The subthalamic microlesion in Parkinson's disease: Investigating electrode insertion-related connectivity differences using resting-state fMRI

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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: Deep-brain stimulation of the subthalamic nucleus (STN) has become a well established neurosurgical treatment strategy for movement difficulties associated with Parkinson's disease (PD) over the past two decades.[1] Yet, mechanisms leading to its striking therapeutic benefit remain unclear. Neurosurgeons and neurologist observe an intriguing phenomenon already in the operating rooms, while implanting the DBS electrodes. Shortly after mechanical insertion of electrodes into the target structure, even in absence of stimulation, motor symptoms of many patients improve markedly. This effect remains noticeable for a certain period of time,[2] in some cases even months.[3] A general term 'microlesion effect' (MLE) has been established to designate this phenomenon. Here, we are first to study the MLE in PD patients who underwent STN implantation using resting-state fMRI (rs-fMRI). In particular, we exploited the notion of *ranking*—in an equivalent fashion as used by bibliometrists, econometrists, sociometrists, or googlists—in the context of functional connectivity and explored reorganization of the highest *ranked* motor communication hubs in brains of PD patients in response to penetration of DBS electrodes in STN.

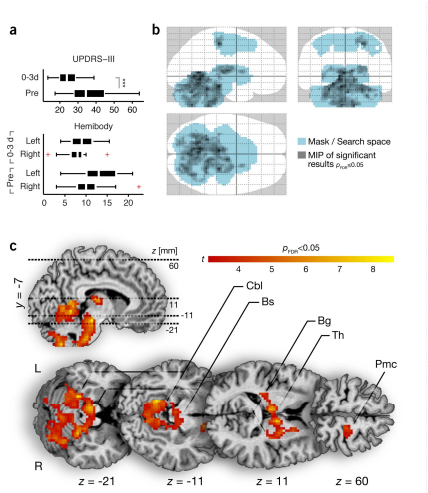

Figure 1. Impact of STN MLE on 13 patients suffering from PD. **(a)** UPDRS-III clinical scores pre- and post-implantation. *Pre*– before implantation; *0-3d* – 0-3 days post-implantation **(b)** Outline of employed search space. *MIP* – maximum intensity projection. **(c)** EC differences between pre- and post-implantation stages. *Cbl* – cerebellum; *Bs* – brainstem; *Bg* – basal ganglia; *Th* – thalamus; *Pmc* – premotor cortex. *STN* – subthalamic nucleus; *MLE* – microlesion effect; *PD* – Parkinson's disease.

Methods: Thirteen patients suffering from idiopathic PD (age/disease duration/levodopa treatment since: 53±(SD)7/13±3/9±3 years) were measured on a 1.5T MAGNETOM Symphony scanner (Siemens, Erlangen, Germany). 200 volumes of rs-fMRI data were collected using gradient-echo echo-planar imaging sequence (*FA/TR/TE* = 90°/3000/51 ms). T_1-weigted structural data were acquired for registration purposes using magnetization-prepared rapid acquisition gradient-echo sequence (*FA/TR/TI/TE* = 15°/2140/1100/3.93 ms). Participants were instructed to follow a fixation-cross on a projector screen while remaining still in a supine position. Functional images were pre-processed using SPM8. Using the WFU PickAtlas, a search space was formed comprising the whole motor system (premotor, motor and sensory cortex, basal ganglia, brainstem, cerebellum) and was used in all subsequent analyses and statistics (**Fig. 1**; **b**). FMRI voxels exhibiting signal drops due to electrode-related artifacts were excluded from the search space. Iterative character of eigenvector centrality (EC)[4] was used to identify the most *central* communication hubs—regions functionally connected with many other central regions—in the motor system of each patient pre- and post-implantation. A paired *t*-test was performed between the normalized EC maps before and after implantation, to observe reorganization of these *central* hubs caused by action of MLE. Resulting maps were corrected for multiple-tests using a false-discovery rate (FDR) error correction on a cluster level at p_{FDR}<0.05. Finally, correlation analysis was performed to discover potential linear relationships between EC maps and scores of Unified Parkinson's Disease Rating Scale (motor part; UPDRS-III).

Results: UPDRS-III scores decreased significantly (p<0.001; **Fig. 1a**) after penetration of electrodes demonstrating beneficial clinical impact of MLE even before initiation of chronic DBS. Patients also expressed trend towards left lateral dominance of PD symptoms (p=0.66; **Fig. 1a**). A significant increase of EC following the electrodes penetration was observed in cerebellum, brainstem, putamen/globus pallidus, thalamus and right premotor cortex (**Fig. 1c**). Moreover, an inverse correlation between total UPDRS-III scores and EC pre- and post-implantation was revealed in cerebellum and brainstem (**Fig. 2a**). Similar pattern was observed with akinesia and rigidity. Tremor was the only symptom inversely correlating with the EC maps in different region, namely right putamen/globus pallidus (**Fig. 2b**). The predominant right-hemispheric centrality changes (**Fig. 1c**; **Fig. 2b**) might be explained by left hemibody symptoms dominance.

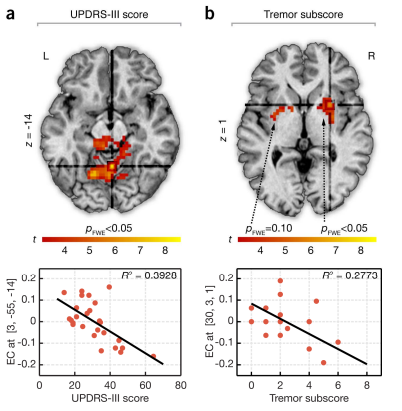

Figure 2. Correlation of centrality maps with clinical symptoms. **(a)** Improved cardinal symptoms in our sample (i.e. akinesia and rigidity) are related to increased centrality of brainstem and cerebellum. **(b)** Improved tremor is associated with increased centrality of putamen/globus pallidus.

Discussion & Conclusion: The invasive intervention in combination with aforementioned hypothesis-free analytic method provided us with a unique opportunity to observe the direct and cardinal impact of disturbed STN on the rest of the motor-circuitry in human PD *in-vivo*. Predominantly affected brainstem and cerebellum presumably compensate for the disrupted motor network to maintain relatively normal motor function in the acute phase of MLE. Diligent histopathological study of Braak et al. showed principal involvement of the brainstem already in the initial, non-symptomatic phases of the disease.[5] Major recruitment of the cerebellar structures in PD has also been recently discussed in a thorough review by Wu and Hallett.[6] Furthermore, improvement of dominant symptoms (akinesia, rigidity) in our study sample seem to be tightly related to increased general connectivity of brainstem and cerebellum, whereas improved tremor appears to be related to increased general connectivity of putamen/globus pallidus with the rest of the motor network. Presented work supports the necessity of increased emphasis on brainstem and cerebellum in research of PD, which was overshadowed over the decades by the discovery of levodopa and its extensive effect on striatal dopaminergic pathways.

References:

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