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Prediction of the effect of deep brain stimulation on gait freezing of Parkinson's disease

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ABSTRACT

Objective: The response of freezing of gait (FOG) to deep brain stimulation of the subthalamic nucleus (STN-DBS) is controversial and depends on many poorly controlled factors. On the other hand, a clinical predictor for the individual patient is needed to counsel the patient regarding this symptom.
Methods: A cohort of 124 patients undergoing STN-DBS was evaluated based on the video-documented Levodopa test at baseline in the OFF- and ON-drug condition and postoperatively in the best condition (ON-drug/ON-stim) and the worst condition (OFF-drug/ON-stim). We compared the freezing item of the Unified Parkinson's disease rating scale (#14), the UPDRS III total score, and FOG severity rated during four provoking situations with regard to its predictive value.
Results: We found 'FOG during the turning task' to be the best predictor with an ROC-value of 0.857 compared to 0.603 for the UPDRS Item 14 and 0.583 for the total UPDRS III. An improvement of 1 or 2 grades of the turning item during the preoperative levodopa test predicts an improvement during the worst condition postoperatively of 1 grade or more with an 80% probability.
Conclusion: This FOG prediction test is simple and clinically useful. The test needs to be studied in a prospective study.

1. Introduction

Deep brain stimulation of the subthalamic nucleus is an evidence-based treatment for advanced Parkinson's disease and patients at an earlier stage with fluctuations and dyskinesia for less than three years [1,2]. The eligibility criteria for DBS involve additional conditions, among which the positive response to levodopa on the UPDRS III motor score of 33% improvement for advanced patients [3–5] or 50% for early patients [6] is one of the most important ones.

FOG can be among the most bothering symptoms for the patients, and predictability of an individual patient's response would be helpful for patient counseling. Such attempts to predict the response to DBS have been approached on a groups level with imaging methods: In a large cohort of patients treated with STN-DBS, a lower volume of the putamen was found to be associated with FOG on a group level and the location of the stimulating electrode within the subthalamic nucleus was predicting a good FOG response [7]. In another cohort of young patients with PD, the level of Abeta42 was associated with FOG [8]. Clinical measures that allow the prognosis of FOG would be welcome. At a group level, this topic is addressed in many papers, which have reported the response of FOG in different patient groups. While the first reports reported only mixed responses of FOG [9,10] or even found FOG as an adverse event [11], clinical decision making has addressed the topic by separating preoperatively into OFF-FOG (Levodopa responsive FOG) and ON-FOG (Levodopa unresponsive FOG). A broad consensus emerged that OFF-FOG subjects may have an improvement in their FOG, but ON-FOG subjects do not. These studies measured FOG with the FOG item (no. 14) of the UPDRS II [12,13], which is addressing FOG as reported by the patient during an interview by the physician or with neurophysiological measures [14,15]. Some others used a standardized protocol with a sit-and-walk paradigm and counted the number of FOG episodes before and after surgery [9]. The number of improvers was reported. Lately, different scales for rating FOG by the percentage of time spent frozen during FOG episodes were proposed [16,17]. The present paper

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uses the information of the video-recorded Levodopa-test at baseline to predict the outcome after DBS. It allows standard tests that are routinely used for preoperative patient evaluation to be used to predict the post-operative response to STN-stimulation. The current results may serve as a template to prospectively test this predictor.

2. Methods

2.1. Patients

This is a retrospective study using the standardized database for DBS-patients of the Department of Neurology, Kiel University. Patients with idiopathic Parkinson's disease were selected who fulfilled the following criteria: (1) underwent bilateral STN-DBS surgery for PD, (2) had a complete videotaped L-dopa test at baseline (OFF- and ON-drug condition) and post-operative in a period between 6 and 12 months after the surgery (in 4 conditions, OFF-drug/ON-stim, OFF-drug/OFF-stim, ON-drug/OFF-stim, ON-drug/ON-stim) and (3) UPDRS II FOG item (no.14) was rated more than 0 in the baseline OFF-drug condition. Exclusion criteria were previous stereotactic surgery, DBS reoperation, or other major complications.

