Title:

Dynamic Brain Mapping of the Functional Effects of Levodopa on Multiple Cortex-basal Ganglia Circuits in Parkinson´s Disease

ID:

H-22010296

Date:

October 5, 2023

STUDY PROTOCOL

For the sub-study, we aim to recruit 25 PD patients with LID, 25 PD patients without LID, and 25 age-matched healthy controls.

Day 1: Clinical and neuropsychological tests

A neurological examination as well as clinical and neuropsychological tests will be performed including Unified Parkinson's Disease Rating Scale (UPDRS), MDS-UPDRS, Unified Dyskinesia Rating Scale (UDysRS), Non-Motor Symptoms Questionnaire & Scale for Parkinson's Disease (NMSQuest & NMSS), Non-Motor Fluctuation Assessment (NoMoFA) Questionnaire, Montreal Cognitive Assessment (MOCA), Lille Apathy Rating Scale (LARS), Barratt Impulsiveness Scale (BIS-11), Questionnaire for Impulsive-Compulsive Disorders (QUIP), Major Depression Scale (MDI), Edinburgh Handedness Inventory (EHI).
Total duration of day 1 is 2-3 hours.

Day 2: Structural and functional 3T MRI

Patients will not take their ordinary morning dose of antiparkinsonian medication before arrival. Patients will be rated using the UPDRS, MDS-UPDRS and UDysRS in the pragmatic off state (after 12 hours of withdrawal of antiparkinsonian medications). First a 3T T1w and T2w sMRI will be performed (10 minutes). Then fMRI in the off state (before levodopa intake) will be performed while doing one run of the task (10 minutes). Hereafter the participating patients will come out of the scanner to take 150 % of their normal levodopa dose as Madopar® Quick. Hereafter the fMRI continues while performing three more runs of the task (30 minutes) or until the patient develops LID. After the scan the patients' Parkinson's symptoms and dyskinesia will be rated using the UPDRS, MDS-UPDRS and UDysRS.
Total duration approximately 2-3 hours including preparation.
For healthy participants, day 1 and 2 will be combined and they will not take Madopar® Quick. Furthermore healthy controls will not be rated with UPDRS, MDS-UPDRS, UDysRS, NMSQuest, NMSS, NoMoFa, or QUIP.

MRI sequences using 3T Siemens Prisma

T1-weighted

Voxel size: 0.9 mm3

TR: 2700 ms

TE: 3.7 ms

TI: 1090 ms

Flip angle: 9 deg

T2-weighted

Voxel size: 0.9 mm3

TR: 2500 ms

TE: 349 ms

BOLD

Voxel size: 2.5 mm3

Number of slices: 62 slices

Multiband accel. factor 2

TR = 1800 ms

TE: 30 ms

Flip angle: 65 deg

Task description

During the BOLD fMRI the participants will perform a task. The task is a novel go/no-go task developed by our research group. Apart from the motor aspect of the task (left, right, no-go) it also involves an emotional component of emotional faces in the background, a reward component when the participant can win or lose a high or low reward, and reward prospect component of two prospects of reward (high or low). Responses are made with MR-compatible grip-force devices.

Day 3: [18F]PE2I-PET

Participants will have 175 MBq [18F]PE2I injected via a venous catheter while lying in the scanner. Then a clinical [18F]PE2I-PET will be performed. Healthy controls will not participate in the PET experiment.

Total duration approximately 2 hours including preparation.

ASSESS TO CLINCAL DATA

Participants will be asked for direct access to their electronical medical records from the regional database of medical records (*Sundhedsplatformen*) and the medication database (*Fælles medicinkort*). Access to electronical medical records will be given to personal with medical background. The assess to medical records will be included in the informed written consent form.

In *Sundhedsplatformen* the following information will be retrieved:

1. Medical history regarding PD including time of symptom onset, date of diagnosis, information regarding Parkinson symptoms and LID.
2. Medical history regarding comorbidities which are potential exclusion criteria.
3. Medical history regarding potential metallic or electrical implants to evaluate the safety of participating in the study.
4. Neuroimaging to confirm the diagnosis of PD including DAT SPECT, PE2I-PET, MR-cerebrum.
5. Imaging to investigate possible electronic or metallic implants e.g., x-ray or MR.

Medical history will be reviewed to make sure that the patient fulfills the inclusion/exclusion criteria and to register key data related to Parkinson's disease. Furthermore, prior imaging will be reviewed to also to check that the participants fulfil the inclusion/exclusion criteria (no sign of other neurological disease).
In *Fælles medicinkort* current list of medication will be retrieved.

QUALITY ASSURANCE PLAN

All acquired data will be quality assessed. MRI data will be visually assessed during the scan and MRI, behavioral, and PET data will be assessed visually and based on quality-assurance parameters (e.g. head movement) during preprocessing.

DATA CHECKS

Will not be performed as only few data are entered manually into registry. Those data will be sanity-checked during analysis.

SOURCE DATA VERIFICATION

Will not be performed as it is not relevant in this study.

