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The reorganization of functional architecture in the early-stages of Parkinson's disease

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ABSTRACT

Introduction: The study aim was to identify longitudinal abnormalities of functional connectivity and its relation with motor disability in early to moderately advanced stages of Parkinson's disease patients.
Methods: 3.0T structural and resting-state functional MRI was performed in healthy subjects (n = 16) and Parkinson's disease patients (n = 16) with mean disease duration of 2.2 ± 1.2 years at baseline with a clinical follow-up of 1.5 ± 0.3 years. Resting-state fMRI analysis included region-to-region connectivity in correlation with UPDRS-III scores and computation of Global Efficiency and Degree Centrality.
Results: At baseline, patients' connectivity increased between the cerebellum and somatomotor network, and decreased between motor regions (Rolandic operculum, precentral gyrus, supplementary motor area, postcentral gyrus) and cingulate connectivity. At 1.5 years follow-up, connectivity remained altered in the same regions identified at baseline. The cerebellum showed additional hyperconnectivity within itself and to the caudate nucleus, thalamus and amygdala compared to controls. These differences correlated with UPDRS-III scores. Seed-based connectivity revealed increased involvement of the default mode network with precentral gyrus in patients at follow-up investigation.
Conclusion: Resting-state fMRI identified marked disturbances of the overall architecture of connectivity in Parkinson's disease. The noted alterations in cortical motor areas were associated with cerebellar hyperconnectivity in early to moderately advanced stages of Parkinson's disease suggesting ongoing attempts of recovery and compensatory mechanism for affected functions. The potential to identify connectivity alterations in regions related to both motor and attentional functions requires further evaluation as an objective marker to monitor disease progression, and medical, as well as surgical interventions.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms, such as resting tremor, rigidity, bradykinesia, as well as non-motor symptoms including autonomic dysfunction, mood disorders and cognitive impairments [1]. The degeneration of the nigro-striatal dopaminergic system associated with Lewy body inclusions, although the neuropathological hallmark of the disease, does not sufficiently explain the heterogeneity of symptoms and the progression of the disease [2]. Although neuropathological studies display the actual lesions involved, they merely reflect the terminal stages of the disease. To date, the availability of quantitative biomarkers to assess

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objectively the progression of the condition is limited. Quantitative surrogates however, are of utmost importance to monitor therapeutic responses in the routine setting and in clinical trials. Despite those profound challenges to identify such markers of cerebral functions [3], recent advances of MRI and application of *resting-state fMRI (rs-fMRI*) allow to study functional connectivity and brain communication longitudinally. To understand the mechanism of PD, it is fundamental to assess internal coupling of resting-state networks and to estimate their cross-connectivity which relates to the efficiency of integration among different functional domains. As networks can be described as graphs consisting of nodes and edges, graph theory methods can be deployed to quantify these measures, and to understand the dynamics of the functional networks and the architecture of the brain. In PD, rs-fMRI so far revealed morphological and functional alterations in cerebellum, involved in both motor and non-motor function [4,5], as well as in *sensorimotor network (SMN),* responsible for motor control and coordination [4,6]. Moreover, patients not only have reduced connectivity of corticostriatal and mesolimbic-striatal loops, but this is in association with some non-motor features in early stage of the disease [7]. A recent PD review on connectivity summarized changes in the default mode network (DMN), which plays a essential role as a connectivity core and deactivates during goal-directed tasks [4]. These studies suggested that decreased DMN connectivity characterizes PD patients [8], and that its dysfunction is more reliable for revealing the presence of early cognitive deficit than changes in other cognitive networks [9]. In addition, FDG-PET imaging revealed progressive changes of regional metabolism in motor- and cognition-related networks correlating with motor and performance features of the disease in PD over two years [10]. Until now, insights upon the progression of degenerative and compensatory connectivity alterations throughout the entire brain volume are still lacking. The aims of this study were i) to determine the evolution of functional connectivity abnormalities in early to moderately advanced stages of PD patients, and ii) to analyze its relation with motor disability by applying rs-fMRI and graph theory methods. We ruled out the longitudinal change in medication as a possible cause for alterations.