2.2. Score

The current approach used a video recorded standard task with the patient sitting on a chair walking towards the camera for 8 m turning 180 deg, walking back to the chair turning 90° and walking another 3 m to the left, turning 180 deg and stopping at the level of the chair. During this sequence the freezing was separated according to the following conditions: when occurring at start (start hesitation, 1 time), during walking (open space hesitation, 4 times), before reaching the destination (reaching hesitation, 4 times) and while turning (turning hesitation, 3 times). Six video sequences of each patient were recorded: 2 conditions at baseline (OFF-drug and ON-drug) and 4 conditions at follow-up (OFF-drug/ON-stim, OFF-drug/OFF-stim, ON-drug/OFF-stim, and ON-drug/ON-stim).

The scoring has been presented in detail in an accompanying paper [18]. Briefly, the clinical FOG's severity was rated (1): shuffling forward with small steps, (2): trembling in place with alternating rapid knee movements (knee-trembling), and (3): complete (or total) akinesia without limbs or trunk movement was measured for each provoking situation (see above). If the patient presented two or more FOG patterns the worst finding was recorded [19]. An overall score was defined as the arithmetic sum of the severity score for all 4 situations. The videos were blinded for the raters who were unaware of the patient condition and randomly presented. Two experienced evaluators (OG and AA) have rated all the 744 walking sequences in a blinded fashion in a 3-month period.

2.3. Outcome parameters

The current study used the following outcome parameters. The freezing-item of the UPDRS (no 14) and the UPDRS III were documented during the original assessment by the investigator in the preoperative OFF- and ON-drug condition and postoperatively in the best condition (ON-drug/ON-stim) and the worst condition (OFF-drug/ON-stim). For the video-assessment, the total FOG score and the turning score were measured for the two preoperative and the four postoperative conditions.

2.4. Statistical analysis

To investigate the predictability of the effect of DBS on FOG, (1) regression analysis and (2) receiver-operating-characteristics (ROC) curve analysis were conducted:

(1) For the regression analysis, the effect of DBS on FOG (Follow-up Stim-On minus pre-operative baseline) was included as the dependent variable. In order to compare the predictability of different outcome measures used to measure the effect of DBS on FOG, separate regression analysis was conducted with the DBS effect measured with (a) Turning Task, (b) FOG total score and (c) UPDRS Item 14 as dependent variables. An ordinal regression analysis was used to account for the ordinal scaling of the dependent variables.

A stepwise backward regression approach was used to identify relevant predictors of the effect of DBS on FOG. After having checked for multicollinearity, the following independent, predictor variables were included: Turning Task Baseline Levodopa-Responsiveness, UPDRS Item 14 baseline Levodopa-Responsiveness and UPDRS III baseline Levodopa-Responsiveness.

McFadden Pseudo R^2 was calculated to assess the model fit. A Pseudo R^2 of >0.2 was considered a good model fit. After having identified which outcome measure is best predictable, an ROC analysis with calculation of the area under the curve (AUC) was performed to investigate the predictive capacity of the predictor variables to identify "improvers" (those patients with a beneficial effect of DBS on FOG) from "non-improvers".

Statistical analyses were performed with R (version 1.1.463) [20].

Ethical approval of the study was obtained by the Ethical committee of the Medical faculty of Kiel University.

3. Results

3.1. Clinical data

A total of 324 Patient data were screened, out of which 124 patients fulfilled the inclusion criteria for this study and were included. The patient group consisted of 82 male (66%) and 42 female (34%) patients. The mean (±SD) age was 61.3 (±7.6); the mean duration of PD was 14.1 (±5.5) years. The UPDRS item 14, FOG total score, the turning task score, and the UPDRS III in all baseline and follow-up conditions are shown in Table 1.

3.2. Selecting the best predictors

Clinically a predictor is needed, predicting if the patient improves during the worst condition after stimulation. This is when stimulation still works, but medication does not work optimally e.g., during OFF-phases or at night. As outcome parameters for prediction, we have chosen the turning task, the total FOG score, and the FOG item (14) of the UPDRS.

