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Clinical short communication

Axial symptoms as main predictors of short-term subthalamic stimulation outcome in Parkinson's disease

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ABSTRACT

Deep brain stimulation (DBS) is an established therapeutic option for Parkinson's disease (PD) patients; however, a clear-cut definition of subthalamic (STN) DBS predictors in PD is lacking.

We analyzed a cohort of 181 STN-treated PD patients and compared pre- vs. 1-year post-surgical motor, dyskinesia, Off time, and daily-life activities (ADL) scores. A multivariate linear regression analysis was used to evaluate the association between clinical/demographic characteristics and the extent of STN-DBS response for outcomes proving a significant change after surgery.

After STN-DBS, we observed a significant improvement of motor symptoms ($P < 0.001$), dyskinesia ($P < 0.001$), and daily Off time ($P < 0.001$). Sex, PD duration, cognitive status, and the motor and axial response to levodopa significantly explained the motor improvement ($R = 0.360$, $P = 0.002$), with presurgical response of axial symptoms (Beta = 0.203, $P = 0.025$) and disease duration (Beta = 0.205, $P = 0.013$) being the strongest predictors. Considering the daily Off time improvement, motor and axial response at the levodopa challenge test and disease duration explained 10.6% of variance ($R = 0.326$, $p < 0.001$), with disease duration being the strongest predictor of improvement (Beta = 0.253, p: 0.001) and axial levodopa response showing a trend of significance in explaining the change (Beta = 0.173, p: 0.056). Dyskinesia improvement was not significantly explained by the model.

Our findings highlight the emerging role of axial symptoms in PD and their response to levodopa as potentially pivotal also in the DBS selection process.

1. Introduction

Deep brain stimulation (DBS) is an established therapeutic option for treating Parkinson's disease (PD) patients who present with symptom fluctuations that cannot be adequately controlled by medical therapy [1].

Despite the use of strict selection criteria for DBS candidates as proposed by expert consensus [1,2], there is a proportion of patients who still fail to obtain a significant benefit from DBS. This is mainly due to lack of efficacious control of motor symptoms and their fluctuations or appearance of stimulus-related side effects [1]. Over time, some presurgical demographic and clinical factors have been associated with the variability of the DBS motor outcome [2]; however, literature data failed to provide a clear-cut definition of demographic and clinical determinants for DBS outcomes.

Against this background, the primary aim of this study was to identify and weigh clinical and demographic factors with the ability to predict bilateral subthalamic DBS (STN-DBS) outcomes one year after surgery in a large cohort of longitudinally characterized PD patients.

2. Methods

2.1. Study design and population

We performed a retrospective study on 267 consecutive PD patients treated with bilateral STN-DBS between 1999 and 2019 at the A.O.U.

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Città della Salute e della Scienza di Torino academic hospital. Patients' clinical records that have been filled in longitudinally as part of regular clinical follow-ups were systematically reviewed, and Local Ethics approval for the study was obtained. The surgical procedure of bilateral STN-DBS device implantation was detailed elsewhere [3]. Briefly, bilateral stereotactic STN implantation was performed under local anesthesia using Magnetic Resonance Imaging (MRI)/Computed Tomography (CT) image fusion for anatomical targeting, intraoperative electrophysiological recording, and microstimulation to evaluate clinical effects. Quadripolar leads were implanted following the selected trajectory. Postoperative CT and MRI were performed to confirm electrode positioning and to exclude surgical complications. The pulse generator was then implanted in the subclavicular area and connected through extension cables to the leads under general anesthesia. The first DBS programming was performed about 10 days after surgery to identify the best contact for each side; then, the amplitude of stimulation was slowly increased in the following weeks until a satisfactory control of motor symptoms and fluctuations was obtained, balancing stimulation settings and dopaminergic therapies.

All patients were selected for DBS eligibility in agreement with the CAPSIT-PD criteria [1] and underwent a comprehensive clinical assessment encompassing data of the Unified Parkinson's Disease Rating Scale (UPDRS) or the MDS-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and dopaminergic therapies. Moreover, a comprehensive neuropsychological evaluation to exclude patients with dementia or severe ongoing psychiatric disorders was consistently performed before surgery [4]. For patients assessed by the old version of UPDRS, a validated conversion formula for part II and part III scores was applied [5]. In our hospital, patients with disabling axial motor symptoms persisting in On therapeutic condition (as demonstrated during the levodopa challenge test) did not undergo DBS procedure; specifically, the presence of freezing of gait (FoG) episodes, fall during the pull test, and inability to stand or walk autonomously in On therapeutic condition were considered exclusion criteria for neurosurgery.

We included in the analyses all patients with clinical data available before surgery (T0) and 10–18 months after DBS surgery (T1). Patients with no follow-up visits at our hospital or > 20% of missing follow-up data were excluded.

2.2. Data collection and outcome measures

We collected sex, age, disease duration, levodopa equivalent daily dose (LEDD), and cognitive status, summarized as normal cognition, mild cognitive impairment (MCI) single domain, MCI multi-domain, or dementia [6].

