Sorbonne Université/China Scholarship Council program 2021

Thesis proposal

Title of the research project: Multimodal MRI modeling of progression of the neurodegenerative process in Parkinson's disease

Keywords: Parkinson Disease, Biomarkers, progression modeling, REM sleep behavior disorders, MRI, diffusion imaging, partial least square-path modeling

Joint supervision: no

Joint PhD (cotutelle): no

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Subject description (2 pages max):

1) Study context

Parkinson disease (PD) is a neurodegenerative disease related to the spread of alpha-synuclein aggregate in the brain. The brain pathways of lesion spread remain highly debated. Braak et al. have proposed a model of disease propagation based on neuropathology, suggesting a caudal-rostral propagation from neuron to neuron beginning in the brainstem (starting in the medulla oblongata, and extending to the locus coeruleus and then to the substantia nigra) and extending to cortical structures, with increasing disease severity. This network-spread hypothesis postulates that neurodegeneration is caused by the propagation of a toxic agent that could enter the brain through the enteric nervous system. The olfactory bulb has been pointed out as another entry point of the causative agent that could extend to olfactory cortical areas and to the amygdala and then to other parts of the brain. This double propagation from the enteric nervous system or olfactory bulb was referred to as the dual-hit hypothesis.
In previous studies, our team has evidenced brainstem damage in PD patients in the medulla oblongata associated with with autonomic dysfunction (Pyatigorskaya et al. 2016), the locus coeruleus-subcoeruleus (LC) associated with REM sleep behavior disorders (RBD) (Garcia-Lorenzo et al. 2013) and in the substantia nigra associated with motor dysfunction (Biondetti et al. 2020). Moreover, we have shown that the LC (Ehrminger et al. 2016) and substantia nigra damage (Pyatigorskaya et al. Sleep 2017) were also present in patients with idiopathic RBD (iRBD)), which is considered a prodromal form of PD.
In the recent cross-sectional study in a small cohort of advanced PD patients, we have observed that PD patients with RBD followed the expected brainstem-to-cortex model of disease propagation while PD without RBD followed a different cortex-to-brainstem model. This study was based on the multimodal MRI analysis and Partial Least Square Path-Modeling.

2) Details of the proposal

The aim of this project is to get a deeper insight on the brain damage and disease progression trajectories in PD patients based on the cross-sectional and longitudinal multimodal MRI and clinical biomarkers. More particularly, we will determine if 1) the pattern of neurodegeneration in patients with iRBD is similar to the one observed in patients with PD with RBD, 2) subgroups of PD patients can be determined according to their brain damage and disease progression pattern using a data-driven approach, 3) the disease progression can be predicted using the brain damage profile determined on the baseline MRI.
We will include subjects from ICEBERG cohort, which is a 5-year longitudinal study of early PD and iRBD patients. In this study, 180 PD patients with and without RBD, 60 iRBD patients and 70 healthy volunteers are prospectively recruited from the Movement Disorders Clinic at the Pitié-Salpêtrière Hospital. All subjects have undergone **multimodal MRI** examinations using a 3 Tesla Prisma system (Siemens, Erlangen, Germany). The protocol includes 3D T1-weighted images, neuromelanin sensitive and iron imaging and diffusion tensor imaging. The **clinical** condition is evaluated using Hoehn and Yahr (H&Y) staging, the motor disability is estimated using the Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) in the "OFF" (12-hour dopaminergic treatment withdrawal) condition, the cognitive impairment is tested using the Mattis Dementia Rating scale score. Polysomnography registration, ECG analysis and the olfactory function evaluation using the Pennsylvania Smell Identification Test (UPSIT) are also performed. The patients

screening includes 4 years of clinical follow-up and 3 MRI examinations at baseline, at 2 years and 4 years that will be available for analysis.

Data analysis: clinical tests will be analyzed to generate scores for each test and each patient. MRI imaging will be preprocessed for motion correction and denoising and then segmented using Freesurfer software for large regions and previously developed inhouse algorithms for small regions. The regions of the olfactory network will be segmented using more specific atlases.

Volume, signal, and DTI settings such as mean diffusivity, axial diffusivity, radial diffusivity, fractional anisotropy and free water will be calculated in the segmented regions. Anatomical connectivity inside implicated networks will also be calculated.

Statistical analysis: In order to determine the relevant regions of interest and the discriminating parameters, the neuroimaging measures detailed above will be compared between the groups by Kruskal-Wallis and U Mann-Whitney tests. Variables that do not show a significant difference between the groups will be excluded. Then, we will calculate a diagnostic threshold value using a ROC curve. The sensitivity and specificity of the thresholds will be estimated using the Youden index. Diagnostic accuracy will be calculated as the ratio of the total number of correct diagnoses to all measurements. The global damage levels will be calculated for each region based on pertinent biomarkers. Next, we will use multiple factor analysis (MFA) as a data-driven exploratory technique to determine the communalities and differences in the patients' groups/biomarkers space.

Logistic regression will be performed using predictors derived from MFA to determine the most significant variables contributing to the separation between groups. After determining the relevant variables, several types of modeling will be used to model the cross-sectional damage level as well as the longitudinal damage progression and the correlation with clinical characterizations evolution of the patient by using data driven approaches and Partial Least Squares path modelling (PLS-PM). Finally, predictive models will be used to predict the disease progression based on the baseline patient's specific damage.

Expected results: we expect to observe different trajectories of damage progression between PD patients with and without RBD as well as in patients with initial iRBD. Using this approach, we expect to categorize patients in different subgroups of disease progression patterns, evolution profiles and prognosis. Results of this study will help better understand the physiopathology of Parkinson's disease progression.

3) References

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4°) Profile of the Applicant (skills/diploma…)

Ideally the applicant should have knowledge in image analysis, computer programing and in neuroscience. Being familiar with Matlab environment and/or Python and /or R will be a strong added value.

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