2. Methods

2.1. Subject characteristics

A total of 100 PD patients and 51 healthy subjects were recruited at Movement Disorders clinic of Department of Neurology at Innsbruck Medical University. Out of this cohort, 16 patients (8 tremor dominant/6 postural instability and gait difficulty-predominant/2 mixed) met the selection criteria (Table e−1): no evident dementia (MMSE<26), both baseline and follow-up rs-scans with head motion limited to < 1.5 mm and <1.5°, clinical probable disease according to established diagnostic criteria [11], disease duration < 5 years, stable disease without motor complications and stable medication longitudinally. All patients had good response to medication [12] and were tested in OFF-state. All of the PD patients had at least a good response on dopaminergic treatment. 16 age and gender-matched healthy subjects with no signs of central nervous system disorders were selected. All subjects signed informed consent form. The study procedures were performed according to the Declaration of Helsinki and approved by the ethics committee of Innsbruck Medical University. Hoehn and Yahr staging [13], *Unified Parkinson's disease rating scale (UPDRS)* [14], *Mini-Mental State Exam (MMSE)* [15] and *The Montreal Cognitive Assessment (MoCA)* [16] values were collected. Time lag at follow-up scans was 1.5 ± 0.3 years.

2.2. MRI acquisition

Structural and functional sequences were acquired with a 3T whole-body MRI scanner (Magnetom Verio, Siemens, Germany). T1-MPRAGE sequence parameters were: TR = 1800 ms, TE = 2.18 ms, inversion time = 900 ms, slice thickness = 1.2 mm, matrix = 256 × 204 pixels, number of excitations = 1, flip angle = 9° and field of view = 220 mm × 165 mm. Rs-fMRI sequence (single-shot gradient EPI) parameters were: TR = 3.00 s, TE = 30 ms, flip angle = 90°, acquisition matrix = 96 × 96, field of view = 220 mm × 220 mm, slice thickness = 3.0 mm and acquisition time 5 min. Subjects were told to lay still and relaxed with their eyes closed during the acquisition.

2.3. Data analysis

2.3.1. Functional connectivity

FSL5.0.8 [17] was used for preprocessing (6 mm smoothing, highpass filtering (100 s) and registration with FLIRT and FNIRT (6/12DOF)). FAST tool was used for tissue segmentation. Functional data was regressed with mean signals of white matter, cerebrospinal fluid and 6 motion parameters. Brain parcellated time courses based on *Anatomical Automatic Labeling (AAL-116)* atlas (Table e−2) [18] were averaged, Pearson-correlated with each other and Fisher-transformed according to $z=ln((1+r)/(1-r))/2$ with Matlab8.5 (The Mathworks Inc.). Average group connectivity matrices were computed, and statistical group and longitudinal differences (alpha <0.01) were inferred and visualized with BrainNet Viewer [19]. Additionally, correlations of each element in the connectivity matrices with UPDRS-III scores were computed (alpha <0.001).

2.3.2. Connectivity measures

Individual connectivity matrices were obtained by varying the density threshold K over a broad range of thresholds from 0.05 to 0.5 with incremental steps of 0.01. This was done to obtain results independent of the choice of the adopted threshold. Then, graph-based measures of *Global Efficiency (GE)* and *Degree Centrality (DC)* were computed using the Brain Connectivity Toolbox [20]. GE provides information on the overall capacity of information transfer and integrated processing, whereas DC locates nodes with topological changes in their centrality (i.e. the importance of a given node for functional performance) [21]. Two-tailed two-group t-tests (alpha <0.05) were used to evaluate group differences.

2.3.3. Seed-based connectivity

Connectivity maps were computed by adopting right and left *precentral gyri (preCG)* based on the AAL-116 as seeds. This SMN node was selected as it was noted to have significant group differences in the previously obtained cross-connectivity matrices and DC values. The selection was also based on the primary motor cortex involvement in execution of voluntary movements and known disruptions in PD. The timecourse of preCG to each voxel for each subject was Pearson-correlated and Fisher-transformed. Then, group averages and differences (alpha <0.02) were computed at baseline and follow-up.

3. Results

3.1. Clinical evaluation

Patients and controls were matched for age and gender. Significant increase of the UPDRS-II and III ($p < 0.001$) as well as UPDRS-I and MoCA ($p < 0.05$) was noted in PD patients compared to controls at baseline and follow-up, as expected. None of patients

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