Differential effects of levodopa and deep brain stimulation on motor networks in Parkinson's disease

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Target audience: Researchers and clinicians interested in movement disorders and their pathophysiology; researchers interested in fMRI and resting-state fMRI.

Purpose: Among current pharmacological and surgical options, levodopa and deep brain stimulation (DBS) have been primarily favoured to treat motor symptoms of Parkinson's disease (PD) in clinical practice [1]. The effects of each have already been investigated using magnetic resonance imaging (MRI), however in a separate manner [2,3]. Although contrastive outcomes of levodopa and DBS have been identified using direct local field potential recordings [4] and [^{18}F]2-fluoro-2-deoxyglucose positron emission tomography [5], to our knowledge, no MRI study coupling the two treatment approaches has been conducted yet. We used resting-state functional MRI (fMRI), eigenvector-centrality mapping [6], and seed-based connectivity analyses to explore potential mutual interactions between levodopa and DBS of the subthalamic nucleus (STN), and to assess their differential effect on connectivity patterns in motor networks impaired by PD.

Methods: 13 subjects with idiopathic akinetic-rigid PD were involved in the study (Hoehn-Yahr stages II-III, 11 males, mean age 53 years). All participants were examined (*a*) after overnight withdrawal of dopaminergic medication (LDOPA OFF), (*b*) after oral administration of 250 mg levodopa/ 25 mg carbidopa (LDOPA ON), (*c*) after surgical implantation of DBS electrodes to STN with the DBS turned off (DBS OFF) and (*d*) with the DBS turned on either on left side (DBS Left ON) or right side (DBS Right ON). Pre- and post-surgery measurements were typically performed 1 day apart. Resting-state fMRI was performed at 1.5 T using the T_2*-weighted gradient-echo echo-planar imaging sequence ($FA/TR/TE$ = 90°/3000/51 ms) with 200 time points. Three-dimensional high-resolution structural images were also obtained for pre-processing purposes. Patients were asked to remain still, awake, and follow a fixation cross on a projection screen. Standard pre-processing of the fMRI data included realignment, registration to the MNI space and spatial smoothing using SPM8. A mask of the whole motor system was created and used as a search space for all subsequent analyses (Fig. 1). Eigenvector centrality (EC) maps were calculated to obtain the central nodes, thus regions highly correlated to other central regions in the motor network. A paired *t*-test was used to reveal significant centrality differences between DBS Left/Right ON (*d*) and LDOPA ON (*b*) states. The mean fMRI signal was then extracted from significant clusters in left and right premotor cortex (PMC) and used separately as seed volumes of interest (VOI) for correlation analyses, to explore the directionality of functional connections (Fig. 1). This was performed by correlating the time courses of VOIs to the rest of the motor network in the search space. Significant difference between LDOPA ON and DBS Left/Right ON states were then inspected using a paired *t*-test. Additionally, a general linear model fitting the EC data from all treatment stages (*a*, *b*, *c*, *d*) was constructed. Using a proper multidimensional *F*-contrast, the effect sizes from significant maxima in left and right PMC were obtained for each treatment state (*a*, *b*, *c*, *d*).

