Anhedonic depression and alterations in the dopaminergic neurocircuitry in Parkinson’s disease

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Primary Objective: Our first aim is to quantify dopaminergic function in mesolimbic/mesocortical dopaminergic pathways (measured with 18F-FE-PE2I PET) in PD-depression with or without anhedonia. We hypothesize that lower DAT-availability (i.e. more...

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON26572

Bron
Nationaal Trial Register

Verkorte titel
TBA

Aandoening

Parkinson's Disease, Depression, Anhedonia

Ondersteuning

Primaire sponsor: RadboudUMC Nijmegen, Department of Psychiatry
Overige ondersteuning: Congressionally Directed Medical Research Pro-grams-Department of Defense USA
Parkinson’s Research Program, Early Investigator Research Award

Department of Psychiatry, RadboudUMC

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Differences between (anhedonic and non-anhedonic) depressed PD patients and non-depressed PD patients in:

• Baseline DAT-availability measured with PET
• Functional connectivity from seeds with aberrant DAT-availability compared to non-depressed PD, in ON and OFF PD medication conditions.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: 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, includ-ing 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 moti-vation for and sensitivity to rewarding experiences and is linked to aberrant DA neurotrans-mission. Prior clinical research in PD-depression was hampered by three limitations: psychiat-ric assessment was not consequently performed according to the art, clinical heterogeneity was not considered, and radiotracers not selective for 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.

Objective: First aim is to quantify DA function of meso-limbic/cortical DA pathways (meas-ured 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 dif-ferences in functional connectivity (measured by resting state functional Magnetic Reso-nance 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 population: The current CMO application concerns 75 (+15 in case of drop-out) pa-tients with PD (who are included in the Personalized Parkinson's Project (in total 650 PD pa-

tients will be included, NL59694.091.16). Eligible are those who score >=14 on Beck Depression Inventory and fulfill the criteria of a depression, or -in contrast- score <=8 and do not ful-fill the depression-criteria. Depressed patients are stratified in 2 different phenotypes: anhe-donic (n=25, +5 in case of drop-out) and non-anhedonic depression (n=25, +5). Subtyping of the depression will be established by a psychiatrist's evaluation of the anhedonia criterion in DSM-5. These groups will be contrasted with a control group of non-depressed PD patients (n=25, +5).To explain additional variance, self-report questionnaires and a behavioral task assessing various aspects of anhedonia will be obtained.

Intervention (if applicable): Not applicable.

Main study parameters/endpoints:
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 parameters
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.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness:

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. Individual participants do not directly benefit from participation. We expect that this study will improve our knowledge about the cerebral mechanisms under-lying (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.

Doel van het onderzoek

Primary Objective:
Our first aim is to quantify dopaminergic function in mesolimbic/mesocortical dopaminergic pathways (measured with 18F-FE-PE2I PET) in PD-depression with or without anhedonia. We hypothesize that lower DAT-availability (i.e. more dopamine depletion) exists in ventral striatum and brainstem (i.e. meso-limbic pathway) with potentially less disturbances in the

prefron-tal cortex) in the anhedonic depressive subtype versus the non-anhedonic subtype. In con-trast, in the non-anhedonic subtype we expect less differences in DAT availability compared to non-depressed PD in the ventral striatum and brainstem and potentially more pronounced differences in the prefrontal cortex (meso-cortical pathway).

Secondary Objective(s):
Our second aim is to associate these DAT-findings with differences in functional connectivity (measured by fMRI) in these mesolimbic/mesocortical networks and examine differences in functional connectivity between groups (anhedonic versus non-anhedonic versus non-depressed PD patients). We expect decreased functional connectivity in the mesolimbic pathway especially in anhedonic PD-depression, while we expect decreased connectivity in the mesocortical pathway in the non-anhedonic subtype. Finally, we expect the decreases in connectivity to be largest when DAT-availability in the pathway is lowest.

Onderzoeksopzet

This is a cross-sectional study, so there is only one time point; the assessments are obtained within three sessions, planned closely together.

Onderzoeksproduct en/of interventie

not applicable

Contactpersonen

Publiek

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

• A diagnosis of PD with <=5 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
• BDI score 14 ánd meeting DSM-criteria for a depression including the criterium of a sad mood (depressed PD group)
• BDI score <8 ánd in the 5 past years and/or currently not meeting DSM-criteria for a depression (non-depressed PD control group)

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

• 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.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm

Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-12-2020
Aantal proefpersonen:	75
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	25-05-2020
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL8664
Ander register	CMO RadboudUMC : 2020-6619

Resultaten