Table 2 shows the stepwise backward ordinal regression results for

Table 1
Patients clinical scores at baseline in OFF-, ON-drug and follow-up both OFF-, ON-stim and OFF-, ON-drug conditions.

	Baseline		Follow-up			
			ON-stim		OFF-stim	
	OFF-drug	ON-drug	OFF-drug	ON-drug	OFF-drug	ON-drug
UPDRS item 14[a]	1.63 ± 0.8	0.68 ± 0.9	0.66 ± 0.9	0.4 ± 0.7	–	–
Turning task score	1.33 ± 1.1	0.35 ± 0.8	0.48 ± 0.8	0.28 ± 0.7	0.86 ± 1.1	0.36 ± 0.8
Total FOG score	4.35 ± 4.3	1.1 ± 2.8	1.42 ± 2.8	0.79 ± 2.2	1.32 ± 2.8	3.01 ± 3.95
UPDRS III	41.9 ± 12.7	19.6 ± 9.9	23.7 ± 11.5	15.6 ± 9.3	41.1 ± 12.4	25.3 ± 11.9

The data is presented as mean ± SD.
[a] UPDRS item 14 at follow-up is rated only during ON-stim conditions.

Table 2
Regression results for the three outcome parameters (A, B, C) with the effect of DBS on FOG measured as the difference between baseline OFF-drug to follow-up OFF-drug/ON-stim for each outcome as the dependent variable.

Dependent Variable (Effect of DBS from Baseline Med-Off to Follow-Up Med-Off/Stim-On)	Remaining predictors (independent variables)	Model			Coefficients	
		Pseudo R2	p-value	Chi-Square	z-value	p-value
A. DBS Effect Turning Task	Turning Task Baseline Levodopa-Responsiveness	0.239	<0.0001	75.028	6.717	<0.0001
	UPDRS III Baseline Levodopa-Responsiveness				1.906	0.057
B. DBS Effect FOG total score	Turning Task Baseline Levodopa-Responsiveness	0.105	<0.0001	54.477	6.021	<0.0001
	UPDRS III Baseline Levodopa-Responsiveness				2.178	0.029
C. DBS Effect UPDRS Item 14	Turning Task Baseline Levodopa-Responsiveness	0.035	0.00339	11.373	2.766	0.006
	UPDRS Item 14 Baseline Levodopa-Responsiveness				−2.541	0.011

the three outcome parameters with the effect of DBS on FOG measured as the difference between baseline OFF-drug to follow-up OFF-drug/ON-stim for each outcome as the dependent variable. Baseline levodopa-responsiveness of FOG for the three outcome parameters were the predictors. The model with the turning task as a dependent variable showed the best model fit (R^2 = 0.239, Chi-Square = 75.028, p < 0001) (Table 2A) while the FOG total score (R^2 = 0.105) (Table 2B) the UPDRS Item 14 (R^2 = 0.035) (Table 2 C) were performing worse.

Given these results, an ROC analysis was conducted to calculate the statistical power to separate improvers (patients who at least improved by 1 point) from baseline OFF-drug to follow-up OFF-drug/ON-stim) from non-improvers (Fig. 1). The AUCs were 0.857 for the turning task, 0.603 for UPDRS Item 14, and 0.583 for the total UPDRS III. Thus, the turning task is the best predictor, and a baseline Levodopa-responsiveness with a cut-off of −0.5 shows the best specificity (0.80) and sensitivity (0.873) to separate improvers from non-improvers.

Table 3 shows the probabilities for improvement of FOG for a patient depending on the turning task's response at baseline.

