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Correspondence

Deep brain stimulation of the substantia nigra for freezing of gait in Parkinson's disease: is it about stimulation frequency?

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ABSTRACT

Converging evidence supports that co-stimulation of the subthalamic nucleus and the substantia nigra pars reticulata can be efficacious for the management of the resistant gait impairment in Parkinson's disease. In this Correspondence, we comment on a recent publication in Parkinsonism & Related Disorders regarding this novel intervention.

Dear Sir,

Deep brain stimulation (DBS) of the substantia nigra pars reticulata (SNr) is under consideration for the treatment of freezing of gait (FOG) in Parkinson's disease (PD). While DBS of the subthalamic nucleus (STN) is effective for the management of segmental motor symptoms and fluctuations, axial motor symptoms show limited therapeutic response as the disease progresses. One correlate of PD is that the inhibitory basal ganglia output structures are overactive. Since the SNr sends non-dopaminergic projections to brainstem structures involved in locomotion, combined stimulation of the SNr (using a caudal electrode) and STN (using rostral electrodes) was suggested to modulate locomotor integration [1,2]. In a first double-blind randomized controlled trial in twelve patients, combined stimulation of the STN and SNr using interleaved stimulation of both structures at a 'high' frequency of 125Hz demonstrated improvement of otherwise resistant FOG [1].

In an innovative study published recently in this journal, Valldeoriola and colleagues modified this approach by co-stimulating STN and SNr at different frequencies in 6 patients, and investigating the effect on FOG and other PD motor symptoms [3]. Previous work demonstrated that subthalamic stimulation at 60Hz could improve axial symptoms in PD patients with severe gait disorders, while 130Hz was ineffective [4]. Thus, the authors selected stimulation of the SNr at 63Hz, which they referred to as 'low-frequency' (LF), while the STN was stimulated at a conventional 'high frequency' (HF) of 126Hz. The results of the study suggest that combined HF-STN and LF-SNr stimulation had the best effect on various measures of FOG, compared to stimulation of a single target alone. Accordingly, four patients preferred to continue combined HF-STN and LF-SNr stimulation at the end of this study. Importantly, of the patients included in the study, the preoperative levodopa response on FOG was negative, which separates this case series from the established DBS selection criteria, and supports the view that 'resistant' FOG was indeed studied. Thus, the study adds to the converging evidence that PD-related gait disorders can be modulated at the level of the SNr [1–3,5,6].

The study makes a strong statement on parameter optimization of nigral stimulation in speculating that SNr stimulation at low frequency might be 'more promising' than high frequency stimulation. This notion requires closer evaluation in the light of the available clinical studies, as well as basic neurophysiological work. Presently, no comparative data between low- and high-frequency SNr stimulation (neither SNr alone nor combined with STN) is available, and such a control condition was not part of this case series. Hence, the notion is not supported by clinical evidence at this time. In addition, a closer look at the available pathophysiological literature may support a different conceptualization instead of arguing whether a given stimulation frequency would be superior over another. Both GABAergic pharmacological intervention [7] as well as high-frequency neurostimulation [8] modulated purportedly overactive nigral firing rates. A study on the 6-hydroxydopamine rat model demonstrated that 50Hz stimulation did not suppress SNr firing rates, whereas 130Hz had a suppressive effect [9]. More recently, the first study in human PD systematically assessed the neurophysiological effect of different stimulation frequencies in an acute intraoperative setting [10]. Specifically, this study investigated the stimulation frequency-dependent effects on cell firing and on short-term plasticity, as well as the effects of high frequency stimulation on the enhancement of synaptic plasticity. Cell firing and evoked field potentials were recorded across a range of stimulation frequencies (1–100Hz). SNr firing was attenuated from baseline with ≥3Hz stimulation, and was silenced with 50Hz, whereas the STN required 100Hz for neuronal silencing. Indeed, the selections of HF-STN stimulation at 126Hz and LF-SNr stimulation at 63 Hz [3] appear to reflect this inhibitory stimulus frequency-selectivity of STN and SNr neurons. Milosevic et al. further found that stimulation trains at ≥20Hz induced synaptic depression [10]. Moreover, the average amplitude of evoked field potentials during 1Hz pulses nearly doubled after a train of continuous high frequency stimulation at 100Hz, and these increases were coupled with increased durations of neuronal inhibition, indicative of enhanced inhibitory synaptic plasticity. In summary, the findings suggest that in addition to the simple frequency-dependent effects on cell firing, the enhancement of inhibitory synaptic plasticity and frequency-dependent effects on short-term plasticity (synaptic depression) need to be considered.

From the available evidence, the stimulation effects of 63Hz or 126Hz seem to interplay with a neurophysiological continuum regarding the local stimulation effects on single unit activity and synaptic plasticity measures, rather than exhibiting controversial neurophysiological or clinical effects. However, the downstream and overall

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network effects of nigral stimulation are not yet characterized and may influence future stimulation protocols beyond the present knowledge. Given the converging evidence of the present clinical and physiological studies, as well as other related studies regarding the role of SNr in PD gait pathophysiology, more detailed basic research and exploratory clinical work is warranted in order to take full advantage of the nigral locomotor hub for neurostimulation therapy.

Conflicts of interest

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