Involvement of cerebellum in the dopaminergic treatment of Parkinson's disease: A resting-state fMRI study

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Target audience: Neuroscientists and clinicians interested in movement disorders and pathophysiology of motor deficits; researchers interested in fMRI and resting-state fMRI.

Purpose: The disruptive mechanisms underlying Parkinson's disease (PD) are not yet fully understood. The classic models based on striatal-thalamo-cortical loops elucidate the disease pathophysiology only partially, discarding explanations for many clinical observations, e.g. resting tremor [1]. Emerging evidence however supports the ancillary involvement of the cerebello-thalamic system in the development of motor dysfunction in PD [2]. Task-related [3] and resting-state [4, 5, 6] functional magnetic resonance imaging (fMRI) studies have already uncovered the cerebellar participation in the diseased motor state of PD patients. We used resting-state fMRI and a model-free approach based on eigenvector centrality (EC) mapping [7]. The purpose was to assess the effect of levodopa therapy on functional connectivity of corrupted motor networks in PD patients. We hypothesized, that dopaminergic treatment might be modulating the changes in connectivity patterns within the diseased motor network, involving both striatal-thalamo-corcital but also cerebello-thalamic loops.

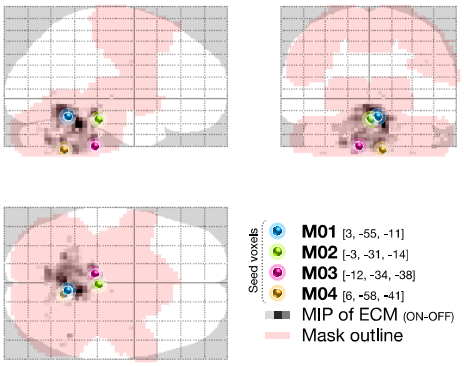

Figure 1. Significant difference of eigenvector centrality (EC) between both treatment states (ON-OFF) as the maximum intensity projection (MIP). Among 16 maxima within the significant cluster, four representatives (M01…M04) were used as the seed voxels for correlation analysis. The search space (mask) is outlined only and does not represent the MIP. p_{FWE}<0.05, cluster level.

Methods: fMRI data were acquired from 24 idiopathic, akinetic-rigid PD patients (Hoehn-Yahr stages II-III, 19 males, 6 females, mean age 55.5), in a task-absent condition using a T_2*-weighted gradient-echo echo-planar imaging (EPI) sequence (*FA/TR/TE* = 90°/3000/51 ms) at 1.5T with 200 repetitions. For image registration, high-resolution 3D T_1-weighted data were acquired using a magnetization-prepared rapid acquisition gradient echo (*TR/TI/TE/FA*=2140/1100/3.93 ms/15°) sequence. The patients were measured in two conditions: (*a*) after overnight withdrawal of levodopa (OFF) and (*b*) one hour after oral administration of 250 mg of levodopa/25 mg carbidopa (ON). Standard registration and normalization procedure to the MNI space was performed using SPM8. EC maps [9] revealing the most central nodes, thus nodes strongly correlated to other central nodes in the motor network, were calculated for every voxel in a mask comprising the entire motor system (Figure 1). This mask was used as a search space in all subsequent analyses. In order to detect significant centrality changes between medication states (ON-OFF), a paired *t*-test was applied between the EC maps of both treatment states. Subsequently, all local maxima representing significant centrality changes between ON and OFF states were systematically used as seed voxels for correlation analyses. Paired *t*-tests were used to uncover target regions of functional connectivity changes between ON and OFF. Additionally, the individual EC maps were correlated with the motor Unified Parkinson's Disease Rating Scale (UPDRS-III) scores of participants in both treatment states.

