Multimodal Brain Associations with Clinical Profiles and Treatment Effects in Parkinson's Disease

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INTRODUCTION

- Longitudinal studies are critical to understand neuropathological progression and treatment effects in neurodegenerative diseases.
- Such knowledge is beneficial to the development of therapeutic interventions.
- We aimed to investigate multimodal brain imaging and behavioural associations and, importantly, how the baseline multimodal brain profiles relate to symptom improvements after treatment.
- This is a crucial step towards implementing precision medicine[1,2].
- We first *explored the associations between resting-state functional connectivity (rsFC) and clinical scores as well as the striatal binding ratios (SBRs) at baseline* in Parkinson's Disease (PD).
- Second, we investigated *whether the baseline rsFC was associated with treatment-induced changes* in motor and non-motor symptoms.

METHODS

Subject

- Baseline: 137 PD subjects (95 M, 42 F, age 60±9.8y) from the Parkinson's Progression Markers Initiative (PPMI) with both resting-state fMRI (rsfMRI) and DaTscan (table 1)
- Follow-up visits: subjects who were on medication and showed improved symptoms (i.e. follow-up visits showed reduced Unified Parkinson's Disease Rating Scale (UPDRS) scores). Subjects from v4 (12 months), v6 (24 months), v8 (36 months), and from v10 (48 months) were included. Details are shown in table 1.

	baseline	follow-up visits			
		V4	V6	V8	V1 0
number of subject	137	103	90	69	53
age ± SD	60.0±9.8	62.4±9.5	63.6±9.4	63.8±9.8	64.9±10.1
education in years ± SD	15.6±3.1	15.9±3.2	16.3±3.4	16.3±3.3	16.1±2.6
UPDRS/UPDRS changes ± SD	18.9±11.6	0.27±0.28	0.21±0.26	0.26±0.32	0.2±0.26
MOCA/MOCA changes ± SD	27.8±2.0	0.01±0.05	0.01±0.05	0.02±0.04	0.01±0.05
SBR in R caudate ± SD	2.03±0.67	NA	NA	NA	NA
SBR in L caudate ± SD	2.03±0.7	NA	NA	NA	NA
SBR in R putamen ± SD	1.04±0.61	NA	NA	NA	NA
SBR in L putamen ± SD	1.0±0.60	NA	NA	NA	NA

Table 1. demographics and clinical data

Data and preprocessing

- rsfMRI: standard preprocessing was done using SPM and DARTEL toolbox[3] in MATLAB. Time courses were extracted based on Desikan-Killiany Atlas[4] with 78 regions-of-interest (ROIs). A 78-by-78 pairwise correlation matrix was calculated for each subject.
- DaTscan: SBRs in bilateral putamen and caudate derived from DaTscan, provided by PPMI, were calculated as (target region/reference region)-1, with reference tissue in the occipital cortex.

Analysis

- Figure 1 shows the analysis steps in the study.

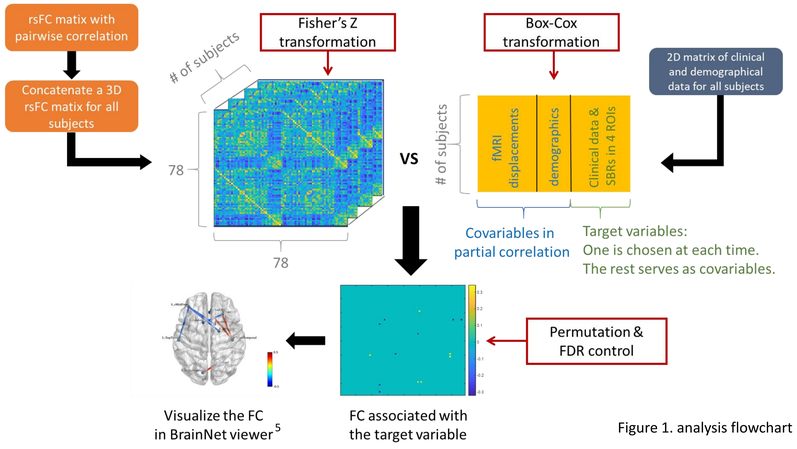

Figure 1. analysis flowchart

Analysis (continued)

- In short, partial correlation was carried out to explore the associations between rsFC matrices and clinical/demographic scores while conditioning on the following variables: fMRI motion parameters, demographics, and clinical data except the variable of interest.
- At baseline, the analysis was applied to rsFC matrices v.s. SBRs, UPDRS, the Montreal Cognitive Assessment (MOCA) scores, and demographics.
- At follow-up time points, only the *changes* of UPDRS and MOCA scores were selected as target variables and the rest analyses remained the same. Changes after medication treatment in UPDRS and MOCA were calculated as $\left|(score_{baseline} - score_{visit})/(score_{baseline} + score_{visit})\right|$.