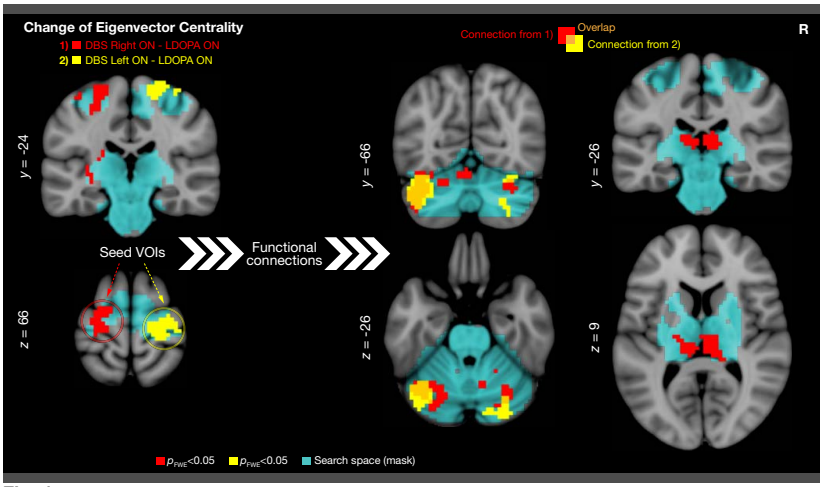

Fig. 1. Differential effect of levodopa and DBS on functional connectivity in motor networks affected by PD. Left column indicates significant difference of eigenvector centrality between both treatment states (DBS Left/Right ON - LDOPA ON) color-coded according to laterality of stimulated site (left STN: yellow, right STN: red). Both significant clusters in PMC were used as the seed volumes of interest. Middle and right columns depict target regions of significantly altered functional connectivity between the two ON states, color-coded accordingly to particular seed region. The blue color shows the search space. p_{FWE}<0.05, cluster level.

Results: The EC mapping revealed a significant centrality difference between the DBS ON (*d*) and LDOPA ON (*b*) states in PMC contralateral to stimulating electrode (Fig. 1, left column). Subsequent correlation analysis showed significant connectivity alterations in lateral cerebellum bilaterally, independently on the stimulated side and predominantly in the left cerebellum (Fig. 1, middle column). In addition to cerebellar structures, DBS of the right STN significantly altered the functional connectivity of left PMC to thalamus, bilaterally (Fig. 1, third column). The effect sizes of EC uncovered a strong differential effect of levodopa (*a*, *b*) and DBS (*c*, *d*) treatment on centrality in PMC (Fig. 2). Additionally, a significantly different effect size for centrality between DBS OFF (*c*) and DBS ON (*d*) was found in PMC.

Discussion: The results demonstrate a differential effect of two major PD treatment approaches on patterns of functional connectivity in the diseased motor networks. A principal centrality difference in PMC contralateral to the stimulated STN was recognized between levodopa and STN DBS. In comparison to levodopa, DBS of STN seems to induce major connectivity alterations between PMC and cerebellar and thalamic structures. However, it is important to consider the effect of microlesion and oedema caused by the surgical procedure, which affects fMRI signaling and the outcome of patients' motor performance considerably [7]. Hence, our results represent an overlay of the two distinct and hardly separable phenomena: the microlesion and the DBS itself. Both might contribute to reorganization of connectivity patterns between treatment states.

Conclusion: Microlesion and the DBS alter the motor networks affected by PD in PMC, cerebellum and thalamus, in comparison to dopaminergic medication. Further research attempts are necessary to discriminate the functional origin of the improved motor outcome of PD patients.

References: **[1]** Smith Y et al. *Neuropsychopharmacol* 2012:37:213-46. **[2]** Rowe JB and Siebner HR *NeuroImage* 2012:61:464-77. **[3]** Jech et al. *Mov Disord* 2001:16:1126-32. **[4]** Giannicola et al. *Exp Neurol* 2010:226:120-7. **[5]** Hilker et al. *J Neural Transm* 2002:109:1257-64. **[6]** Lohmann et al. *PLoS ONE* 2010:5:e10232. **[7]** Jech et al. *PLoS ONE* 2012:7:e49056.

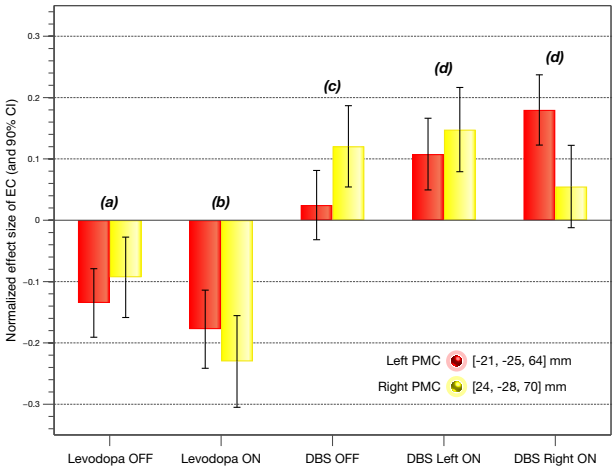

Fig. 2. Normalized effect sizes of eigenvector centrality with 90% confidence interval. Values were extracted from left and right PMC according to the stimulated STN (left/right). A significant effect of surgery/DBS compared to levodopa and centrality change between DBS ON/OFF are observed.