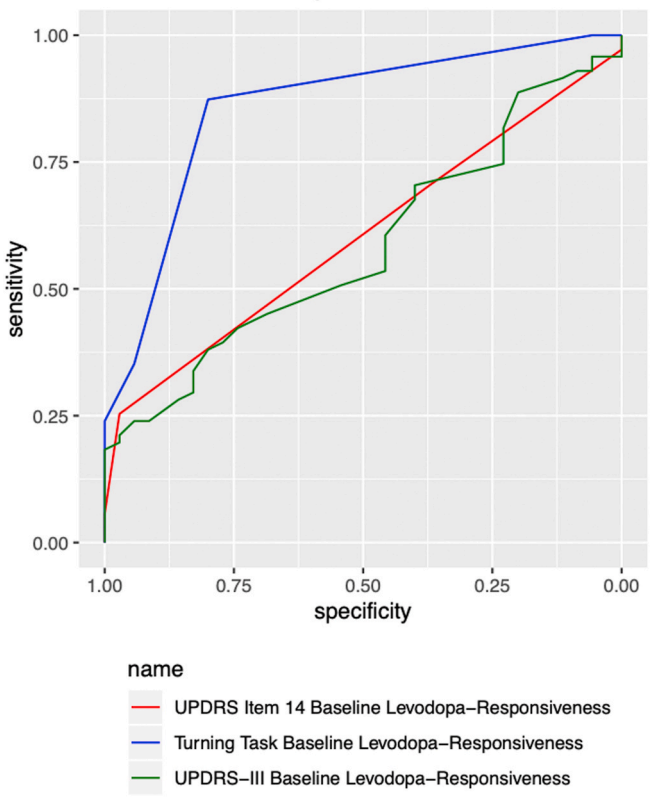

Fig. 1. Prediction of DBS effect baseline OFF-drug to follow-up OFF-drug/ON-stim.

4. Discussion

The ability to predict the effect of DBS on FOG has important implications for clinicians, patients, and caregivers. It may assist clinical decision making and help to individualize the therapeutic approach for each patient. This study aimed to identify the best clinical test that can quantify the effect of STN-DBS on FOG. We conclude that the improvement of FOG while turning 180° with dopaminergic medication before surgery is the best predictor.

The most important and routinely used predictor for the effect of DBS on the symptoms of PD is the UPDRS III total score during the preoperative L-Dopa-Test [21]. In this routine procedure, the UPDRS III score for all the 14 items (not including topographic separation) is rated without and with a suprathreshold dose of L-dopa as a sum value [22]. This is meant to be an individual prediction for this sum score, but this does not necessarily include that all symptoms are improved and particularly not to which percentage. FOG is not measured during the motor examination but included as an interview question in the activities of daily living (UPDRS, item 14). Certainly, this can equally be asked for during the best and worst motor conditions, and this is common practice. Our study shows that this item's predictive value is not very strong, with an AUC of only 0.603 of the ROC curve.

The values based on our video-rating of FOG have shown the highest predictive value. Interestingly the best predictor was not the total FOG score but the FOG while turning alone. A similar video-score was also used in another study on the effect of STN-DBS on gait [23], and they have shown that both occurrence and severity regarding FOG can be

Table 3
Probabilities to improve by DBS in the worst condition postoperatively (OFF-drug/ON-stim) after having improved by medication at baseline. Data of the turning task only are shown.

Improvement by medication at baseline (Turning Task) (points)	Improvement by DBS from baseline to Follow-Up (Turning Task) (points)					
	−1	0	1	2	3	≥1
1	0.07	0.12	0.74	0.05	0	0.79
2	0	0.2	0	0.5	0.3	0.8
3	0	0	0.18	0.29	0.53	1

Note. Values represent probabilities.

reduced at one and even two years postoperatively. Another controlled prospective study on FOG has used several measures, including a gait test [15]. Finally, a secondary analysis of an uncontrolled prospective study [24] has used a similar video-rating, demonstrating that the different FOG types were improved [25]. All these studies have not looked at the predictive value of the test for the individual patient. It should also be mentioned that turning has been found a useful clinical test to adapt stimulation strength during programming when the patient is asked to do the 'Pirouette' task [26]. During circling, the outer leg indicates the side with a higher risk of inducing FOG and therefore needs higher stimulation strength. Again, FOG while turning is a sensitive instrument.