RESULTS

Baseline

- UPDRS was mostly negatively-associated with cortical-subcortical connections (figure 2).
- The rsFC significantly related to MOCA were roughly divided into two clusters: frontal/temporal and parietal regimes with both positive and negative correlations (figure 2).
- With both permutation and false discovery rate (FDR) control, the SBRs did not show significant correlation with rsFC.

Follow-up visits

- Longitudinal changes in MOCA were negatively related to connections between distributed regions at V4 and *frontal clusters* at V10 (figure 3).
- Improved overall symptom reflected by UPDRS was mostly positively-associated with connections between the *limbic system* and a few cortical-to-cortical connections (figure 3).

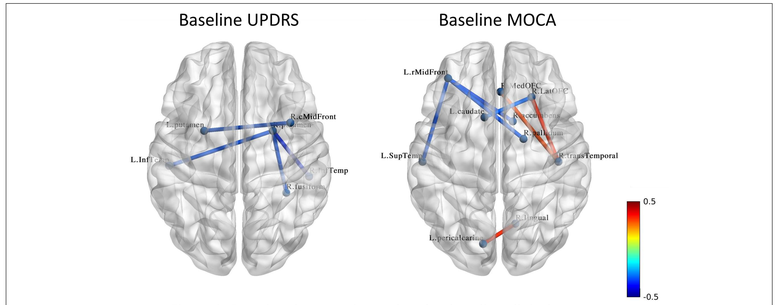

Figure 2. Functional connections related to baseline clinical scores.
Colourbar indicates the partial correlation coefficient between connections and scores.

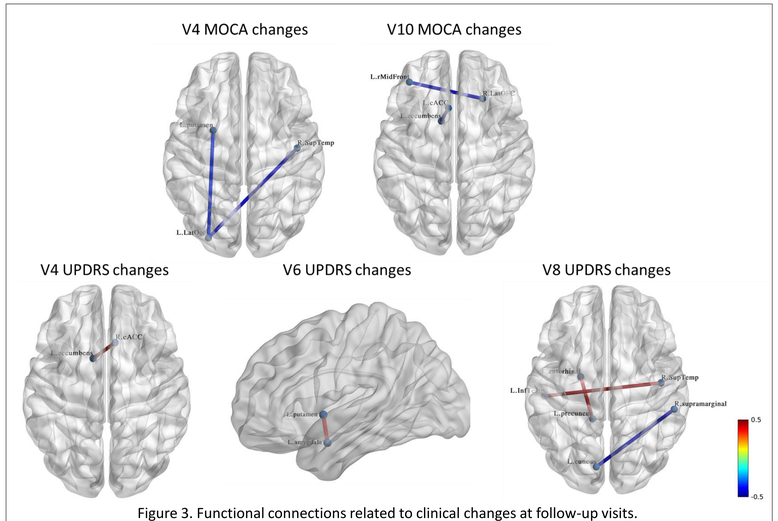

Figure 3. Functional connections related to clinical changes at follow-up visits.
Colourbar indicates the partial correlation coefficient between connections and scores.

CONCLUSIONS

- Altered cortical-subcortical connectivity in PD has been thought of as the major representation of nigrostriatal dysfunction and recent studies have shown a more distributed pattern of rsFC[6].
  - Our results further echoed the role of cortical-subcortical connectivity and distributed patterns in PD between frontal, putamen, and temporal regions at baseline. In addition, as UPDRS was anti-correlated with rsFC, higher UPDRS scores were associated with reduced connectivity strength.
  - Interestingly, most of the connections at longitudinal visits were positively related to rsFC in the limbic system, which is heavily modulated by dopaminergic pathways. The results indicated that higher improvements of UPDRS were related to stronger limbic connectivity.
- Cognitive decline in PD has been categorized into two patterns: frontal and posterior subtypes[7].
  - The global cognition demonstrated relations to frontal and posterior clusters at baseline.
  - Longitudinally, subjects with improved motor symptoms showed that stronger changes of MOCA were related to decreased rsFC in remoted regions and a frontal cluster.
- Overall, the brain associations with clinical profiles provided insights into i) the understanding of PD at baseline and ii) how rsFC reacts to clinical improvements longitudinally.

FUTURE WORK

- Although we included both rsfMRI and DaTscan, relations between two modalities only exhibited with looser statistical criteria (not shown here). Perhaps, different features in each modality are required to establish robust multimodal associations.
- The current methods require statistical approaches to control for multiple comparisons. With different statistical parameters, the results could vary. Furthermore, the analysis assumes a linear relation between brain and behaviour and utilizes an univariate approach, which may not be ideal given the complexity of the brain. Further studies shall implement robust and stable methods to overcome these issues.

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