CONNECTIVITY BETWEEN BRAIN NETWORKS DYNAMICALLY REFLECTS COGNITIVE STATUS OF PARKINSON'S DISEASE

Patrícia Klobušiaková

Bachelor Degree Programme (2), FEEC BUT

E-mail: xklobu02@stud.feec.vutbr.cz

Supervised by: Irena Rektorová

E-mail: irena.rektorova@fnusa.cz

Abstract: Parkinson's disease patients display a less efficient transfer of information globally and reduced between-network connectivity of large-scale brain networks as compared to healthy controls. Between-network connectivity increases with worse cognitive status, reflecting compensatory efforts. This pattern is observed in the results of each complementary method applied: seed-based between-network connectivity analysis, partial least squares analysis and graph theory measures analysis. Longitudinal studies with longer follow-up periods might show whether distinct inter-network connectivity patterns may predict dementia conversion in Parkinson's disease.

Keywords: Parkinson's disease, frontoparietal control network, resting state fMRI, mild cognitive impairment, between-network connectivity, graph measures, partial least squares

1 INTRODUCTION

Parkinson's disease and cognitive impairment are associated with altered connectivity of large-scale brain networks. Between-network functional interplay and whole-brain graph measures might provide deeper insight into the dynamic processes related to brain pathophysiology and brain adaptation to cognitive demands. The aim of this study was to assess changes of the whole-brain connectivity and between-network connectivity (BNC) of large-scale functional networks related to cognition in well characterized PD patients using a longitudinal study design and various analytical methods.

Frontoparietal control network (FPCN) plays a central role in cognitive task performance control and is thought to regulate switching between default mode network (DMN) and task-negative networks, such as dorsal attentional (DAN) and visual (VN) network. Therefore, aside from whole-brain connectivity we were specifically interested in connectivity between FPCN and other brain networks.

2 METHODS

Our cohort consisted of 99 subjects: 58 healthy controls (HC) and 41 PD patients (PD-all) including 17 PD patients with normal cognition (PD-NC) and 24 PD patients with mild cognitive impairment (PD-MCI). All participants were examined clinically and underwent neuropsychological and MRI examination at baseline and one-year follow-up visit.

2.1 PREPROCESSING

Resting state BOLD MRI data (200 scans) were preprocessed using SPM 12 toolbox and Matlab 2014b. Preprocessing included realignment and unwarping, normalization into standard anatomical space (MNI) and spatial smoothing with 5 mm FWHM. The level of motion was thoroughly

checked in terms of frame-wise displacement (FD). In addition, the six movement regressors (obtained during realignment and unwarping), FD and extracted signals from white matter and cerebrospinal fluid were regressed out of the data in subsequent analysis.

2.2 BETWEEN-NETWORK CONNECTIVITY (BNC) ANALYSIS

Characteristic seeds (spheres with 6 mm radius) for the FPCN, DMN, DAN, and VN were chosen based on the publication Gao et Lin (2012)[1]. The time-series of each seed of the studied networks was averaged and cross-correlated using Pearson's correlation coefficient to form a correlation matrix for each subject. Representative BNC was calculated as mean of Fisher's z-transformed values belonging to each pair of networks. Differences in BNC among the HC group and PD subgroups were calculated for the baseline data (Kruskal-Wallis and post-hoc tests). Age, gender, education, and levodopa equivalent dose were included as covariates of no interest.

2.3 PARTIAL LEAST SQUARES (PLS) ANALYSIS

To assess inter-group differences in resting-state functional connectivity at the baseline between the selected networks, PLS analysis was used. This method was applied to connectivity matrices (adjusted for the abovementioned covariates) based on the AAL atlas, which consisted of a limited number of ROIs that were assigned to our networks of interest. PLS decomposed the input data into three latent variables (LVs), each described by three features: vector $\boldsymbol{v}$ showing group-related differences, singular value $\boldsymbol{s}$ indicating the amount of explained variability in the input matrix, and vector $\boldsymbol{u}$ (saliences), which demonstrates the weighted contributions of individual edges to the effect depicted by $\boldsymbol{v}$. The significance of the LVs was evaluated using 5000 permutations of group membership and the reliability of saliences was determined by calculating the standard error using bootstrap sampling of group members (1000 iterations), with recalculating the PLS for each permutation and bootstrap. In the end, vector u was reshaped into the matrix resembling the original connectivity matrices, the significant edges ($p < 0.05$, values obtained using bootstrap steps) were visualized, and False Discovery Rate correction was applied.

2.4 GRAPH THEORY (GT) MEASURES ANALYSIS

The whole brain was parceled into 78 regions of interest (ROIs) according to the AAL atlas. The time-series of each ROI was averaged and cross-correlated using Pearson's correlation coefficient to form a correlation matrix for each subject. Fisher's r-to-z transformation was applied and weighted networks were analyzed on both global and regional levels. To describe the network structure at a global level, average clustering coefficient, characteristic path length, average node strength, global efficiency, and modularity were computed using the Brain Connectivity toolbox. To investigate the cognitive brain networks of interest, local clustering coefficient, nodal path length, node strength, eigenvector centrality, and betweenness centrality were computed for ROIs of the whole brain. Average value of each measure for four brain networks' ROIs was computed and used as a representative local measure for these networks. Differences among the HC group and PD subgroups in determined measures were then evaluated for the baseline data using Kruskal-Wallis and post-hoc tests after regressing out the effect of the abovementioned covariates. In terms of multiple comparison correction, False Discovery Rate was applied.

