# Explorations into the cerebral mechanisms of dopa-responsive and dopa-resistant Parkinson*s resting tremor

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We hypothesize that PD patients with dopa-responsive and dopa-resistant tremor have different tremor-related brain activity, different inter-regional functional connectivity, and different GABA-ergic tone in the thalamus. Furthermore, we expect that...

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| **Ethical review** | Approved WMO |
| **Status** | Recruiting |
| **Health condition type** | Movement disorders (incl parkinsonism) |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON40810

**Source**
ToetsingOnline

**Brief title**
Dopa-responsive vs. dopa-resistant tremor in PD

### Condition

- Movement disorders (incl parkinsonism)

**Synonym**
Parkinson's disease, tremor

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Sint Radboud

**Source(s) of monetary or material Support:** Dutch Brain Foundation (Hersenstichting)

## Intervention

**Keyword:** functional MRI, Magnetic resonance spectroscopy, Parkinson's disease, Tremor

## Outcome measures

### Primary outcome

The primary outcome measure of this study is the difference in tremor-related brain activity at rest, during a motor task, and during a simple cognitive task, with and without dopaminergic therapy, between Parkinson patients with dopa-resistant and dopa-responsive tremor.

### Secondary outcome

Secondary outcome measures are the difference in GABA concentrations in the thalamus, structural integrity of the brain stem (DTI), and functional connectivity between basal ganglia and the cerebello-thalamo-cortical circuit, between both Parkinson groups and healthy controls. We will also compare tremor characteristics (frequency, distribution over the body) between Parkinson patient with dopa-responsive and dopa-resistant tremor, and we will compare cognitive performance on dopamine-sensitive and dopamine-insensitive behavioral tasks.

# Study description

### Background summary

Resting tremor is a core symptom of Parkinson*s disease (PD). Unlike other motor symptoms, the response of tremor to levodopa varies greatly between PD patients. The reason for this variability is unclear, preventing treatment and development of new therapies. Using concurrent fMRI and EMG recordings, we have

previously developed a new technique to localize brain regions involved in tremor. This approach allows us to detect differences in cerebral activity between patients with dopa-resistant and dopa-responsive tremor. Furthermore, we will investigate the role of GABA in both tremor types, since GABA is the most important inhibitory neurotransmitter in the human brain, and since inhibition of the thalamus is strongly linked to the expression of tremor. Finally, we investigate differences in the structural integrity of the brain stem (using DTI) between Parkinson patients with a dopamine-responsive and dopamine-resistant tremor.

## Study objective

We hypothesize that PD patients with dopa-responsive and dopa-resistant tremor have different tremor-related brain activity, different inter-regional functional connectivity, and different GABA-ergic tone in the thalamus. Furthermore, we expect that both groups have different cerebral responses to levodopa.

## Study design

This research takes place in two phases. In phase 1, we will measure tremor severity before and after dopaminergic treatment (i.e. Levodopa-Benserazide 250 mg) in 80 patients with Parkinson's disease. From this group we will select 25 patients Parkinson with dopa-responsive tremor and 25 patients with dopa-resistant tremor, who will take part in phase 2. We will also include 25 healthy controls. In all 3 groups, we will measure brain activity using fMRI, and tremor variations with EMG. This allows us to test for tremor-related activity. We will test all patients twice: without their normal medication, and after having taken Levodopa-Benserazide 250 mg. We will also measure GABA concentrations in the thalamus using magnetic resonance spectroscopy (MRS), and structural integrity of the brain stem using DTI.

## Intervention

All Parkinson patients (n=80) will be tested without dopaminergic medication (their own medication stopped for at least 12 hours). On one day they will receive a placebo (with 10 mg Domperidon), on the other day dopaminergic medication (250 mg Levodopa-Benserazide and 10 mg Domperidone). The goal of the intervention is to distinguish patients with a dopamine-responsive tremor from patients with a dopamine-resistant tremor, and to test if tremor-related brain regions in both groups are dopamine-responsive. This is not a randomized research. The controls will not get an intervention.

## Study burden and risks

The experimental protocol will consist of clinical measurements, and

performance of a simple motor and cognitive task in the fMRI scanner. These measurements will be performed on 3 mornings (duration: 4-4.5 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 two sessions, patients will receive a standard dose of Levodopa-Benserazide (250 mg) that may (or may not) be higher than the patient's own 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.

## 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 criteria.
- Presence of a clear resting tremor of at least one arm (UPDRS tremor-score 2 or more).
- Dopaminergic therapy with a clear clinical response of non-tremor symptoms (bradykinesia, rigidity).
- Milde tot 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.
- Age < 25 years.

## Study design

### Design

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

### Recruitment

NL

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|---|---|
| Recruitment status: | Recruiting |
| Start date (anticipated): | 06-06-2014 |
| Enrollment: | 105 |

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| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 27-03-2014 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 17-12-2014 |
| Application type: | Amendment |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 08-10-2015 |
| 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

ID: 20997
Source: Nationaal Trial Register
Title:

### In other registers

| Register | ID |
|---|---|
| CCMO | NL47614.091.14 |
| OMON | NL-OMON20997 |