Acta Neurochirurgica (2023) 165:3943–3945
https://doi.org/10.1007/s00701-023-05796-z

EDITORIAL (BY INVITATION)

"Suboptimal" placement of STN DBS electrodes as a novel strategy in Parkinson's disease?

Gastón Schechtmann[1] · Andreas Nørgaard Glud[1,2] · Vincent A. Jourdain[3] · Bo Bergholt[1] · Jens Christian Hedemann Sørensen[1,2]

Received: 3 September 2023 / Accepted: 4 September 2023 / Published online: 4 October 2023

We would like to thank Youssef El Ouadih et al. for their manuscript published in this issue of Acta Neurochirurgica [14]. A first approach to the article might suggest to the reader that a "suboptimal" placed electrode in the subthalamic nucleus (STN) in bilateral deep brain stimulation (DBS) for Parkinson's disease (PD), defined as asymmetrical contact balance (CB) by the authors, may be a novel strategy. The authors showed that STN DBS in a symmetrically dual-contact setting within the posterior and lateral part of the STN might be associated with worsening of speech and gait disorders at 1-year follow-up. Interestingly, an electrode implanted slightly off the optimal target within the STN in bilateral DBS procedures appears to improve the outcomes in PD patients with these PD-associated symptoms. Therefore, avoiding the use of symmetrical contacts in the STN may improve the clinical outcome. We believe that this hypothesis and the method used deserve further considerations.

Gait and speech disorders are common disabling concerns in PD and are associated with poor quality of life. More specifically, up to 75% and 90% of PD patients will develop speech and gait disabilities, respectively, in the later stages of the disease [4]. These problems remain a challenge in advanced treatments for PD [22]. In addition, the progression of the disease involving asymmetrical degenerative process in nigrostriatal networks argues against identical stimulation parameters of the STN or other structures in the basal ganglia [9, 15]. Many studies have proposed different strategies aiming to avoid bilateral topographically symmetric stimulation in the STN (cf. [10]).

Historically, the effectiveness of stereotactic lesional procedures for PD, such as thalamotomies, pallidotomies, and subthalamotomies by radiofrequency, gamma knife, and now MRgFUS, has been challenged by the fact that patients subject to bilateral treatments may present a significant negative impact on cognitive functions, speech, and balance [2, 6, 23]. This is also true for DBS despite a lower risk of complications in bilateral procedures [19, 21]. As a consequence, unilateral procedures have been advocated to be safer and more beneficial for selected patients [1, 3]. A variety of neuromodulation strategies to mitigate those side effects induced by bilateral STN DBS have been investigated. For instance, in a randomized, double-blind, cross-over trial testing asymmetric STN DBS for freezing of gait (FOG), Meoni et al. studied the effects of reducing the stimulation amplitude by 30% in PD patients who experienced FOG contralateral to the least affected body side. Unfortunately, the study was interrupted in an early stage since most patients did not tolerate this approach due to the considerable worsening of motor symptoms [11]. Also, Lizarraga et al. proposed that unilateral, particularly right-sided STN stimulation, might improve gait compared to left-sided stimulation, but to a lesser extent than bilateral STN DBS [9]. Others have shown that gait may improve by diminishing the frequency of stimulation from 130 to 60 Hz or lowering by 50% the amplitude on the contralateral side of the most affected hemibody [5, 13].

The current study by Youssef El Ouadih et al. lacks, in our view, a relevant comparison, which is to test symmetrical vs. asymmetrical stimulation of the STN by simply changing the active contacts from symmetrical to asymmetrical settings. This is regarded as one of the key advantages of DBS compared to the irreversible nature of lesional methods: if symmetrical dual-contact settings in the left and right STN appear related to speech and gait disturbances,