RECRUITMENT

Patient with Parkinson's disease will be recruited in the ambulatory care setting at the Department of Neurology, Bispebjerg Hospital and through private practicing neurologists. As part of the clinical assessment relevant PD patients will be asked if they would be interested in participating in the study. This can occur as part of the clinical assessment by a neurologist or when patients have a PE2I-PET scan. Also, letters with an invitation to participate in the study will be sent to patients with PD who are followed in the movement disorder clinics of the department. The text of the letters include is a description presentation of the research project and a notification that we will make a telephone call within a few weeks. Within 1-2 weeks after receiving the letter, we will call the patients to ask if they are interested in participating in the study. Spouses accompanying enrolled PD patients at study visits will be given the opportunity to participate as healthy controls. Written information is handed out or sent to the participants.

Furthermore, Parkinson's patients and healthy controls will be recruited through advertisement. Participants will be recruited from the following websites: https://www.sundhed.dk/, http://www.forsoegsperson.dk/, https://www.parkinson.dk/, and social media (Facebook, Twitter, and LinkedIn).
Volunteers will also be recruited via advertisements in local newspapers or posts at sites such as culture centres, libraries, locally in the department.

DATA MANAGEMENT

Confidential documents will be stored in a locked closet. Electronic information that can be traced to an identifiable person will be stored on password-protected cluster (Thinlinc) behind secure "firewall" in accordance with the Privacy Act and notified to the Danish data agency (*Datatilsynet*) via the Region's common notification (IDEA0003712/DMND0448431). Collected data will be anonymized. The participant's name will never be used in scientific publications or presentations. However, participants will, to the extent they wish, be informed of their own results. All personally identifiable information will be destroyed (corresponding to total anonymity) no later than 10 years after project completion.

All sensitive personal data will be stored according to the Danish law on data protection ”Databeskyttelsesloven” and the General Dataprotection Regulation.
Participants will receive written information about the handling of data.
Behavioral and imaging data are stored in the BIDS (Brain Imaging Data Structure, bids.neuroimaging.io) standard.

STATISTICAL ANALYSIS PLAN

Preprocessing

The raw fMRI data will be preprocessed using standard procedures, including motion correction, slice-timing correction, spatial normalization, and spatial smoothing.
fMRIprep will be used for preprocessing.

First level analyses of single-person data

For each participant and each run, we will create general linear models to model the BOLD (Blood Oxygen Level Dependent) response to the task-related events (regressors of interest) in each voxel (mass-univariate approach). First-level contrast maps will be generated for each participant, comparing the task conditions of interest. We will add a linear time modulation to all regressors to model dynamic changes in activation over time.

Contrasts of interest

1. Motor response: Left, right, no-go
2. Emotion: Happy, neutral, sad
3. Reward: High/low reward, high/low loss
4. Reward context: High, low

Contrasts of no interest

1. Physiological noise (pulse and respiration)
2. Movement

Second level analyses at group level

Group Inference: Group-level analysis will involve random-effects models (ANOVA and t-test) to assess task-related activation across participants. Significance level will be set at $p<0.05$ after correction for multiple comparison.

First and second level analysis will be performed using the freely available software package "NILEARN".

Behavioral data

Behavioral data will be analyzed in Python.

SAMPLE SIZE ASSESSMENT

We aim at a beta risk of .8 and an alpha risk of .05 and anticipate a drop-out rate of 20-25 %. Furthermore, biological variation in MRI measurements and the signal to noise ratio associated with these modalities should be considered. In our previous study (Herz et al., Ann Neurol. 2014 Jun;75(6):829-36. doi: 10.1002/ana.24138), we used a similar dynamic pharmacological functional MRI approach and a similar task paradigm. In this study, a group difference between patients with and without LID was robustly expressed in a sample size of 13 per group. In prior functional MRI studies comparing patients with PD and healthy controls, the necessary number of participants ranged from 10 to 30, depending on the scientific question. Therefore, we aim to recruit at least 25 participants per group with useable data, so that we can include 25 data sets per group in the between-group analyses.

PLAN FOR MISSING DATA

In case of missing data, those data will not be imputed. The analysis will be made without the missing data.

Informed consent for participation in a biomedical research project

Title of the research project:

Dynamic mapping of changes in brain structure and function in Levodopa-induced dyskinesias in Parkinson's disease

Statement from the research participant

I have received written and oral information and I know enough about the purpose, method, advantages, and disadvantages to agree to participate.

I know that participation is voluntary and that I can always withdraw my consent without losing my current or future rights to treatment.

I have received a copy of this consent form and a copy of the written information about the project for my own use.

I am aware that I will be informed if abnormal changes are observed in my brain, and that relevant information will, if necessary, be forwarded to my general practitioner or relevant hospital/department.

Do you want to be informed about the results of the research project and any consequences for you? **Yes _____ (x)** **No _____ (x)**

May we contact you again to obtain additional information, should it prove relevant?

Yes _____ (x) **No _____ (x)**

May we contact you again with inquiries about participation in other research projects?

Yes _____ (x) **No _____ (x)**

Can we post your medical record on the health platform and your medication list on the joint medicine card (FMK)?

Yes _____ (x) **No _____ (x)**

Can we film you during the examinations? – This will not be shared with third parties without further consent.

Yes _____ (x) **No _____ (x)**

Name of participant:

_____

Date: _____ Signature:

Statement from the experimenter:

I declare that the subject has received oral and written information about the experiment and has had the opportunity to ask me questions.

In my opinion, sufficient information has been provided for a decision to be made regarding participation in the trial.

Name of the person who gave the information:

_____

Date: _____ Signature: