Levodopa increases functional connectivity in the cerebellum and brainstem in Parkinson’s disease

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Sir, we would like to comment on a recent article published in Brain by Hacker et al. (2012), which reported functional connectivity alteration in 13 patients with Parkinson’s disease in the medicated state compared with healthy control subjects. Although the authors showed very interesting results, they could not disentangle the effects of levodopa within the patient group. We investigated the influence of dopaminergic medication on patients with Parkinson’s disease in an intra-individual design based on functional connectivity derived from resting state functional MRI. We used a model-free and data-driven approach with eigenvector centrality mapping (Lohmann et al., 2010)—an algorithm similar to Google’s PageRank routine. The method automatically detects all brain areas serving as communication hubs, which—unlike other areas—have greater connectivity with many other parts of the brain. Hence, as distinct from previously used methods, this approach is unbiased by manual selection of the seed regions and thereby independent of the expert’s decision.

Using the eigenvector centrality analysis we found, concurrently with Hacker et al. (2012), a significant functional connectivity reduction in the cerebellum and brainstem regions in patients with Parkinson’s disease. We observed new facts related exclusively to treatment. Unlike Hacker et al. (2012), we studied resting state functional MRI after an overnight discontinuation of antiparkinsonian medication (OFF condition) and after a 250 mg dose of levodopa (ON condition). The study was approved by the local ethics committee. We examined 24 patients with Parkinson’s disease [19 males, 5 females, aged 55.5 ± 7.9 (SD) years, Hoehn and Yahr stage II–III, Parkinson’s disease duration 9–19 years, Unified Parkinson’s Disease Rating Scale motor score OFF: 35.1 ± 10.8, ON: 11.8 ± 5.5] who gave their written informed consent for participation. They were instructed to watch a cross while lying motionless in the supine position for 10 min during functional MRI acquisition (1.5 T, T2*-weighted gradient-echo echo-planar imaging: flip angle/repetition time/echo time = 90°/3000/51 ms, voxel size 3 × 3 × 3 mm, 200 repetitions). We received good quality data with a maximum head displacement within the voxel size. Preprocessing involving realignment, slice time correction and normalization was performed in SPM8 software (Wellcome Trust Centre for Neuroimaging, London, UK). Eigenvector centrality analysis was conducted in the Lipsia software package (Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany) restricted to expanded mask comprising premotor, motor and sensory cortex, basal ganglia, brainstem and cerebellum. The random effects analysis was based on comparison between the eigenvector centrality maps in the ON and OFF conditions.

Compared with the OFF state, post-levodopa functional connectivity showed a significant increase, which was seen in the cerebellum and in the upper and lower brainstem (Fig. 1). In contrast, no significant decrease in connectivity appeared in any brain regions. On closer examination, levodopa increased functional connectivity in the posterior mesencephalon (including pedunculopontine nucleus), inferior pons and especially in the cerebellar vermis with adjacent parts of hemispheres (lobules V and IX) with...
From our results and considering findings of Hacker et al. (2012), levodopa has a normalizing rather than compensatory effect on the activity of the brainstem and cerebellum, whose function as an information node is significantly attenuated in Parkinson’s disease while medication is withdrawn. To our knowledge this has not been described before. A functional connectivity increase in the cerebellum was previously reported in relation to resting tremor (Helmich et al., 2011). In our view, our results are related to a different phenomenon as the functional connectivity increased instead of decreased in the ON condition because levodopa causes improvement for a resting tremor. In addition, there were no patients with tremor dominant Parkinson’s disease in our study since the majority suffered from the akinetic-rigid (n = 18) or the mixed type (n = 7) of disease.

We believe that the functional connectivity increase in the infratentorial region is attributed to another fundamental mechanism by which dopaminergic medication acts on dysfunctional communication within the motor network in Parkinson’s disease. In addition, our robust results of eigenvector centrality analysis are complementary to the findings of Hacker et al. (2012), they support a decisive relevance of brainstem dysfunction in the neuropathogenesis of Parkinson’s disease (Braak et al., 2003) and define the main hubs in motor network that are sensitive to antiparkinsonian treatment.

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