Letter Regarding the Article Entitled: "The Effect of Dual Tasking and Deep Brain Stimulation Frequency Parameters on Gait in Advanced Parkinson's Disease"

Dear Editor,

The recent article by Tandra *et al*.[1] reports crucial findings focusing on an interesting issue of the impact of deep brain stimulation (DBS) frequency on gait in Parkinson's disease (PD) subjects.[1] Remarkably, contrasting with the classical data remarking on the benefit of low-frequency stimulation (STIM) on axial symptoms,[2-4] they found that most patients had demonstrated significant improvement in gait at a single frequency differing between patients. We think that there may be some points to be further deliberated for a better understanding of this crucial report.

In a prospective study by Khoo *et al*.,[2] the authors demonstrated that 60 Hz STIM provided superior efficacy over 130 Hz in improving the total unified Parkinson's disease rating scale (UPDRS) motor score, axial motor signs including gait and freezing of gait (FOG). However, the optimal contacts for 60 Hz STIM were found to be situated more ventrally than those for 130 Hz STIM. Such that, they emphasized that optimizing the active contacts with respect to frequency is very important in augmenting the beneficial effect of 60 Hz STIM. However, no compelling explanation was proposed to explain their observation.[2] In another study, Ricchi *et al*.[4] also demonstrated a significant improvement of gait after switching the STIM frequency from 130 to 80 Hz. However, at the same time, they had adapted the voltage to maintain the same total delivered energy that might be efficient in the results.[4] Remarkably, despite the immediate improvement provided after the frequency change, the improvements were no longer detectable at follow-up evaluations 1, 5, and 15 months later.[4] The other study[3] also referred by the authors detected that FOG episodes were significantly lower at the 60 Hz "high voltage/equivalent energy" and higher at the 130 Hz/high voltage than for the period of stimulation is turned off which was substantially contrasting with the results of Tandra *et al*.[1] Nevertheless, in that study[3] the voltage amplitudes were also increased to maintain the same total energy delivered. To clarify this point, Phibbs *et al*.[5] conducted a study on 20 PD subjects with subthalamic nucleus (STN)–DBS at which they compared the efficiency of 60 and 130 Hz STIM in a blinded fashion with all other parameters held constant. In conclusion, they did not find an improvement in gait parameters at 60 Hz STIM.[5] Besides, there was also less tremor control at 60 Hz. It is remarkable to state that, Tandra *et al*.[1] also kept the voltage and pulse width constant and supported the results of the Phibbs *et al*.[5] in a larger group of patients.[1] Taken together with the results of Tandra *et al*.,[1] we think that the improvement in the low-frequency STIM pattern that had been reported previously,[2-4] might rather be related to the increment in the STIM voltages or other parameters to adapt the same total energy. The observation of differing optimal contact for low-frequency STIM[2] is also an intriguing point that needs to be clarified in this regard. More complicating this issue, a recent study also demonstrated that optimal frequency varied between patients, and it was also associated with electrode contact site and severity of axial symptoms.[6]

Investigating the clinical phenotypes of the patients with distinct optimal STIM frequencies in detail and comparing some specific features differing between groups may also provide interesting perspectives. Tandra *et al*.[1] demonstrate that patients best at 90 and 180 Hz STIM do not show difference in terms of age, disease duration, UPDRS scores, voltage amplitudes. However, we wonder if they might also include the intergroup comparisons of some clinical features such as "on" medication FOG, postural instability, speech, or other axial symptoms that are rather not responsive to DBS STIM which might also provide critical contributions.

Another point is that the effects of the STIM on axial symptoms including gait and FOG occur the latest in comparison to other motor signs such as tremor, rigidity, or bradykinesia. Such that, the onset of the effect of DBS therapy on gait may take hours to weeks.[7] Therefore, the 20 min interval between the distinct STIM frequencies may not be sufficient for the evaluation

of the clear effect of the new frequency on axial symptoms. We know that the negative effect of the DBS STIM on axial symptoms generally occurs in the long term. Such that, there is evidence of increased gait asymmetry and discoordination of gait after STN–DBS in the chronic phase of the STIM particularly in the postural instability and gait disorder subtype.[8] Although the pathophysiology of the possible disturbance of gait after STN–DBS is unclear, it is rather explained in the setting of STIM-induced network dysfunctions in essential tremor subjects with thalamic DBS.[9] Some authors have found evidence regarding the reversible nature of gait disturbance after DBS in patients with essential tremors and they hypothesized that this may be a maladaptive response to neurostimulation of the subthalamic area.[9] However, the possible contribution of the irreversible neuroanatomical and pathological changes in DBS-related gait disturbance is unknown and remains to be elucidated. Therefore, the optimal DBS adjustments to provide the best outcome in the long term may also constitute another critical issue to be investigated.

In conclusion, the results of Tandra *et al*.,[1] demonstrating the variability of the best STIM frequency between patients for the optimal treatment of gait and FOG, are critical. The results of this study in light of the related literature suggest that the clinical approach to gait disorders in PD subjects on DBS therapy is strictly a complicated issue and should vary individually depending on the heterogeneous pathology. Future studies are warranted to clarify also the influence of parameters other than frequency; including voltage, pulse width, and optimal contact. The results of these studies to address these discussions may provide critical contributions to the clinical grounds.

Abbreviations

STN–DBS = Subthalamic nucleus–deep brain stimulation, UPDRS = Unified Parkinson's disease rating scale, FOG = freezing of gait, STIM = Stimulation.

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Conflicts of interest

There are no conflicts of interest.

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infection and 7 patients after a SARS-CoV-2 vaccination.[3] encephalomyelitis (ADEM),[3] neuromyelitis optica spectrum