The limitations of this study are, firstly, the subjective nature of the assessment. However, the test has been highly reliable when two raters were compared [18]. Secondly, the patient population was advanced, and the results may differ for a less affected population. The strength of the study is the large patient group compared to all previous studies and the rigorous statistical analysis.

In conclusion, we found that item 14 of the UPDRS and the total UPDRS III scores are weak predictors for the response of FOG to DBS in the worst condition of the patient after surgery. The FOG status can be best predicted from the result of the turning task during the preoperative levodopa-test. When grading the FOG's severity during turning (0: no FOG, 1: shuffling forward with small steps, 2: trembling in place with alternating rapid knee movements, 3: complete akinesia without limbs or trunk movement), the following postoperative FOG improvement can be expected: If the patient improves during levodopa-test by 1, 2 or 3 points, respectively, the likelihood for an improvement $\geq$ 1 point by STN-DBS in the worst condition after surgery is 0.79, 0.80 or 1.0. These predictors need now be tested in prospective studies. Then, they may assist patient counseling regarding the FOG.

Documentation of author roles

OG, AA and GD: 1A, B, C; 2B, C; 3A.
SP, AH: 1A, B; 2C; 3B.
CS: 1A, B 2 A, C; 3B.

1. Research project: A. Conception, B. Organization, C. Execution.
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique.
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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References

[1] J.J. Ferreira, R. Katzenschlager, B.R. Bloem, U. Bonuccelli, D. Burn, G. Deuschl, E. Dietrichs, G. Fabbrini, A. Friedman, P. Kanovsky, V. Kostic, A. Nieuwboer, P. Odin, W. Poewe, O. Rascol, C. Sampaio, M. Schüpbach, E. Tolosa, C. Trenkwalder, A. Schapira, A. Berardelli, W.H. Oertel, Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson's disease, Eur. J. Neurol. 20 (2013) 5–15, https://doi.org/10.1111/j.1468-1331.2012.03866.x.

[2] R. Hilker, R. Benecke, G. Deuschl, W. Fogel, A. Kupsch, C. Schrader, F. Sixel-Döring, L. Timmermann, J. Volkmann, M. Lange, Tiefe Hirnstimulation bei Idiopathischem Parkinson-Syndrom: empfehlungen der Deutschen Arbeitsgemeinschaft Tiefe Hirnstimulation, Nervenarzt 80 (2009) 646–655, https://doi.org/10.1007/s00115-009-2695-3.

[3] A. Williams, S. Gill, T. Varma, C. Jenkinson, N. Quinn, R. Mitchell, R. Scott, N. Ives, C. Rick, J. Daniels, S. Patel, K. Wheatley, Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, Lancet Neurol. 9 (2010) 581–591, https://doi.org/10.1016/S1474-4422(10)70093-4.

[4] M.S. Okun, B.V. Gallo, G. Mandybur, J. Jagid, K.D. Foote, F.J. Revilla, R. Alterman, J. Jankovic, R. Simpson, F. Junn, L. Verhagen, J.E. Arle, B. Ford, R.R. Goodman, R. M. Stewart, S. Horn, G.H. Baltuch, B.H. Kopell, F. Marshall, D.L. Peichel, R. Pahwa, K.E. Lyons, A.I. Tröster, J.L. Vitek, M. Tagliati, Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial, Lancet Neurol. 11 (2012) 140–149, https://doi.org/10.1016/S1474-4422(11)70308-8.

[5] G. Deuschl, A randomized trial of deep-brain stimulation for Parkinson, N. Engl. J. Med. 355 (2006) 896–908, https://doi.org/10.1056/NEJMoa060281.