✉ Gastón Schechtmann
gassch@rm.dk

1 Department of Neurosurgery, Aarhus University Hospital, Aarhus, Denmark

2 Department of Clinical Medicine, Aarhus University, Aarhus N, Denmark

3 AbbVie Corporation, Montreal, Canada

why not test other possible combinations of active contacts within the STN? This study design to explore lateralisation has been widely used [7] and should be the preferred method to measure within-subjects changes. PD is a complex disease in which multiple and individual clinical variables are to be taken into consideration, including disease duration, comorbidities, and medication. Therefore, it would be a preferable and fair comparison to test the symmetrical versus asymmetrical hypothesis by using a design with fewer possible confounders concerning speech and gait. This would, in turn, ensure an enhanced methodology and results. Instead of comparing two groups using symmetrical vs. asymmetrical stimulation, every patient becomes its own control (cf. [17]). Using such intra-individual comparison in a randomized, double-blind crossover study would reduce numbers needed to treat and could provide more compelling results and strengthen the conclusion that symmetric stimulation may cause the worsening of gait and speech in long-term follow-up.

It is worth noting that the DBS targeting procedure was performed in two different ways in this investigational study. Initially, the results of two treatments were compared: symmetrical vs. non-intentional asymmetrical placement of stimulation. Later in the study, the neurosurgeon intentionally targeted the STN asymmetrically, which resulted in introducing a new selection bias to the obtained results. The authors have put great efforts into a 3D volumetric mapping of the STN to define the specific location of the contacts within the nucleus, aiming to divide the cohort into two groups depending on the active contact topography. However, the estimated volumes affected by stimulation were not taken into account. Changes in DBS parameters such as intensity, polarity, pulse width, and frequency may affect the symmetry of the stimulation within the STN and surrounding fibers. This is a further reason why the results of this study should be interpreted with caution.

Despite robust data showing functional and structural differences in brain hemispheres, the evidence of lateralisation in the effect of DBS on gait and speech has not been established yet [8]. Considering the asymmetrical loss of neurons in the basal ganglia of PD patients [15] affecting asymmetrically neuronal circuits and distribution of the symptoms, it would be valuable for the proposed asymmetrical CB approach to elucidate if the DBS effect presents such a pattern of lateralisation. It has been established that PD patients subject to left pallidotomy suffer a speech decline compared to lesions on the right side [20]. Also, some studies indicate the left STN DBS appears to be dominant in speech [18], while stimulation of the right STN can be more effective on gait, but these results have not been observed in all patients [16]. For example, placing the contact within the STN on the dominant side, i.e., right STN on gait and left STN on speech impairments, may provide valuable data on preoperatively choosing the side to place the asymmetrical contact. With the knowledge available today, the rationale for placing a contact of the DBS electrode off target in an asymmetrical fashion to change a pre-operative targeting strategy appears to be premature. However, it is likely that using a dual-contact topographic setting, taking advantage of new directional leads [12], or stimulating non-symmetric volumes of the STN could be part of the armamentarium for troubleshooting in neuromodulation therapies. We suggest that cerebral dominance and lateralisation of the basal ganglia should be taken into account in the design of future studies.

