Subthalamic nucleus deep brain stimulation reduces freezing of gait subtypes and patterns in Parkinson's disease

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Dear Sirs,

Freezing of gait (FOG) is a specific gait disorder in Parkinson's Disease (PD). FOG occurs mainly in the medication-off state and usually improves with dopaminergic medication. FOG episodes can be clinically grouped into three patterns (small steps forward, trembling in place, complete akinesia) and five provoking subtypes (starting to walk hesitation, moving in tight quarters hesitation, reaching destination hesitation, turning hesitation, and walking in open space hesitation) [1]. FOG is a debilitating symptom, limiting activities of daily living, leading to falls or fall-related injuries, and diminishing quality of life [2].

The effect of deep brain stimulation of the subthalamic nucleus (STN-DBS) on freezing of gait (FOG) remains under debate since the prior results were conflicting. Whereas some studies [3,4] found an overall reduction of FOG under STN-DBS (although in most cases not to the same extent as non-axial symptoms), others reported no effect or even a deterioration of FOG [5–7]. The aim of this study was to evaluate the effect of STN-DBS on FOG with a special focus on the different FOG subtypes and patterns, as observed during a FOG provoking walking test performed before and at three follow ups after implantation.

The VANTAGE study [8] – a multicenter, prospective, open-label, non-randomized trial – assessed the effect of an implantable DBS system (Vercise™, Boston Scientific, Valencia, CA, USA) for bilateral stimulation of the STN in subjects with moderate to severe PD. In this preplanned sub-study, FOG was evaluated both subjectively (FOG questionnaire (FOGQ), the PDQ-39 mobility items, and FOG-specific items of the UPDRS II (items 13 [falls] and 14 [freezing])) and objectively with a standardized walking test provoking FOG (adapted from Ref. [1]). It was performed at baseline and at weeks 12, 26, and 52 postoperatively in the medication-on and -off state. STN-DBS was activated at all follow ups. The walking test was videotaped and made available for offline analysis by an independent and fully blinded rater (CB), who was unaware of the subject’s treatment status (i.e. before or after implantation) and the timepoint of the measurement.

The FOG data of 38 subjects (of 40 implanted) were analyzed (two subjects did not complete the FOGQ at baseline due to incomplete data collection). At the group level, the FOGQ showed an overall improvement (p < 0.0001) at week 26 compared to baseline. Separating subjects into subjective freezers or non-freezers at baseline (according to item 3 of the FOGQ), 10 freezers remained freezers, 15 freezers became non-freezers, 10 non-freezers remained non-freezers, and one non-freezer became a freezer. Two additional subjects dropped out at week 26, as the FOGQ was not completed at that timepoint (see Supplementary Fig. 1). The effect of STN-DBS on gait-specific questionnaires and subscores at baseline, and postoperatively can be found in the Supplementary Table 1. Of the 38 subjects, 20 performed the walking test at all time points during the medication-off state, and their data were taken for sub-analysis. There were no significant differences between the subgroup (n = 20) and the total subject group (n = 38) for baseline demographics and clinical characteristics. Importantly, FOG severity according to the FOGQ did not differ between the two groups. For the subgroup (n = 20), FOG at baseline responded to L-dopa (mean percentage time frozen: 0.21 ± 0.32 for medication-off and 0.02 ± 0.07 for medication-on; p = 0.0012). Total walking time (Fig. 1A), the percentage of time frozen (Fig. 1B), and number of FOG episodes (Fig. 1C) were reduced at weeks 12, 26, and 52 compared to baseline during medication-off. The different FOG subtypes (Fig. 1 D) and patterns (Fig. 1 E) all responded to STN-DBS. As seen in Supplementary Table 2, the additional application of L-dopa improved FOG even further compared to DBS alone in most cases. Our results show a profound ameliorating effect of STN-DBS on FOG in this cohort of subjects with PD within the first year of treatment. Our present findings are comparable with the overall trend observed in prior work, i.e., STN-DBS reduces FOG severity within the first year of treatment. However, our study adds valuable new insights, because we collected subjective information (questionnaires and objective data (blinding analyzed by an independent rater). Our study is the first to prospectively demonstrate a direct effect of STN-DBS on FOG patterns and subtypes. We found that STN-DBS was effective for all three patterns and for all provoking circumstances. Besides using a current- (not voltage-) controlled DBS system, the subjects were treated with routine, high-frequency stimulation parameters and were implanted at regular stereotactic coordinates. Therefore, our study represents standard clinical practice and is in principle comparable with other STN-DBS studies.

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Besides limitations (missing control group, low number of patients, walking test in a subset of patients only), our results confirm the overall positive effect of STN-DBS in the first year of treatment of PD, and extend our current understanding concerning the effect on the manifestations and subtypes of FOG.

Authors’ roles

Michael T. Barbe participated in writing of the first draft of the paper, analysis and interpretation of data, and revising the different versions of the manuscript for important intellectual content; Claudia Barthel participated in the analysis and interpretation of the data, writing of the first draft of the paper and revising the different versions of the manuscript for important intellectual content; Lilly Chen participated in statistical analysis of the data and critically revised the manuscript for important intellectual content; Nic Van Dyck, Thomas Brücke, Fernando Seijo, Esther Suarez San Martin, Claire Haegelen, Marc Verin, Martin Amarell, Steve Gill, Alan Whone, Mauro Porta, Domenico Servello, Gereon R. Fink and François Alesch critically revised the manuscript for important intellectual content; Bastiaan R. Bloem and Lars Timmermann participated in the conception and design of the study and critically revised the manuscript for important intellectual content.

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Declaration of interest

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Disclosures
None of the others report disclosures.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2018.08.016.

References

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