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

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON26572

Source
Nationaal Trial Register

Brief title
TBA

Health condition

Parkinson's Disease, Depression, Anhedonia

Sponsors and support

Primary sponsor: RadboudUMC Nijmegen, Department of Psychiatry
Source(s) of monetary or material Support: Congressionally Directed Medical Research Pro-grams-Department of Defense USA
Parkinson’s Research Program, Early Investigator Research Award

Department of Psychiatry, RadboudUMC

Intervention

Outcome measures

Primary outcome

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.

Secondary outcome

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

• Effort-reward weighting on a behavioural computerized task -the effort-reward-choice-task (ERCT) - (Bonnelle 2016) to assess aspects of anhedonia in ON and OFF PD medication conditions.
• fMRI-based BOLD signal when performing the ERCT during the decisional phase in ON and OFF PD medication conditions.
• fMRI-based BOLD signal when performing a reinforcement learning task (Schmidt 2014) in ON and OFF PD medication conditions.
• Subjective self-report measurements (self-report questionnaires Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith 1995) and the Temporal Experience of Pleasure Scale (TEPS) (Gard 2006) to assess aspects of
anhedonia, the Apathy Evaluation Scale (AES)-12PD to quantify the rate of apathy (Marin 1991, Beck Depression In-ventory (Beck 1961) and Inventory of Depressive Symptomatology (IDS) (Rush 1996) to quantify severity of depression, and the State-Trait Anxiety Questionnaire (STAI) (Spielberger 1983) and the Parkinson Anxiety Scale (Leentjens 2014) to quantify anxiety.

Study description

Background summary

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 (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 population: The current CMO application concerns 75 (+15 in case of drop-out) patients with PD (who are included in the Personalized Parkinson's Project (in total 650 PD patients 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.

Study objective

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 stria-tum 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.

Study design

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

Intervention

not applicable

Contacts

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Eligibility criteria

Inclusion criteria

• 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)

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 non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2020
Enrollment:	75
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	25-05-2020
Application type:	First submission

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
NTR-new	NL8664
Other	CMO RadboudUMC : 2020-6619

Study results