Reply: Levodopa increases functional connectivity in the cerebellum and brainstem in Parkinson's disease

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Sir, Jech et al. (2013) report that L-DOPA increased functional connectivity in the cerebellum and brainstem of patients with moderately severe Parkinson's disease. This result is broadly complementary to our recent demonstration that functional connectivity between the striatum and a large region encompassing brainstem and cerebellum is abnormally decreased in advanced Parkinson's disease compared with age-matched control subjects, despite continued treatment with L-DOPA (Hacker et al., 2012). Whereas Jech et al. (2013) did not compare patients with Parkinson's disease to control subjects, we did not study the effects of L-DOPA in patients with Parkinson's disease. However, Kelly et al. (2009) administered L-DOPA to neurologically normal young adults and observed that this intervention increased functional connectivity between striatum and cortical regions, that is, induced effects consistent with Jech et al. (2013) and opposite to the Parkinson's disease versus control group effects in our study. Taken together, these studies suggest two major points concerning Parkinson's disease. First, exogenous L-DOPA does not fully reverse the effects of Parkinson's disease, at least as manifested in the statistical properties of intrinsic blood oxygen level-dependent fluctuations, which is the basis of resting state functional MRI. This point mirrors the clinical experience of all physicians treating patients with advanced Parkinson's disease. Second, our observations as well as those of Jech et al. (2013), reinforce the importance of the brainstem and cerebellum in the pathophysiology in Parkinson's disease. Despite recent attribution of certain clinical aspects of Parkinson's disease to brainstem dysfunction (Grinberg et al., 2010), this perspective has been largely neglected in the Parkinson's disease literature during the past three decades, which, instead, has focused primarily on cortical-striatal-thalamic loop dysfunction, albeit consequent to withdrawal of brainstem dopaminergic input (Albin et al., 1989). An increased emphasis on the brainstem would be appropriate given the meticulous histopathological studies of Braak et al. (2003). In fact, the importance of lower brainstem pathology in the understanding of Parkinson's disease was well established by the mid-1960s (Eadie, 1963). It seems that this perspective was overshadowed by the landmark discovery of the clinical value of L-DOPA (Cotzias et al., 1969).

Some caution is appropriate in considering the letter of Jech et al. (2013). The blood oxygen level-dependent analysis methodology is somewhat novel and does not specifically target the striatum. Also, data ‘with a maximum of head displacement within the voxel size’ (3 × 3 × 3 mm) may be significantly contaminated by artefact (Power et al., 2011), especially in parkinsonian patients prone to involuntary movements including L-DOPA-induced dyskinesias. We look forward to reading the authors’ peer-reviewed publication.

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References