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Supplementary motor area functional connectivity in drug-naïve Parkinson's disease patients with fatigue

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Introduction: Fatigue is a common and disabling nonmotor manifestation in patients with Parkinson's disease (PD), and the supplementary motor area (SMA) has been implicated in its pathophysiology. SMA is usually divided in its rostro-caudal axis, with the rostral (pre-) SMA playing a major role in motor planning, and the caudal (proper) SMA related to movement execution.

Aims: To investigate brain functional connectivity (FC) of SMA subregions in early, drug-naïve PD patients and its correlation with fatigue.

Methods: Seventeen PD patients affected by fatigue, 18 without fatigue, and 16 matched healthy controls were recruited. Parkinson Fatigue Scale (PFS) was used for fatigue screening (cut-off > 3.3 points) and severity rating. Seed-based resting-state functional MRI was used to compare the FC from bilateral SMA subregions to the whole brain. Voxel-based morphometry analysis was also employed to test whether FC results were related to brain structural differences. Linear correlations were run between imaging and behavioural data.

Results: PD-related fatigue was associated with an increased FC between the left pre-SMA and the left postcentral gyrus as well as a decreased FC between the left SMA proper and the left middle frontal gyrus ($ps < 0.01$). These patterns of FC were tightly correlated with PFS scores (Pearson's $rs < 0.01$). No structural brain changes were observed.

Conclusions: In early PD, altered FC of both SMA subregions might play a crucial role in fatigue pathophysiology. The altered FC of the pre-SMA might underlie a poor attenuation of sensory signals from the somatosensory systems to higher order motor system, whereas the altered FC of the SMA proper might be associated to poor explicit contingency awareness causing an overgeneralization of perceived physical effort load. These results offer new insights into the mechanisms responsible for fatigue in PD and possible targets for neuromodulation strategies oriented to modulate the SMA activity.