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Reply to: Letter to the Editor by Martínez-Fernández

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► To cite this version:

Yvan Vachez, Carole Carcenac, Robin Magnard, Lydia Kerkerian-le Goff, Pascal Salin, et al.. Reply to: Letter to the Editor by Martínez-Fernández. *Movement Disorders*, 2020, 35 (6), pp.1084-1085. 10.1002/mds.28082 . hal-04700941

HAL Id: hal-04700941

<https://hal.science/hal-04700941v1>

Submitted on 18 Sep 2024

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Reply to the Letter to the editor regarding “Subthalamic nucleus stimulation impairs motivation: implication for apathy in Parkinson’s Disease”

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Word count: 471

We thank Dr Raul Martínez-Fernández for his comment concerning our publication¹ and for the opportunity to discuss our data in more detail, especially with an expert on apathy in Parkinson's Disease (PD).

Whether apathy associated with subthalamic nucleus deep brain stimulation (STN-DBS) is a consequence of the reduction of dopaminergic replacement therapy (DRT), as considered in the prevailing clinical opinion, or a direct psychiatric side effect of the stimulation itself, remains an unsolved issue. Exploring this question with preclinical approaches allows examining separately potentially interacting factors. However, we agree it also presents limitations, as pointed out by Dr Martínez-Fernández, and already acknowledged in the discussion of the present publication⁴. Although, in our work, the effects of STN-DBS were consistent in all the animals carefully and rigorously included based on correct placement of the electrode, given the size of the STN, spreading outside the targeted STN region, such as to zona incerta, cannot be excluded, especially when applying a monopolar stimulation. Of note however, monopolar stimulation was consciously chosen in our study to model at best DBS as in the clinic¹.

In this context, our work showed in rats that chronic STN-DBS diminishes reward seeking and basal activity in both control animals, without any dopamine degeneration, and in a model of PD-neuropsychiatric manifestations, in the absence of any prior dopamine medication¹. It thus provides evidence that STN-DBS by itself could promote loss of motivation reminiscent of apathy in PD, without excluding interaction with the neurodegeneration profile and medication history in patients. Even though the pathophysiological explanations afforded by our study remain limited, the reversion of the STN-DBS-induced motivational deficit by pramipexole, a D₂R/D₃R agonist that alleviates apathy in PD patients, argues for a mechanism involving these receptors, in line with our previous observation of decreased D₂R/D₃R under acute STN-DBS², which we will try to dissect in the future.

In addition, the bivalent role of STN, in positive and negative reward and emotional processes³, as well as its complex implication at the intersection of the motor, associative

and limbic interconnected basal ganglia loops have been extensively investigated and can largely account for paradoxical effects of DBS ranging from apathy to euphoria, depending on the parameters of stimulation as well as localization. For instance, location within or close to the border of the so called “limbic” ventral STN has been described either to improve⁴ or worsen apathy⁵ in PD patients, revealing not only a complex action of DBS in animal models but also in the clinic. Also, regarding stimulation setting, whether the spectrum cursor for motor function and for behavior is the same remains to be established.

To conclude, while acknowledging its limitations, our work brought new relevant elements, perhaps counterintuitive, but not at odds with our current understanding of the STN, fueling constructively the debate on the question “can STN-DBS induce apathy?”.

Authors roles: YV and SB performed the concept and writing of the manuscript with the input of all authors.

Financial disclosures: Authors did not receive any funding relevant to this manuscript.

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