3 RESULTS

The FPCN-DAN, FPCN-VN, and FPCN-DMN connectivities were significantly reduced in the PD-NC group as compared to the HC group ($p = 0.010$, $p = 0.0001$, $p = 0.029$). All investigated BNC decreased in the following order: HC > PD-MCI > PD-NC. Partial least squares analysis yielded significant LV ($p = 0.0038$), which showed the effect depicted in Figure 1, demonstrating the strong difference between HC and PD-NC, with the PD-MCI group being between these two groups, i.e., the BNC and PLS analytical methods provided very similar results. As for GT results, at the global level, average clustering coefficient, average node strength, and global efficiency were

significantly reduced in the PD-NC group as compared to HC, and decreases in the graph measures were present in the order: HC > PD-MCI > PD-NC. Characteristic path length was increased in PD-NC as compared to HC, and it increased in the order: HC <PD-MCI < PDNC. At the local level, all studied cognitive brain networks showed a similar direction of changes across groups as the whole brain analysis for the average clustering coefficient and the average node strength. The differences in characteristic path length described at the global level were significant for the FPCN and VN networks, with DAN and DMN showing trends. In addition, for the DMN, increased betweenness centrality was observed in both the PD-NC and PD-MCI groups in comparison to HC.

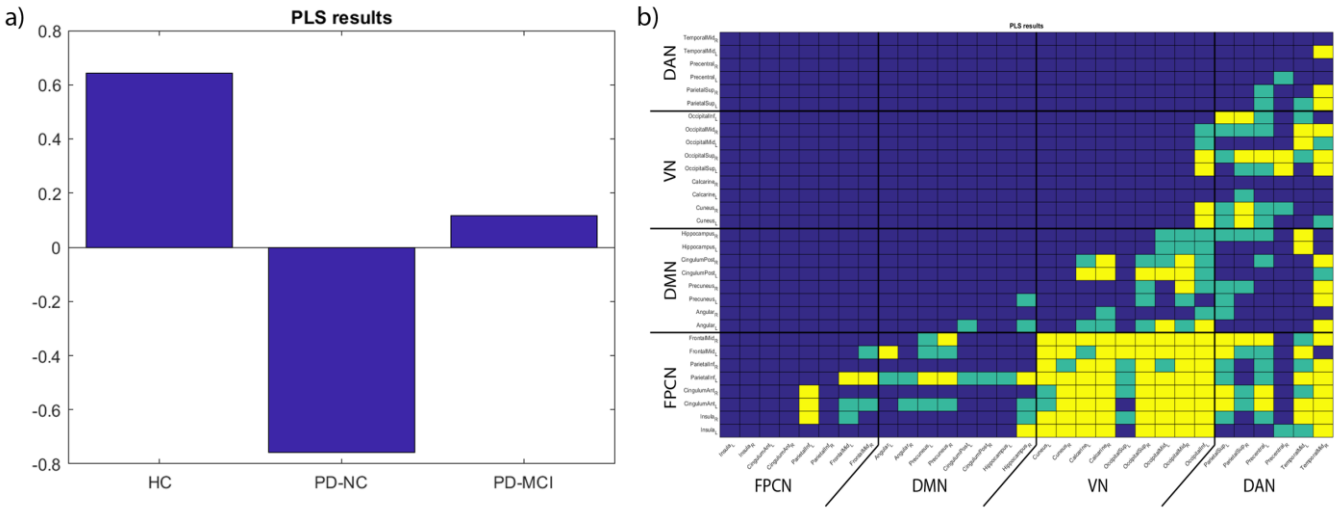

Figure 1: Baseline PLS results. a) group-related differences (indicated by vector v of significant LV); b) reshaped matrix of significant saliences contributing correspondingly to the effect depicted in a), green – $p < 0.05$ uncorrected, yellow – $p < 0.05$ FDR corrected

4 CONCLUSION

In conclusion, we found decreased BNC of major brain networks (and of the FPCN-VN connectivity in particular) related to cognition in the PD-NC subjects as compared to age-matched HC. With cognitive deterioration, the BNC of the FPCN increased, probably in an attempt to compensate [2]. Of note, all the analytical methods employed produced a similar direction of changes across the studied groups. Understanding the temporal dynamics of functional interplay between major cognitive brain networks may help monitor potential cognitive treatment effects including effects of invasive and non-invasive brain stimulation.

ACKNOWLEDGEMENT

This work was supported by EU Joint Programming initiative within Neurodegenerative Diseases, funded by the Norwegian Strategic Research Council (APGeM—Preclinical genotype-phenotype predictors of Alzheimer's disease and other dementias). We acknowledge the core facility MAFIL of CEITEC supported by the MEYS CR (LM2015062 CzechBioImaging).

REFERENCES

[1] W. Gao and W. Lin, "Frontal Parietal Control Nework Regulates the Anti-Correlated Default and Dorsal Attention Networks," *Hum. Brain Mapp.*, vol. 33, no. 1, pp. 192–202, 2012.

[2] M. Tahmasian *et al.*, "Resting-state functional reorganization in Parkinson's disease: An activation likelihood estimation meta-analysis," *Cortex*, vol. 92. pp. 119–138, 2017.