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Functional connectivity alterations of striato-cortical circuits in multiple sclerosis

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Fatigue is one of the most common and disabling symptoms in multiple sclerosis (MS), yet the underlying pathophysiology remains poorly understood.[1] One current hypothesis posits that disturbance of non-motor basal ganglia functions and consecutive disruption of striato-cortical pathways plays a key role in the development of fatigue. Given that the striatum is a central part of the reward system, it has been suggested that dysfunction of the striato-cortical network results in an effort-reward imbalance. This biased perception of high performance costs and low benefits has been proposed as one of the central features of fatigue.[2] Indeed, resting-state functional magnetic resonance imaging (fMRI) analyses identified distinct alterations of basal ganglia functional connectivity associated with fatigue severity in patients with MS.[3] Recently, we observed a reduced connectivity of the striatum (especially of the superior ventral striatum) with the sensorimotor network as well with attention and reward networks in MS patients with fatigue.[4]

As in previous studies, fatigue and depressive symptom severity were highly correlated in our study—indeed, items in depression and fatigue scales (e.g. beck depression inventory (BDI) and fatigue severity scale (FSS)) show a high overlap in many questions (e.g. exhaustion, tiredness, and lack of drive). Consequently, most patients with fatigue also yield high scores on depression scales. To disentangle the contributions of fatigue and depression to connectivity changes, we excluded all patients with moderate to severe depressive symptoms as indicated by BDI-II scores $\geqslant$20. Nevertheless, the severity of depressive symptoms was negatively correlated with functional connectivity between the ventral striatum superior and the somatosensory cortex, that is, patients with higher depression symptoms showed a reduced connectivity between these regions.

Tecchio et al.[5] performed a pilot study with 14 MS patients with low BDI scores that received transcranial direct current stimulation (tDCS) of the bilateral primary somatosensory cortices. The authors found a significant reduction of BDI scores in patients receiving this stimulation, but not in patients with sham stimulation. We agree with the authors that these are very interesting findings that require further studies with refined protocols and that include MS patients with the full spectrum of depressive symptom severity (i.e. include patients with low and high BDI scores). It would furthermore be interesting to study whether tDCS of the bilateral primary somatosensory has a similar or distinct effect on depression and fatigue severity. Finally, we believe that studies combining resting-state fMRI with tDCS would be specifically

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promising: First, resting-state fMRI can be used to precisely locate (subject-specific) cortical stimulation targets when preferred target structures cannot be stimulated directly (e.g. basal ganglia). Second, fMRI scans before and after tDCS can assess whether potential improvement of targeted symptoms (e.g. fatigue, depression) correlates with change/normalization of pre-stimulation functional connectivity alterations. This latter approach could help to validate or falsify current pathophysiological concepts and to develop novel hypotheses about MS-related symptoms such as fatigue, depression, and cognitive impairment.

Declaration of Conflicting Interests

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