Nonreproducible connectome changes hint at functional heterogeneity of Parkinson’s Disease

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**Background:** Determining Parkinson’s Disease (PD)-specific resting state functional connectivity (FC) changes seems to be a promising approach toward developing non-invasive and non-radioactive neuroimaging markers for this disease. While several groups have reported such FC changes in PD, our meta-analysis of existing literature revealed significant discrepancies between studies. Investigating the reproducibility of PD FC changes on independent datasets is therefore of crucial importance.

**Methods:** We acquired resting-state scans for 43 subjects (27 patients and 16 normal controls, with 2 replicate scans per subject) and compared the observed functional connectivity changes with those obtained on a second independent dataset of the PPMI consortium (134 patients, 19 controls). Functional connectivity was computed between the ROIs of several brain parcellations, but for brevity we only report results for the AAL atlas, which are typical. For all ROI pairs, we used unpaired t-tests to determine significant connectivity changes between the two groups (controls versus patients). The reproducibility between datasets was assessed using scatterplots of ROI-pair t-values computed separately for the two datasets, as well as by computing the Pearson correlation between the corresponding t-values.

**Results:** The scatterplot of ROI-pair t-values for the two datasets as well as the low correlation between these t-values (-0.0859) indicate a lack of reproducibility of FC changes in the two datasets. This lack of reproducibility could be due to disease heterogeneity, as well as to technical differences. To distinguish between the two:

1. Instead of comparing two distinct datasets, we compared two random splits of the same dataset, either:
   1.1) by placing different subjects in the two splits (with all the replicate scans of a subject in the same split), or
   1.2) by placing each replicate scan of the same subject in a different split, so that the two splits contain (different) scans of the same subjects.

2. In contrast to PD, we observed reproducibility of analysis (1a) for a different group contrast on a different rs-fMRI dataset (Beijing eyes open-eyes closed).

3. We also found good reproducibility when changing various technical factors or processing options, such as: doubling the TR, registration (linear vs nonlinear), global signal regression (with vs without).

**Conclusions:** Our analyses suggest that functional heterogeneity may be a dominating factor behind the lack of reproducibility of functional connectivity changes in different rs-fMRI studies of Parkinson’s disease. This could be due to the heterogeneous multilesional topography and progression of the neurodegenerative process, accompanied by variable compensatory functional circuit changes.