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BRAIN CONNECTIVITY CHANGES DURING THE DEGENERATIVE PROCESS IN PARKINSON'S DISEASE

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1. Summary of the project

Background: Parkinson's disease (PD) patients fulfilling mild cognitive impairment (MCI) criteria often evolve to dementia. MCI criteria include the presence of neuropsychological impairment but do not consider magnetic resonance imaging (MRI) biomarkers (functional and structural connectivity changes) or PD-comorbidities (idiopathic rapid eye movement sleep behavior disorder (iRBD), or presence of olfactory dysfunction) as features related to cognitive decline.

Main objective: The main objective of this project is to characterize brain connectivity changes during the degenerative process in PD, as a continuum from preclinical stages to dementia, and the identification of neuropsychological and MRI markers of cognitive decline.

Methodology:
Design: cross-sectional and longitudinal studies.
Participants: 30 healthy controls; 20 iRBD; 30 non-demented PD MCI and 30 PD non-MCI; 20 PD-dementia patients.

Procedures: clinical protocol (motor and neuropsychological assessment) and 3T MRI protocol (3D T1-weighted images, T2-weighted images, FLAIR, diffusion weighted EPI, gradient-echo echo-planar imaging-EPI sequence). Participants will undergo procedures at baseline and at 18 months follow-up.

Statistical analyses: Statistical software for multimodality imaging analysis (FSL, Freesurfer and AFNI) will be used to perform cross-sectional comparisons, correlations with clinical data and to identify the longitudinal changes.

Expected results: We will identify different patterns of structural and functional connectivity related to the clinical diagnosis, and to motor and cognitive scores. Longitudinal data will show decreases in structural connectivity accompanied by both increases and decreases in functional connectivity. We expect to identify network changes even in absence of clinical worsening, sensitive to short time period evolution. This could aid to monitor therapeutic approaches.

2. Results

The main objective of our project was to investigate the connectivity changes associated to Parkinson's disease (PD). The description of brain networks as graphs where nodes represent different brain regions and edges represent a measure of connectivity between a pair of nodes is an increasingly used approach in neuroimaging research. In the first step, we found that connectivity threshold-free network-based statistics (TFNBS) is an appropriate technique for the statistical assessment of brain graphs (Baggio et al., *Hum Brain Mapping* 2018). The most interesting result we found regarding brain connectivity was that the cognitive status of PD patients could be discriminated through functional connectomics using machine learning algorithms. From our patients' resting state fMRI, we achieved a mean accuracy of 82.6% to classify patients with and without cognitive impairment. Correlation analyses showed that the connectivity level on the edges most consistently selected as features of PD was associated with memory and executive function performance in patients (Abos, *Scientific Reports*, 2017).

From the structural MRI acquisition, we found that MRI data-driven analysis techniques are useful to detect subtypes of cortical atrophy even in "de novo patients". We detected two different patterns of cortical atrophy: one mainly involving the orbitofrontal regions and other with parieto-occipital predominance. These MRI patterns were associated to clinical and cognitive characteristics of patients. Thus, they may be considered as markers of the speed progression in cognitive decline (Uribe et al. *Parkinsonism and Related Disorders* 2018). On the other hand, we described that the gray/white matter contrast is an excellent MRI measure of aging effects even superior to cortical thickness. However, this measure did not show specific value for PD patients' identification. Accordingly, it is not an alternative MRI marker to replace cortical thickness as a measure of brain atrophy in PD patients (Uribe et al. *Frontiers in Aging Neuroscience 2018a*). Moreover, looking for variables sensitive to PD progression, we detected a different vulnerability to hippocampal subfields atrophy in PD compared to normal aging. CA1 volume reduction was related to aging effects per se, but in PD, there was extensive atrophy in both anterior and posterior hippocampus segments, showing right hemisphere predominance. The right hemisphere hippocampal atrophy is different from atrophy patterns classically reported in amnestic mild cognitive impairment and other degenerative illnesses such as Alzheimer's disease.

Interestingly, changes in several hippocampal subfields showed a predictive value for memory loss over time (Uribe et al. *Frontiers in Aging Neuroscience 2018b*).

Idiopathic REM sleep behavior disorder (iRBD) is considered prodromal stages of PD. In addition, olfactory dysfunctions are present in almost all patients with PD. In this setting, we investigated the accuracy of the University of Pennsylvania Smell Identification Test (UPSIT-40) and Sniffin' Sticks Extended test in distinguishing IRBD patients from controls. We also investigated the gray-matter volume correlates of these tests. We found that patients differed from controls in all olfactory measures of both olfactory assessment tools. The Sniffin-Identification correctly classified 89.1% of cases; the UPSIT, 85.4%; the Sniffin-Discrimination, 82.6%; the Sniffin-Total, 81.8%; and the Sniffin-Threshold, 77.3%. Respective AUROC, optimal cut-off, sensitivity, and specificity for each test were: 0.902, ≤26, 85.7%, and 85.2% for the UPSIT; 0.884, ≤29, 89.5%, and 76.0% for the Sniffin-Total; 0.922, ≤11, 90.5%, and 88.0% for the Sniffin-Identification; 0.739, ≤4, 73.7%, and 76.0% for the Sniffin-Threshold; and 0.838, ≤11, 85.7%, and 76.0% for the Sniffin-Discrimination. UPSIT scores correlated with orbitofrontal gray matter volumes in iRBD anosmic patients. (Campababal et al. *Parkinsonism and Related Disorders,* 2019).