[6] W.M.M. Schuepbach, J. Rau, K. Knudsen, J. Volkmann, P. Krack, L. Timmermann, T.D. Hälbig, H. Hesekamp, S.M. Navarro, N. Meier, D. Falk, M. Mehdorn, S. Paschen, M. Maarouf, M.T. Barbe, G.R. Fink, A. Kupsch, D. Gruber, G.-H. Schneider, E. Seigneuret, A. Kistner, P. Chaynes, F. Ory-Magne, C. Brefel Courbon, J. Vesper, A. Schnitzler, L. Wojtecki, J.-L. Houeto, B. Bataille, D. Maltête, P. Damier, S. Raoul, F. Sixel-Doering, D. Hellwig, A. Gharabaghi, R. Krüger, M. O. Pinsker, F. Amtage, J.-M. Régis, T. Witjas, S. Thobois, P. Mertens, M. Kloss, A. Hartmann, W.H. Oertel, B. Post, H. Speelman, Y. Agid, C. Schade-Brittinger, G. Deuschl, Neurostimulation for Parkinson's disease with early motor complications, N. Engl. J. Med. 368 (2013) 610–622, https://doi.org/10.1056/NEJMoa1205158.

[7] C. Karachi, F. Cormier-Dequaire, D. Grabli, B. Lau, H. Belaid, S. Navarro, M. Vidailhet, E. Bardinet, S. Fernandez-Vidal, M.L. Welter, Clinical and anatomical predictors for freezing of gait and falls after subthalamic deep brain stimulation in Parkinson's disease patients, Park. Relat. Disord. 62 (2019) 91–97, https://doi.org/10.1016/j.parkreldis.2019.01.021.

[8] R. Kim, J. Lee, H.J. Kim, A. Kim, M. Jang, B. Jeon, U.J. Kang, CSF β-amyloid 42 and risk of freezing of gait in early Parkinson disease, Neurology 92 (2019) E40–E47, https://doi.org/10.1212/WNL.0000000000006692.

[9] M.U. Ferraye, B. Debû, V. Fraix, J. Xie-Brustolin, S. Chabardès, P. Krack, A. L. Benabid, P. Pollak, Effects of subthalamic nucleus stimulation and levodopa on freezing of gait in Parkinson disease, Neurology 70 (2008) 1431–1437, https://doi.org/10.1212/01.wnl.0000310416.90757.85.

[10] M.H. Stolze, S. Klebe, M. Poepping, D. Lorenz, J. Herzog, M.W. Hamel, B. Schrader, J. Raethjen, R. Wenzelburger, H.M. Mehdorn, G. Deuschl, P. Krack, Bilateral, Effects of bilateral subthalamic nucleus stimulation on parkinsonian gait, Neurology 57 (2001) 144–146, https://doi.org/10.1016/j.jvoice.2006.10.010.

[11] G. Kleiner-Fisman, J. Herzog, D.N. Fisman, F. Tamma, K.E. Lyons, R. Pahwa, A. E. Lang, G. Deuschl, Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes, Mov. Disord. 21 (2006) 290–304, https://doi.org/10.1002/mds.20962.

[12] C. Schlenstedt, A. Shalash, M. Muthuraman, D. Falk, K. Witt, G. Deuschl, Effect of high-frequency subthalamic neurostimulation on gait and freezing of gait in Parkinson's disease: a systematic review and meta-analysis, Eur. J. Neurol. 24 (2017) 18–26, https://doi.org/10.1111/ene.13167.

[13] J.T. Davis, K.E. Lyons, R. Pahwa, Freezing of gait after bilateral subthalamic nucleus stimulation for Parkinson, s disease 108 (2006) 461–464, https://doi.org/10.1016/j.clineuro.2005.07.008.

[14] K.A. Ehgoetz Martens, J.M. Hall, M.J. Georgiades, M. Gilat, C.C. Walton, E. Matar, S.J.G. Lewis, J.M. Shine, The functional network signature of heterogeneity in freezing of gait, Brain 141 (2018) 1145–1160, https://doi.org/10.1093/brain/awy019.

[15] S. Vercruysse, W. Vandenberghe, L. Munks, B. Nuttin, H. Devos, A. Nieuwboer, Effects of deep brain stimulation of the subthalamic nucleus on freezing of gait in Parkinson's disease: a prospective controlled study, J. Neurol. Neurosurg. Psychiatry 85 (2014) 871–877, https://doi.org/10.1136/jnnp-2013-306336.