References

1. Alberts JL, Hass CJ, Vitek JL, Okun MS (2008) Are two leads always better than one: an emerging case for unilateral subthalamic deep brain stimulation in Parkinson's disease. Exp Neurol 214(1):1–5
2. Alshaikh J, Fishman PS (2017) Revisiting bilateral thalamotomy for tremor. Clin Neurol Neurosurg 158:103–107
3. Castrioto A, Meaney C, Hamani C, Mazzella F, Poon YY, Lozano AM et al (2011) The dominant-STN phenomenon in bilateral STN DBS for Parkinson's disease. Neurobiol Dis 41(1):131–137
4. Cilia R, Cereda E, Klersy C, Canesi M, Zecchinelli AL, Mariani CB et al (2015) Parkinson's disease beyond 20 years. J Neurol Neurosurg Psychiatry 86(8):849–855
5. Fasano A, Herzog J, Seifert E, Stolze H, Falk D, Reese R et al (2011) Modulation of gait coordination by subthalamic stimulation improves freezing of gait. Mov Disord 26(5):844–851
6. Gallay MN, Moser D, Magara AE, Haufler F, Jeanmonod D (2021) Bilateral MR-guided focused ultrasound pallidothalamic tractotomy for Parkinson's disease with 1-year follow-up. Front Neurol 12:601153
7. Hershey T, Wu J, Weaver PM, Perantie DC, Karimi M, Tabbal SD et al (2008) Unilateral vs. bilateral STN DBS effects on working memory and motor function in Parkinson disease. Exp Neurol 210(2):402–408
8. Lin Z, Zhang C, Li D, Sun B (2021) Lateralized effects of deep brain stimulation in Parkinson's disease: evidence and controversies. NPJ Parkinsons Dis 7(1):64
9. Lizarraga KJ, Jagid JR, Luca CC (2016) Comparative effects of unilateral and bilateral subthalamic nucleus deep brain stimulation on gait kinematics in Parkinson's disease: a randomized, blinded study. J Neurol 263(8):1652–1656
10. Lizarraga KJ, Luca CC, De Salles A, Gorgulho A, Lang AE, Fasano A (2017) Asymmetric neuromodulation of motor circuits in Parkinson's disease: The role of subthalamic deep brain stimulation. Surg Neurol Int 8:261
11. Meoni S, Debu B, Pelissier P, Scelzo E, Castrioto A, Seigneuret E et al (2019) Asymmetric STN DBS for FOG in Parkinson's disease: A pilot trial. Parkinsonism Relat Disord 63:94–99
12. Merola A, Romagnolo A, Krishna V, Pallavaram S, Carcieri S, Goetz S et al (2020) Current directions in deep brain stimulation for Parkinson's disease-directing current to maximize clinical benefit. Neurol Ther 9(1):25–41
13. Moreau C, Defebvre L, Destee A, Bleuse S, Clement F, Blatt JL et al (2008) STN-DBS frequency effects on freezing of gait in advanced Parkinson disease. Neurology 71(2):80–84

14. Ouadih YE, Marques A, Pereira B, Luisoni M, Claise B, Coste J et al (2023) Deep brain stimulation of the subthalamic nucleus in severe Parkinson's disease: Relationships between dual-contact topographic setting and 1-year worsening of speech and gait. Acta Neurochir (in press)
15. Pieperhoff P, Sudmeyer M, Dinkelbach L, Hartmann CJ, Ferrea S, Moldovan AS et al (2022) Regional changes of brain structure during progression of idiopathic Parkinson's disease – A longitudinal study using deformation based morphometry. Cortex 151:188–210
16. Rizzone MG, Ferrarin M, Lanotte MM, Lopiano L, Carpinella I (2017) The dominant-subthalamic nucleus phenomenon in bilateral deep brain stimulation for Pparkinson's disease: Evidence from a gait analysis study. Front Neurol 8:575
17. Schulz GM, Hosey LA, Bradberry TJ, Stager SV, Lee LC, Pawha R et al (2012) Selective left, right and bilateral stimulation of subthalamic nuclei in Parkinson's disease: differential effects on motor, speech and language function. J Parkinsons Dis 2(1):29–40
18. Sjoberg RL, Lidman E, Haggstrom B, Hariz MI, Linder J, Fredricks A et al (2012) Verbal fluency in patients receiving bilateral versus left-sided deep brain stimulation of the subthalamic nucleus for Parkinson's disease. J Int Neuropsychol Soc 18(3):606–611
19. Tripoliti E, Zrinzo L, Martinez-Torres I, Frost E, Pinto S, Foltynie T et al (2011) Effects of subthalamic stimulation on speech of consecutive patients with Parkinson disease. Neurology 76(1):80–86
20. Troster AI, Woods SP, Fields JA (2003) Verbal fluency declines after pallidotomy: an interaction between task and lesion laterality. Appl Neuropsychol 10(2):69–75
21. van Nuenen BF, Esselink RA, Munneke M, Speelman JD, van Laar T, Bloem BR (2008) Postoperative gait deterioration after bilateral subthalamic nucleus stimulation in Parkinson's disease. Mov Disord 23(16):2404–2406
22. Vu TC, Nutt JG, Holford NH (2012) Progression of motor and nonmotor features of Parkinson's disease and their response to treatment. Br J Clin Pharmacol 74(2):267–283
23. Walter BL, Vitek JL (2004) Surgical treatment for Parkinson's disease. Lancet Neurol 3(12):719–728