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RESPONSE TO THE LETTER TO THE EDITOR

Reply from Jumes Leopoldino Oliveira Lira, Carlos Ugrinowitsch, Daniel Boari Coelho, Luis Augusto Teixeira, Andrea Cristina de Lima-Pardini, Fernando Henrique Magalhães, Egberto Reis Barbosa, Fay B. Horak, and Carla Silva-Batista

We read with interest and enthusiasm the positive comments of Onder *et al.* (2022) on our innovative results about the loss of presynaptic inhibition (PSI) for step initiation in people with Parkinson's disease (PD) and freezing of gait (FOG (freezers)) and the recommendations for future studies.

Onder *et al.* found our study important considering the rarity of electrophysiological studies evaluating the relationship between FOG and PSI. Onder *et al.* (2022) raised two important questions from our findings: (1) Does PSI play a role as a primary target in the pathophysiology of FOG or does it represent a contributory mechanism to the cortical motor dysfunction? (2) And does PSI represent an insufficient compensatory process for FOG?

Regarding the first question, we have found that loss of PSI, FOG severity, and decreased anticipatory postural adjustment (APA) are all related (Lira *et al.* 2020), which suggests that similar neural correlates explain all three. The mesencephalic locomotor region (MLR) may play an important role in the relationships among PSI, FOG and APAs. MLR is a region of the midbrain that, when stimulated, increases postural tone for standing posture and induces stepping and running in the decerebrate cat (Shik & Orlovsky, 1976). MLR also has neurons related to APAs preceding step initiation (Sinnamon *et al.* 2000). Freezers have worse structural and functional deficits in pedunculopontine nucleus (PPN), one of the major nuclei of the MLR, than non-freezers and healthy controls (Fling *et al.* 2013). Over-activity of the output nuclei of the basal ganglia in freezers may lead to excessive paroxysmal inhibition of the already disordered PPN (Lewis & Barker, 2009). Inhibition of PPN probably has a negative influence on spinal inhibitory mechanisms related to postural preparation, such as PSI, before triggering FOG. PSI is crucial for postural preparation and walking (Faist *et al.* 1996; Nielsen, 2004) and FOG may be due to an inability to inhibit stance postural tone and initiate stepping (Nutt *et al.* 2011; Fling *et al.* 2013; Cohen *et al.* 2014). Taken together, we hypothesized that loss of PSI is due to lack of central inhibition (decreased MLR activation) when standing to allow for step initiation, which may contribute to occurrence of FOG events.

Regarding the second question, we agree that restoring PSI may compensate for supraspinal dysfunction during FOG episodes, as we have recently demonstrated that healthy elderly individuals have higher PSI levels associated with weaker APAs compared to healthy young individuals (Filho *et al.* 2021). The increase in PSI levels in elderly individuals has been considered an adaptive/compensatory phenomenon, due to age-related deterioration of supraspinal modulation (Morita *et al.* 1995; Filho *et al.* 2021). It is important to highlight that although we assessed PSI in the ON-medication state during no FOG episodes, we will test the hypothesis that the loss of PSI is greater during OFF-medication state than in ON state, as levodopa changes the excitability of the H-reflex in PD (McLeod & Walsh, 1972).

Onder *et al.* (2022) also suggest that to clarify the precise causal association between the loss of PSI and FOG, the use of physical therapy with visual cues is important. Although cues are applied to evoke a more goal-directed type of motor control, long-term consolidation and transfer of effects of visual cues are hampered in freezers (Ginis *et al.* 2018), suggesting that visual cues may not increase PSI in this population. Thus, we hypothesize that therapies need to cause persistent and permanent neurophysiological adaptations to restore PSI during APAs in freezers. As PSI is important for modulating muscle coordination by adjusting both supraspinal motor commands and sensory feedback at the spinal level (Nielsen, 2004), rehabilitation interventions focused on sensorimotor integration might restore PSI during APA in freezers.

We have recently demonstrated that 12 weeks of motor-cognitive balance training on unstable surfaces increases MLR activation and APA amplitude and decreases FOG severity in freezers (Silva-Batista *et al.* 2020). Previously, we found that 12 weeks of resistance training with instability were more effective than 12 weeks of resistance training alone in increasing PSI levels, at rest, in non-freezers (Silva-Batista *et al.* 2017). Taken together, we believe that interventions focused on challenging sensorimotor integration could restore PSI levels during APA in freezers, which in turn, would compensate for supraspinal dysfunction and overcome FOG episodes. From these considerations, we propose that large-scale trials investigating sensorimotor rehabilitation strategies specifically aimed at restoring PSI and reducing FOG in the long term are urgently needed to treat this disabling symptom in PD.

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Additional information

Competing interests

The authors declare that there are no competing interests.

Author contributions

All authors contributed to the design of the study. J.L.O.L., D.B.C., A.C.L.P., F.H.M., E.R.B., C.S.B. collected the data. J.L.O.L., D.B.C., A.C.L.P., F.H.M., C.U., L.A.T., E.R.B., C.S.B. analysed the data, and all authors contributed to the interpretation of the data. J.L.O.L. and C.S.B. prepared the first draft of the manuscript. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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Keywords

anticipatory postural adjustment, freezers, H-reflex, mesencephalic locomotor region, sensorimotor integration, spinal inhibitory mechanism

Supporting information

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