Eigenvector centrality of resting-state fMRI in the brainstem: A potential marker for Parkinson's disease pathology

Štefan Holiga[1,2], Robert Jech[3], Karsten Mueller[1], Dušan Urgošík[4], Matthias L. Schroeter[1,2], and Harald E. Möller[1]

[1]Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany, [2]Clinic for Cognitive Neurology & Leipzig Research Center for Civilization Diseases, University of Leipzig, Leipzig, Germany, [3]Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague, Czech Republic, [4]Department of Radiation and Stereotactic Neurosurgery, Na Homolce Hospital, Prague, Czech Republic

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

Purpose: Main motor manifestations of Parkinson's disease (PD) are associated with the death of dopamine-producing neurons in the substantia nigra pars compacta (SN) and consequent disruption of dopaminergic projections to the striatum. However, as discovered by a thorough histopathological study of Braak et al., the PD pathology has already reached its advanced stages after the motor dysfunction appears clinically.[1] In the initial non-symptomatic stages of PD, the pathological process targets the lower brainstem and follows a gradual, pre-determined ascending course towards the SN and the cortex, with the upward gradient of brainstem lesions remaining present throughout all stages of the disease (Fig. 1). Our previous resting-state (rs)-fMRI investigations identified the lower brainstem as the central hub associated with the improvement of PD patients' motor symptoms.[2,3] This signifies that rs-fMRI could be a potential candidate for providing pre-symptomatic biomarkers of the disease. In this work, we aimed to reveal a correspondence between the histopathology and the rs-fMRI in the topographical progression of the disease. In particular, we hypothesized that the ascending course of the brainstem pathology is reflected in an upward gradient of the braintem's rs-fMRI functional connectivity (Fig. 1). Such a link could open up a viable possibility of detecting PD using rs-fMRI well before the nigrostriatal neurons have undergone degeneration, eventually providing an early non-invasive diagnostic option, and thus facilitating discoveries of novel neuroprotective therapies.

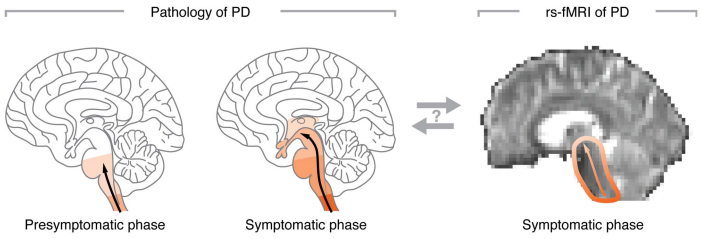

Figure 1. Does the ascending progression of the PD pathology relate to an upward gradient of a specific feature of low-frequency BOLD signal fluctuations? **(Left)** In the premotor stages of the disease, the PD pathology occurs in the lower brainstem and gradually progresses towards the neocortex. PD is already in its later stages when Lewy bodies target the SN and motor symptoms become apparent. Still, the gradual course of the pathology in the brainstem persists in all stages of the disease, only to a different degree and a distinct topographical extent.[1] **(Right)** Hypothetically, the ascending gradient of the PD pathology should be mirrored in the functional connectivity patterns of the rs-fMRI in the brainstem. Then, rs-fMRI of the brainstem could be of considerable importance as a predictive, non-invasive imaging marker for early phases of PD. *BOLD*: Blood oxygenation level-dependent, *PD*: Parkinson's disease, *rs-fMRI*: resting-state fMRI, *SN*: substantia nigra.

