Investigation the use of radiomics for analysis of DAT SPECT imaging in Parkinson's Disease

Academic Year 2022/2023

HOMEWORK STUDY PROTOCOL

Summary

The data for this homework have been derived from the PET NODE REPOSITORY available at the King's College London. Specifically, it refers to a set of radiomics features derived for DAT SPECT imaging scans acquired from 33 idiopathic PD patients and 20 matched healthy controls. All the relevant information derived from the study protocol are reported below, while imaging analysis methods and quantification of radiomic features is reported at the end of the document.

Protocol relevant information

Type of control	This is an open-label study. All patients will receive a screening visit, a clinical a neurological visit and an imaging assessment. Non-demented subjects will be used as control group for comparison.
Number of study subjects	(1) 33 idiopathic PD patients (2) 20 matched HC subjects for age and gender
Methodology	**Screening**: Subject eligibility is evaluated at the Screening Visit. **Clinical/neuropsychological visit:** General motor function (MDS-UPDRS part 2 and 3, H&Y staging), non-motor symptoms (MDS-UPDRS part 1; NMSS; SCOPA for autonomic symptoms; PDSS, ESS and RBDQ to detect sleep problems; MCAS for constipation; PD Fatigue Scale for fatigue, King's Pain Scale for pain; UPSIT for olfactory function), global cognitive function (MMSE, MoCA), mood problems (BDI-II and GDS), anxiety (STAI), apathy (Apathy scale), global neuropsychiatric battery (NPI), Semantic Fluency, Symbol Digit, Benton Judgment of Line Orientation, Hopkins verbal Delayed Recognition False Alarms, Delayed Recognition Hits and Immediate Recall, Letter Number Sequencing and on quality of life (PDQ-39) and exercise (PASE). **Imaging assessments:**

	The study includes a SPECT imaging scan for all the participants. The radioligand for this study is [123I]FP-CIT targeting the dopamine transporter system (for hereafter referred as SPECT DATSCAN). SPECT measurements consists of radioactivity counts in the brain. SPECT DATSCAN images will be obtained 4 ± 0.5 h after administrating an injection of approximately 185 MBq [123I]FP-CIT. SPECT [123I]FP-CIT image volumes will be spatially normalized to an [123I]FP-CIT template. The eight most prominent axial slices containing the striatum will be summed and a standardized volume of interest (VOI) template will be then applied to this image. VOI analyses will be performed on putamen, employing the cerebellum region as the reference tissue. Standardise Uptake Value Ratios (SUVRs) are calculated as the ratio of the putamen VOI count density divided by the cerebellum count density. This measure approximates the binding potential, when the radioligand is in equilibrium at the target site and has previously been reported with [123I]FP-CIT SPECT. For patients treated with dopaminergic supplementation, the visits and the evaluation (clinical and imaging) will be performed in OFF state and after 12 hours of withdrawal for immediate release and 24 hours for controlled release dopaminergic supplementation.
Diagnosis and main criteria for Inclusion and Exclusion	(1) early and levodopa-treated idiopathic PD patients and (2) healthy non-demented (MoCA>25) control subjects, must all the following eligibility criteria to be eligible for enrolment into the study: **Inclusion criteria (for all groups):** • Subjects must understand the nature of the study and must provide signed and dated written HRA-approved informed consent in accordance with local regulations before any protocol-specific screening procedures are performed. • Male and women, age 30-85 years, inclusive. • Women of child-bearing potential (WOCBP) must use protocol-defined contraceptive measures and must have a negative β-hCG test at screening. For sexually active subjects (except females of non-childbearing potential—e.g., at

	least 2 years postmenopausal or surgically sterile), condoms should be used in addition to other birth control methods for the duration of the study and for 3 months after the last administration of SPECT ligands. These patients must be willing to remain on their current form of contraception for the duration of the study. Postmenopausal females must have follicle-stimulating hormone (FSH) ≥ 38 mIU/mL at screen. All male subjects must agree to refrain from donating sperm for the duration of the study and for 3 months after the last administration of SPECT ligands (i.e. for 15 consecutive months following baseline SPECT scans). Sexually active male subjects must agree to use condoms to protect their partners from becoming pregnant for the duration of the study and for 3 months after the last administration of SPECT ligands (i.e. for 15 consecutive months following baseline SPECT scans); agree to ensure that they and their partners are routinely using a medically approved contraceptive method. It is important that male subjects not impregnate others for the duration of the study and for 3 months after the last administration of SPECT ligands (i.e. for 15 consecutive months following baseline SPECT scans). • Able and willing to participate in all scheduled evaluations, abide by all study restrictions, and complete all required tests and procedures. • Adequate visual and auditory acuity to complete the psychological testing. • In the opinion of the investigator, the subject must be considered likely to comply with the study protocol and to have a high probability of completing the study. **Inclusion criteria (Idiopathic PD group):** • Patients who have idiopathic PD according to the Movement Disorder Society Clinical Diagnostic Criteria (i.e. not induced by drugs or other diseases or carriers of PD risk genes such as