Considering (iRBD) as a prodromal stage of PD and other parkinsonisms, we investigated cortical and subcortical gray matter structures in iRBD patients and their relation to cognitive performance. In comparison to healthy controls, IRBD patients showed impairment in facial recognition, verbal learning, processing speed, attention and naming. Structural MRI data showed that iRBD patients had cortical thinning in the left superior parietal, postcentral, and fusiform regions, as well as in the right superior frontal and lateral occipital regions, similarly to the atrophy seen in PD patients. Volumetric and shape analyses found right hippocampal atrophy in IRBD, specifically in posterior regions. An exploratory analysis of hippocampal subfields identified significant atrophy in IRBD in comparison to healthy controls in the right CA1, molecular layer, granule cell layer of dentate gyrus, and CA4 (Campabadal et al. *Frontiers in Neurology*, 2019).

Finally, to address early translational applications of our research to clinical practice, we investigated the neuroanatomical correlates of certain visuospatial/visuoperceptual tests as it has been suggested that these test can be predictors of progression to

dementia. We identified that the Judgment of Line Orientation Test (JLOT), Visual Form Discrimination Test (VFDT) Symbol Digit Modalities Test (SMDT), Pentagon Copying Test (PCT) are able to differentiate patients from controls and are associated with cortical thinning in lateral temporoparietal regions in PD patients (Garcia Diaz et al. *Journal of the International Neuropsychological Society;* 2018). In a longitudinal study, we found that PD patients with normal cognition (PD-NC) and PD patients with mild cognitive impairment (PD-MCI) differed significantly in the cortical thinning progression of posterior regions. In a longitudinal study, we found that PD patients with normal cognition (PD-NC) and PD patients with mild cognitive impairment (PD-MCI) differed significantly in the cortical thinning progression of posterior regions. In PD-NC patients, we also observed a correlation between Facial Recognition Test changes and cortical thinning in parieto-occipital regions (Garcia Diaz et al, *Parkinsonism and Related Disorders* 2018). On the other hand, we also investigated the psychometric characteristics of UPSIT-40 Spanish version as a clinical tool to assess olfactory impairment in *PD (*Campabadal et al, *Archives of Clinical Neuropsychology*, 2018)

3. Relevance and future implications

We demonstrated for the first time that multivariate patterns of resting-state functional connectivity alteration can be used to distinguish non-demented PD patients according to their cognitive status through a machine-learning approach. As such, data extracted from functional connectomes have the potential to serve as biomarkers for cognitive impairment severity in PD.

From our current research, we can conclude that patients with Idiopathic REM-sleep behavior disorder (iRBD) share some structural and neuropsychological characteristics with Parkinson's disease patients. However, iRBD patients are also very heterogeneous group in terms of cortical thickness patterns, neuropsychological performance and olfactory deficits. The follow-up of these patients with multicenter samples is mandatory to identify their prognosis.

According to our results, we recommend the *Sniffin's* Identification test as a useful clinical tool to assess preclinical PD patients since it has similar discrimination accuracy

to the UPSIT-40, but requires less administration time and is easier to use in routine clinical practice.

Moreover, we suggest that the symbol digit modalities test is a suitable neuropsychological tool to detect mild cognitive impairment in PD, as well as to monitor the progression of the disease. For this reason, this test should be included in the PD neuropsychological assessment protocols.

In line with this, our results suggested the interest of incorporating neuropsychological tests focus on identifying the clinical manifestations of orbitofrontal degeneration. These evaluation tools are not included in the neuropsychological protocol recommended by the *Movement Disorders Society task force*. Therefore, these recommendations should be revised.

Overall, our results suggest that MRI structural and functional data reflect the patterns and degree of the neurodegenerative process in Parkinson's disease. MRI data could be considered a relevant tool to characterize and monitor the progression of the illness. In the future, MRI measure would be clinically useful to prove the efficacy of new therapeutic approaches.

4. Publications

Abós A, Baggio HC, Segura B, García-Díaz AI, Compta Y, Martí MJ, Valldeoriola F, Junqué C. Discriminating cognitive status in Parkinson's disease through functional connectomics and machine learning. *Sci Rep.* 2017 Mar 28;7:45347. doi: 10.1038/srep45347

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