The neurobiological correlates of anhedonic depression in Parkinson*s disease; associations between dopamine function and functional pathways

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

Summary

ID

NL-OMON54140

Source
ToetsingOnline

Brief title
AnHedonic dEpression&Alteration in Dopamine-neurocircuit in Parkinson:AHEAD

Condition

- Movement disorders (incl parkinsonism)
- Mood disorders and disturbances NEC

Synonym
depression, 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,Congressionally Directed Medical Research Programs-Department of Defense USA

Intervention

Keyword: anhedonia, depression, dopamine, Parkinson's Disease

Outcome measures

Primary outcome

Differences between (anhedonic and non-anhedonic) depressed PD patients and non-depressed PD patients in: (1) Baseline DAT-availability measured with PET; (2) Functional connectivity from seeds with aberrant DAT-availability compared to non-depressed PD.

Secondary outcome

Differences between (anhedonic and non-anhedonic) depressed PD patients and non-depressed PD patients in effort-reward weighting on an effort-reward-choice-task (ERCT), fMRI-based BOLD signal when performing the ERCT during the decisional phase, fMRI-based BOLD signal when performing a reinforcement learning task, neuromelanin, and subjective self-report measurements assessing depression, anhedonia, apathy and anxiety.

Study description

Background summary

Parkinson*s Disease (PD) is the second most prevalent neurodegenerative brain disease, characterized by degeneration of dopaminergic (DA) neurons. In PD, depression is very common (35%) with a high disease burden. Although the etiology of PD-depression is likely multifactorial, specific brain regions and

neurotransmitters have been implicated, including dopamine. Despite increasing interest in identifying underlying mechanisms of depression in PD, we still lack insight needed to tailor individual treatments. Moreover, studies in (non-PD) depression indicate the need to distinguish psychiatric phenotypes of depression. The anhedonic subtype is of particular interest in PD. Anhedonia is defined as a decreased motivation for and sensitivity to rewarding experiences and is linked to aberrant DA neurotransmission. Prior clinical research in PD-depression was hampered by three limitations: psychiatric assessment was not performed according to the state of the art, clinical heterogeneity was not considered, and radiotracers not selective for dopamine transporter (DAT) were used. In the present study, we explicitly focus on clinically carefully defined subgroups, anhedonic vs. non-anhedonic depression, and use a selective DAT tracer.

Study objective

First aim is to quantify DA function of meso-limbic/cortical DA pathways (measured with 18F-FE-PE2I Position Emission Tomography (PET) in PD-depression with or without anhedonia (vs. non-depressed PD). Second aim is to associate these DAT findings with differences in functional connectivity (measured by resting state functional Magnetic Resonance Imaging (fMRI) (vs. non-depressed PD) in these networks.

Study design

This observational cross-sectional multimodal neuroimaging study combines fMRI with a novel, highly selective DAT PET tracer (18F-FE-PE2I) in a comparison of three groups of PD-patients.

Study burden and risks

Participants will attend screening session with a psychiatric interview of approximately 90 minutes, followed by two study days of approximately 5-6 hours each; entailing two assessments with fMRI, questionnaires and behavior tasks and one PET-session. At least 12 hours preceding one of the two fMRI sessions, participants will have to refrain from dopaminergic medication, and as such, patients will arrive in a practically defined OFF state. At the end of the measurement, they will resume their normal medication regime.
The load on participants consists of the time spent on this project, potentially a temporary worsening of symptoms caused by withholding medication, and the low-dose nuclear radiation due to the PET session (of the same order of magnitude as the annual background radiation in various parts of the world.). Individual participants do not directly benefit from participation. We expect that this study will improve our knowledge about the cerebral mechanisms underlying (anhedonic versus non-anhedonic) depression in PD, which may lead to new ways of treating depression in PD, a disease with high burden on patients

and their relatives.

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

For the present study, we will select patients from the PPP and PRIME cohorts and from clinical samples from neurologists embedded in Parkinsonnet and/or in the service area of the RadboudUMC. The PPP study is a pro-spective, longitudinal, single-center cohort study of the Radboudumc in the Netherlands which started in October 2017. Enrollment period will take 2 years, in which a total of 650 adult patients diagnosed with PD with <=5 years duration will be included. PRIME is a prospective longitudinal study of the RadboudUMC of the Netherlands which started in 2019 and enrolls 1200 patients with either clinically diagnosed PD or parkinsonism.

ParkinsonNet is an innovative health care concept that consists of 70 professional networks for PD covering all of the Netherlands
In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• A diagnosis of PD with <=10 years duration, defined as time since diagnosis made by a neurologist.
• Subject can read and understand Dutch.
• Subject is willing, competent, and able to comply with all aspects of the protocol
• meeting DSM-criteria for a depression including the criterium of a sad mood (depressed PD group)
• in the 5 past years and/or currently not meeting DSM-criteria for a depression (non-depressed PD control group)

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

Exclusion criteria:
• Contraindications for MRI, e.g., claustrophobia, presence of an active implant, pacemaker, insulin pump, neurostimulator, ossicle prosthesis, pregnancy, and/or other medical device or other non-removable metal part incompatible with MRI.
• Contraindications for PET e.g., inability to lie flat or lie still for the duration of the scan, claustrophobia (occasionally).
• Use of medication or drugs with evident DAT-binding like methylphenidate, buproprion, amphetamines, cocaine that cannot be discontinued according to the PET-protocol. Note that we allow use of anti-depressants with the exception of those antidepressants with a high DAT binding defined as a relatively low Ki of <1000 (, i.e. for the Netherlands buproprion, duloxetine and sertraline). Moreover, we will exclude patients using antidepressants at higher than minimal effective dosages used for antidepressive effects when the Ki is <10000 (i.e. for the Netherlands amitryptiline, clomipramine, maprotiline, nortriptyline, fluoxetine, paroxetine).
• Being diagnosed with dementia (defined as a Montreal Cognitive Assessment (MoCA) <21/30 (Dalymple-Alford 2010), assessed ON Parkinson medication).
• Psychiatric diagnosis of bipolar disorder.
• Presence of current psychotic symptoms.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-03-2022
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO Date:	14-09-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-07-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-02-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-04-2023
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
CCMO	NL74241.091.20
Other	NL8664