	LRRK2, *SNCA*, *PARK2* etc.), diagnosed after the age of 30 years. • Patients who are classified between Stage 1 to 3 inclusive (in the ON state) on the modified Hoehn and Yahr scale for PD severity. Patients who are *drug-naïve* (never been treated with dopamine agonists or levodopa) or on dopamine replacement therapy. **Exclusion criteria (for all groups):** • Subjects taking serotonin acting drugs such as antidepressants (i.e. tricyclic or selective serotonin reuptake inhibitors etc.) within 60 days prior to baseline and SPECT scans. • Subjects taking drugs acting on SV2A such as antiepileptics (i.e. levetiracetam or brivaracetam etc.). • Pregnancy or breastfeeding or intent to become pregnant in the next 18 months. • Subjects with current or a recent history of drug or alcohol abuse/dependence. • Subjects who have other neurological disorders and known intracranial co-morbidities such as stroke, haemorrhage, space-occupying lesions. • Presence of any clinically significant medical condition (including cardiovascular, respiratory, cerebrovascular, hematological, hepatic, renal, gastrointestinal, or other disease) that, based on the judgment of the investigator, is clinically unstable, is likely to deteriorate during the course of the study, could put the patient at risk because of participation in the study, could affect the subject's ability to complete the study, or could influence the study results. • History of suicidal behavior or active suicidal ideation. • Within 1 year prior to screen or between screen and baseline (Day -1), any of the following: myocardial infarction; hospitalization for congestive heart failure; hospitalization for, or symptoms of, unstable angina; or syncope not related to PD.

	• History or presence of renal disease or impaired renal function. • Clinically important infection (e.g., chronic, persistent, or acute infection) within 30 days prior to screen or between screen and baseline (Day -1). • History of cancer within the last 5 years, with the exception of nonmetastatic basal cell carcinoma of the skin. • Clinically significant blood clotting or bleeding disorder, including clinically significant abnormal findings in laboratory assessments of coagulation or hematology. • Use of antipsychotic medication within 3 months prior to screen or between screen and baseline (Day -1). • Use of any oral corticosteroid within 30 days prior to baseline and follow-up PET scans. • Use of metoclopramide within 30 days prior to baseline and follow-up (Day -1). • Use of any thyroid medication within 30 days prior to baseline and follow-up (Day -1). • Regular use (e.g., taken > 3 days/week) of narcotic pain medications within 30 days prior to baseline and follow-up (Day -1). • Claustrophobia and history of back pain that makes prolonged laying on the PET or MRI scanner intolerable. • History of severe skin allergy **Exclusion criteria (for PD groups):** • Patients who had previous surgery for PD (including but not limited to deep brain stimulation [DBS] or cell transplantation). • Patients who are treated with duodopa or apomorphine. • Initiation or change in pharmacologic therapy for symptoms of PD within 30 days prior to screen or between screen and baseline (Day -1). • Radiation exposure >10 mSv for research or occupational purposes in the 12 month period prior to study enrolment.

	Exclusion criteria (for healthy controls): • Radiation exposure >10 mSv for research or occupational purposes in the 12 month period prior to study enrolment.
Statistical Methods	
Demographics	All data for background and demographic variables will be listed. For these parameters, summary statistics will be provided by group. Relevant medical history, current medical conditions, results of laboratory screens, and any other relevant information will be listed by group.
Safety	Analysis of safety parameters will include all vital signs, laboratory, and adverse event data listed by subject and visit/time. Summary statistics will be provided by visit/time.

Imaging data analysis and quantification

DAT SPECT imaging is a measure of pre-synaptic dopaminergic integrity and function through specific binding to dopamine transporters. For all the subjects, the imaging data analysis pipeline included the segmentation of brain anatomical regions using the CIC v2.0 neuroanatomical atlas and coregistration to subject's structural MRI.

Standard uptake value ratio (SUVR) was used as main parameter of interest to represent pre-synaptic dopaminergic integrity and function, where cerebellum grey matter was used as reference region.

The putamen (both right and left) were chosen as the main regions for the radiomics analysis.

Radiomics features extraction

Features were extracted for each subject using the MIRP Python package (https://github.com/oncoray/mirp). Calculations were performed in 3D: the ROI corresponding to the putamen was resegmented from the SUVR images to eliminate voxels with an intensity value below a threshold equal to 1.2 (selected after visual inspection of the available data). Discretisation was then performed by setting a fixed bin size of 0.0125 for the intensity histogram of the image. This value was set to have around 64 grey levels in the image.
When necessary, features were aggregated using the 3D average method.