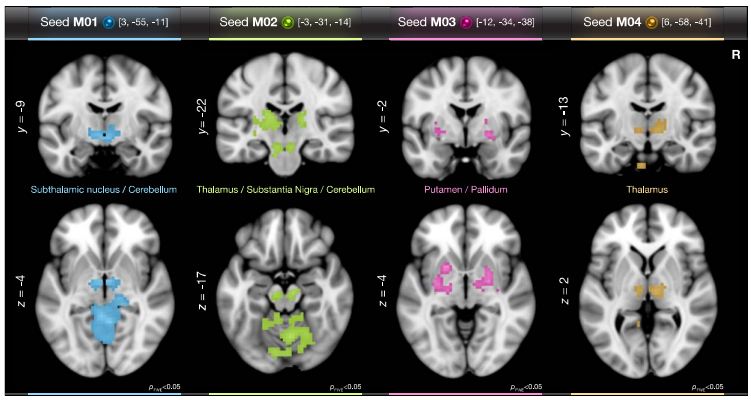

Figure 2. Increased functional connectivity between seed maxima selected from centrality analyses and key brain structures involved in motor control after levodopa administration. p_{FWE}<0.05, cluster level.

Results: EC mapping revealed significantly higher centrality in the medial part of cerebellum in ON state as compared to OFF state (Figure 1). Using global and local maxima of centrality differences as seed voxels demonstrated significantly increased functional connectivity between the medial cerebellar structures and the subthalamic nucleus (STN), thalamus, substantia nigra (SN), basal ganglia (BG) and interestingly, cerebellum itself after administration of levodopa (Figure 2). The centrality differences in medial cerebellum between the treatment states were also confirmed by a significant negative correlation of patients' motor clinical outcome (UPDRS-III scores) and the EC maps (Figure 3).

Discussion: The presented results support the hypothesis, that additionally to striatal-thalamo-cortical networks, levodopa affects the dopaminergic pathways in the cerebello-thalamic system, leading to an increased connectivity of the cerebellum with key brain structures responsible for motor control. Previous studies investigating levodopa treatment in PD patients using resting-state fMRI already revealed alterations in cerebellar structures after dopaminergic medication, however, using different methods such as regional homogeneity, or granger causality, and leading to different statements [4, 6].

Conclusion: Findings from our model-free approach demonstrate the altered pattern of cerebellar connectivity altered connectivity of patients suffering from PD. The cerebellum might thus play a critical role in pathophysiology of PD and should be strongly considered in future PD research.

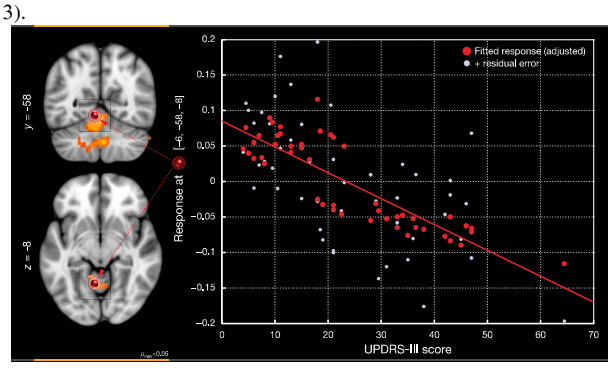

Figure 3. Changes in cerebellar centrality observed by a significant negative correlation between the PD patients' centrality and their UPDRS-III scores in both treatment stages. The better the clinical picture of participants, the more connected cerebellum with the other motor regions in the network. The dot-plot demonstrates this relationship in a maximum selected from the correlation map. p_{FWE}<0.05, cluster level.

References: **[1]** Rodriguez-Oroz MC et al. (2009). Lancet Neurol 8: 1128-1139. **[2]** Rolland AS, et al. (2007). Brain 130: 265-275. **[3]** Helmich et al. (2011). Ann Neurol 69: 269-281. **[4]** Wu et al. (2009). Hum Brain Mapp 30:1502-1510. **[5]** Wu et al. (2009). Neurosci Lett 460: 6-10. **[6]** Wu et al. (2012). Neurosci Lett 524: 55-59. **[7]** Lohmann et al. (2010). PLoS One 5: e10232.