Methods: 24 patients suffering from advanced idiopathic PD (age/disease duration/Unified Parkinson's Disease Rating Scale motor score OFF/ON: 56±8/9±19 years/35±11/12±6) were measured task-free on a 1.5T MAGNETOM Symphony scanner (Siemens, Erlangen, Germany) in two stages: *(i)* after overnight withdrawal of the dopaminergic medication (OFF) and *(ii)* after an oral 250 mg dose of levodopa (ON). 200 volumes of rs-fMRI data (3 mm^3) were collected using a gradient-echo echo-planar imaging sequence (*FA/TR/TE* = 90°/3000/51 ms). T_1-weigted structural data were acquired for display and registration purposes using magnetization-prepared rapid acquisition gradient-echo sequence (*FA/TR/TI/TE* = 15°/2140/1100/3.93 ms). Functional images were pre-processed conventionally. A common anatomical search-space was formed comprising the whole motor system. Eigenvector centrality (EC)[4] was used to identify the main communication hubs—central regions functionally connected with many other central regions in the search-space—in both treatment stages. An average EC value was calculated in each slice of the brainstem mask in *z*-direction (Fig. 2A) (by ascending from inferior [−50 mm] by 3 mm to superior [1 mm]; 18 slices/values in total). Mean and standard deviation were computed from the *z*-coordinate-dependent EC values across all patients in both treatment stages separately (OFF, ON). A linear model was fitted, and the Pearson's correlation coefficient was calculated to assess the strength of the potential linear relationship between the slice coordinates and average EC responses. To evaluate the effect of the dopaminergic medication, a paired *t*-test was performed using the average *z*-coordinate-dependent EC samples before and after levodopa administration.

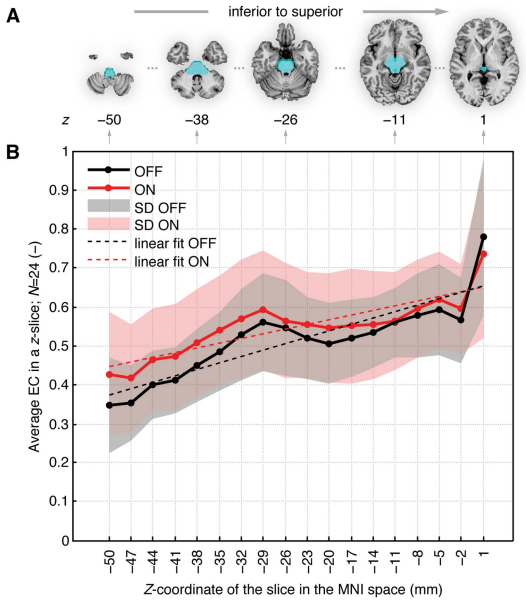

Figure 2. Correlation of axial MNI coordinate of the brainstem mask **(A)** (marked blue) and the average EC in the particular slice of the mask in 24 PD patients off (black) and on (red) levodopa. The linear dependencies **(B)** indicate a correspondence between the pathology and the functional connectivity of the brainstem, and a normalizing effect of levodopa on the upward functional integrity of the brainstem in PD. *EC*: eigenvector centrality, *MNI*: Montreal Neurological Institute, *N*: number of patients, *PD*: Parkinson's disease, *SD*: standard deviation.

Results: A clear linear trend of increasing centrality of functional connectivity depending on the axial brain coordinate was revealed in the brainstem (r=0.876, p=1.9·10^{-6} and r=0.862, p= 4.3·10^{-6} for OFF and ON, respectively), although the relationship included distinct fragments of non-linearity (Fig. 2B). Further, a significant difference (p= 6.2·10^{-5}) was discovered by comparing the dependence of the EC and the *z*-coordinate between both treatment stages (Fig. 2B), suggesting a normalizing effect of levodopa on the functional connectivity of the brainstem.[3]

Discussion & Conclusion: The gradual elevation of the interconnectedness of the brainstem seems to correspond to the evolving topographical progression of the brainstem pathology—the inferior portions of the brainstem being less connected (exhibiting more lesions) as compared to those located superior. Thus, inferior-superior functional integrity of the brainstem, as assessed by the EC of functional connectivity, should be considered a potential imaging marker of the PD pathology. These findings invigorate the overlooked brainstem perspective in the understanding of PD and support the current trend towards its early diagnosis. The degree and the topographical extent of the upward centrality gradient still need to be corroborated in the rs-fMRI of early-diagnosed patients. More importantly, healthy participants—where no such ascending trend is to be expected—also need to be evaluated as to verify the proposed link. Then, the EC of the brainstem could be employed as a feature for pattern classification techniques in a potential diagnostic setting for early diagnosis of PD.

References:

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