[16] M.T. Barbe, L. Tonder, P. Krack, B. Debû, M. Schüpbach, S. Paschen, T.A. Dembek, A.A. Kühn, V. Fraix, C. Brefel-courbon, L. Wojtecki, D. Maltête, J. Houeto, A. Hartmann, L. Timmermann, U. Lyon, U. Claude, B. Lyon, F. De Médecine, L. Sud, C. Mérieux, Deep Brain Stimulation for Freezing of Gait in Parkinson ' S Disease with Early Motor Complications, 2019, pp. 1–9, https://doi.org/10.1002/mds.27892.

[17] M. Gilat, How to annotate freezing of gait from video: a standardized method using open-source software, J. Parkinsons Dis. 9 (2019) 821–824, https://doi.org/10.3233/JPD-191700.

[18] O. Gavriliuc, S. Paschen, A. Andrusca, A. Helmers, C. Schlenstedt, G. Deuschl, Clinical patterns of gait freezing in Parkinson ' s disease and their response to interventions : an observer-blinded study, Park. Relat. Disord. 80 (2020) 175–180, https://doi.org/10.1016/j.parkreldis.2020.09.043.

[19] J.D. Schaafsma, Y. Balash, T. Gurevich, A.L. Bartels, J.M. Hausdorff, N. Giladi, Characterization of freezing of gait subtypes and the response of each to levodopa in Parkinson's disease, Eur. J. Neurol. 10 (2003) 391–398, https://doi.org/10.1046/j.1468-1331.2003.00611.x.

[20] R Core Development Team, R, A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2010, https://doi.org/10.1007/978-3-540-74686-7, 2015.

[21] P.D. Charles, N. Van Blercom, P. Krack, S.L. Lee, J. Xie, G. Besson, A.L. Benabid, P. Pollak, Predictors of effective bilateral subthalamic nucleus stimulation for PD, Neurology 59 (2002) 932–934, https://doi.org/10.1212/WNL.59.6.932.

[22] R. Pahwa, S.B. Wilkinson, J. Overman, K.E. Lyons, Preoperative clinical predictors of response to bilateral subthalamic stimulation in patients with Parkinson's disease, Stereotact. Funct. Neurosurg. 83 (2005) 80–83, https://doi.org/10.1159/000086866.

[23] A. Kim, S.H. Paek, B. Jeon, Long-term effect of subthalamic nucleus deep brain stimulation on freezing of gait in Parkinson's disease, J. Neurosurg. (2019) 1–8, https://doi.org/10.3171/2018.8.JNS18350.

[24] L. Timmermann, R. Jain, L. Chen, M. Maarouf, M.T. Barbe, N. Allert, T. Brücke, I. Kaiser, S. Beirer, F. Sejio, E. Suarez, B. Lozano, C. Haegelen, M. Vérin, M. Porta, D. Servello, S. Gill, A. Whone, N. Van Dyck, F. Alesch, Multiple-source current steering in subthalamic nucleus deep brain stimulation for Parkinson's disease (the VANTAGE study): a non-randomised, prospective, multicentre, open-label study, Lancet Neurol. 14 (2015) 693–701, https://doi.org/10.1016/S1474-4422(15)00087-3.

[25] M.T. Barbe, C. Barthel, L. Chen, N. Van Dyck, T. Brücke, F. Seijo, E.S. San Martin, C. Haegelen, M. Verin, M. Amarell, S. Gill, A. Whone, M. Porta, D. Servello, G. R. Fink, F. Alesch, B.R. Bloem, L. Timmermann, Subthalamic nucleus deep brain stimulation reduces freezing of gait subtypes and patterns in Parkinson's disease, Brain Stimul (2018) 8–10, https://doi.org/10.1016/j.brs.2018.08.016.

[26] M.M. Reich, A.D. Sawalhe, F. Steigerwald, S. Johannes, C. Matthies, J. Volkmann, The pirouette test to evaluate asymmetry in parkinsonian gait freezing, Mov. Disord. Clin. Pract. 1 (2014) 136–138, https://doi.org/10.1002/mdc3.12018.