Tremor (trembling) is one of the cardinal motor symptoms of Parkinson\*s disease (PD) and patients report tremor to be one of the main symptoms they wish to see improvement upon. Parkinsonian tremor often occurs at rest in the hands, which is called a resting tremor. However, tremor is often suppressed during voluntary movement and may re-emerge several seconds later after adopting a stable posture against gravity. This is called re-emergent postural tremor. Unfortunately, usual dopaminergic medication (e.g., levodopa) is not or moderately effective in alleviating resting tremor and medication effects are even worse for re-emergent postural tremor. Limited knowledge regarding the cerebral mechanisms of re-emergent tremor hinders development of novel therapies.

# **Study objective**

To unravel the cerebral mechanisms of re-emergent postural tremor in PD and understand to what extent these mechanisms overlap with those involved in resting tremor. A secondary objective is to understand how cerebral tremor-related mechanisms relate to MRI correlates of nigrostriatal (dopaminergic) cell loss.

# Study design

This study involves an observational fMRI study in PD patients exhibiting both resting and re-emergent postural tremor (n=40).

Clinical, electrophysiological, and MRI measures will be collected. This study will involve two sessions on separate days with the second visit preferably scheduled <1 month after the first visit. The first visit will not involve fMRI and will mainly be used to characterize re-emergent postural tremor and confirm tremor-specific eligibility criteria for the second (fMRI) visit. These eligibility criteria are based on two main factors: 1) there is clear tremor suppression after abrupt voluntary movement, and 2) tremor suppression does not last more than 20 seconds. The study will take place at the Donders Centre for Cognitive Neuroimaging (DCCN) and the sponsor is the Radboud University Medical Center (Radboudumc).

### Study burden and risks

The burden on the patients mainly consist of the time spent during this study (two sessions of ~95 minutes, 3 hours total) and potentially a worsening Parkinsonian symptoms as a result of withholding medication on the morning before the study assessments. All measurements are non-invasive, painless, and without ionizing radiation. Patients do not directly benefit from participating in this study. However, we are convinced that this study will provide novel insights into the mechanisms of Parkinsonian tremor which will improve future research regarding novel therapeutic targets for tremor treatment.

# Contacts

### Public

Radboud Universitair Medisch Centrum

Reinier Postlaan 4 Nijmegen 6525 GC NL **Scientific** Radboud Universitair Medisch Centrum

Reinier Postlaan 4 Nijmegen 6525 GC NL

# **Trial sites**

# **Listed location countries**

Netherlands

# **Eligibility criteria**

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

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# **Inclusion criteria**

- A diagnosis of idiopathic PD made by a movement disorder specialist
- PD disease duration of 7 years or less, defined as time since diagnosis by a neurologist

- A history of both resting and re-emergent postural tremor in the same arm

# **Exclusion criteria**

- Severe neurological co-morbidity
- Co-existing other tremor (e.g., functional tremor, dystonic tremor, essential tremor)
- Significant cognitive impairment: Montreal Cognitive Assessment (MoCA) <21 points
- Contra-indications for MRI
- Moderate to severe head tremor
- Tremor latency duration >20 seconds after abrupt voluntary movement
- Unclear tremor suppression after voluntary movement
- Taking dopamine-agonists with a levodopa equivalent dose of more than 150mg per day

# Study design

# Design

Study type: Observational non invasive		
Masking:	Open (masking not used)	
Control:	Uncontrolled	
Primary purpose:	Basic science	

# Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	26-02-2025
Enrollment:	40
Туре:	Actual

# Medical products/devices used

Registration:

No

# Ethics reviewApproved WMO<br/>Date:12-09-2024Application type:First submissionReview 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 CCMO **ID** NL85143.091.24