Neurological Sciences (2019) 40:2635–2636
https://doi.org/10.1007/s10072-019-03978-1

LETTER TO THE EDITOR

Non-motor symptoms of Parkinson's disease: dopaminergic basis or not?

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Received: 23 February 2019 / Accepted: 10 June 2019 / Published online: 17 June 2019

Dear Editor,

I read with much interest a recently published article by Park et al. investigating the association between striatal dopaminergic loss and non-motor symptoms (NMS) in Parkinson's disease (PD) patients [1]. Motor symptoms such as tremor, bradykinesia, and rigidity are cardinal components for the diagnosis of PD, which are caused by degeneration of dopaminergic neurons in substantia nigra pars compacta. However, PD is now considered a multisystem disorder causing diverse NMS as well. The authors obtained abundant data on various NMS including cognition, anxiety, depression, frontal execution, fatigue, and sleep. The correlations of these NMS with dopaminergic deficit were assessed by analyzing dopamine transporter imaging with ^{18}F-FP-CIT PET.

The authors found no significant correlations and concluded that nigrostriatal dopamine deficiency was not implicated in NMS of PD, which was derived from subregional dopamine transporter analysis of 12 striatal volumes of interest. They defined the striatal subregions using anatomical landmarks, but this anatomical subdivision is somewhat arbitrary. The striatum is functionally organized based on its cortical inputs [2]. The corticostriatal projections largely divide functional striatal clusters into sensorimotor, associative, and limbic striatum, and this functional subdivision is anatomically indistinctive. Each functional cluster has its own distinctive cortico-striato-pallido-thalamo-cortical circuit; each striatal compartment receives inputs from specific cortical areas and sends output to different domains of basal ganglia and back to the cortex via different nuclei of the thalamus. Selective dysfunction of each circuit causes specific motor symptoms or NMS, with the sensorimotor striatum contributing to movement disorder, the associative striatum to cognitive disorder, and the limbic striatum to behavioral disorder [3]. The previous study with resting-state fMRI also revealed the functional corticostriatal connectivities between the dorsal striatum and cortices with cognitive function and between the ventral striatum and cortices with affective function [4]. The rostral putamen was connected with the cortical areas involved in the cognitive process, while the caudal putamen had connections with the cortical areas involved in the motor process. Therefore, subregional analysis based on anatomical segmentation does not fully represent the pathophysiology of NMS in PD patients.

Moreover, PD patients in relatively early stages (Hoehn and Yahr stage, 1.7 ± 0.6) were involved in this study. While some NMS such as hyposmia and REM sleep behavior disorder develop in the prodromal stage of PD, other NMS including cognitive and autonomic dysfunctions manifest in later stages [5, 6]. Along the natural course of PD, the striatal dopamine depletion is more prominent in the sensorimotor striatum than the associative striatum. The ventral striatum which corresponds to the limbic striatum is the least affected region by the neurodegeneration, and part of various NMS is involved in the mesocorticolimbic pathway. Presumably limited inclusion of PD patients in early to moderate stages thus may have affected the results of the study.

Although non-dopaminergic neurotransmitters such as noradrenalin, serotonin, and acetylcholine also contribute to the development of NMS in PD, a large body of research demonstrates a dopaminergic basis for them [7]. For example, PD patients showed decreased functional connectivity in the frontostriatal network in resting-state fMRI studies, which generates diverse cognitive and behavioral impairments [8]. Another recent resting-state fMRI study also reported that the disturbed functional connections of the striatum with the default mode network as well as the visual and somatosensory cortices were associated with developing depression and anxiety in patients with primary insomnia [9]. Striatal subdivision

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according to functional connection rather than anatomical structure has closer relation with the pathogenesis of NMS. Therefore, I believe that subregional analysis of striatal dopaminergic loss based on functional compartments in a wider spectrum of PD patients would lead to a different conclusion.

Compliance with ethical standards

Ethical standards This article does not contain any studies with human or animal subjects performed by the author.

Conflict of interest The author declares that he has no conflict of interest.

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