The presurgical motor evaluation was performed during a levodopa challenge test carried out in Off (at least 12 h after the last levodopa dose) and in On condition (about 45 min after the administration of a levodopa challenge dose, consisting of 1.5× the usual patient morning dose). The motor response to levodopa was calculated according to the following formula: [(MDS-UPDRS part III score Off - MDS-UPDRS part III score On)/MDS-UPDRS part III score Off]. The axial subscore in Off and On condition was calculated by the sum of the following MDS-UPDRS items: 2.13 (freezing), 3.1 (speech), 3.3 (neck rigidity), 3.9 (arising from chair), 3.10 (gait), 3.12 (postural stability), 3.13 (posture). The response of axial symptoms to levodopa was calculated according to the following formula: [(axial subscore Off – axial subscore On)/axial subscore Off].

The medication Off/stimulation On MDS-UPDRS scores were collected at T1 and the following DBS outcome measures were analyzed, using the formula [(T0 score – T1 score)/T0 score]: motor symptoms, as per the MDS-UPDRS part III score; dyskinesia, as per the MDS-UPDRS item 4.1 score; daily Off time, as per the MDS-UPDRS item 4.3 score; activities of daily living (ADL), as per the MDS-UPDRS part II score.

2.3. Statistical analysis

Descriptive statistics was used for continuous variables and frequency for categorical data. The Wilcoxon Signed rank-test was used for comparisons between pre- vs. post-surgical scores. To identify predictors of DBS outcome improvement, we performed a multivariate linear regression analysis for outcomes proving a significant change after surgery. First, we performed univariate regression analyses including, as dependent variables, the DBS outcome measures, and, as independent variables, sex, age at surgery, PD duration at surgery, cognitive status at surgery, LEDD, change of MDS-UPDRS part III score at the presurgical levodopa challenge test, and change of axial subscore at the presurgical levodopa challenge test. Independent variables obtaining a p-value <0.2 at the univariate analyses were used to perform the multivariate regression. The Durbin Watson was performed to test the level of autocorrelation between variables. All p-values are two-tailed, with a cut-off level of significance of 0.05. Statistics was performed by the Statistical Package for the Social Sciences 27.0 for iOs (SPSS, Chicago, IL).

3. Results

We included in the analysis 181 PD patients treated with bilateral STN-DBS according to data availability. The main demographic and

Table 1
Demographic and clinical data.

Demographic and presurgical clinical data	
Sex (males/females)	111/70
Age at STN-DBS (years) (mean ± SD)	60.09 ± 6.88
PD duration at STN-DBS (years) (mean ± SD)	13.93 ± 4.81
Presurgical LEDD (mean ± SD)	1053.77 ± 393.30
MDS-UPDRS III percentage levodopa response[^]	62 ± 12.19%
Presurgical axial symptoms (OFF condition) (mean ± SD)	1.97 ± 0.75
Presurgical axial symptoms (ON condition) (mean ± SD)	0.86 ± 0.52
Axial subscore response to levodopa[§]	55 ± 0.26%

Deep Brain Stimulation outcomes			
	T0	T1	p-value
MDS-UPDRS II	10.63 ± 6.83	11.27 ± 6.80	0.183
MDS-UPDRS III	58.28 ± 18.20	34.27 ± 13.85	<0.001*
MDS-UPDRS 4.1	1.49 ± 0.98	0.51 ± 0.74	<0.001*
MDS- UPDRS 4.3	1.36 ± 0.76	0.47 ± 0.66	<0.001*

Results were reported as mean ± SD.
STN-DBS: subthalamic Deep Brain Stimulation.
LEDD: Levodopa equivalent daily dose.
MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale.
T0: before surgery.
T1: 1-year post-DBS follow-up.
Each evaluation of MDS-UPDRS part III was performed in OFF condition at T0 and medication OFF/stimulation ON condition at T1.
MDS–UPDRS II: activities of daily living; MDS-UPDRS III: motor score; MDS-UPDRS 4.1 = time spent with dyskinesia; MDS-UPDRS 4.3 = time spent in the OFF state.
[^] (MDS-UPDRS in OFF condition – MDS-UPDRS in ON condition) / (MDS-UPDRS in OFF condition). This % represents the percentage of score improvement after Levodopa testing before surgery.
[§] (axial subscore in OFF condition – axial subscore in ON condition) / (axial subscore in OFF condition). This % represents the percentage of score improvement after Levodopa testing before surgery.
* Statistically significant difference.

clinical characteristics of the cohort are summarized in Table 1. Causes of exclusion of STN-DBS treated patients were: absence of baseline data ($n = 5$ patients), absence of follow-up data/patients followed up in other centers ($n = 80$ patients), death within 1 year after surgery ($n = 1$ patient).

3.1. STN-DBS outcomes

Comparing T0 (baseline) and T1 (1 year after surgery), we observed a significant improvement of motor symptoms (MDS-UPDRS part III score from 58.3 ± 18.2 to 34.3 ± 13.8; $p < 0.001$), dyskinesia (MDS-UPDRS item 4.1 score from 1.5 ± 0.9 to 0.5 ± 0.7; $p < 0.001$), and daily Off time (MDS-UPDRS item 4.3 score from 1.4 ± 0.8 to 0.5 ± 0.7; $p < 0.001$). ADL did not improve after surgery, with an MDS-UPDRS part II score of 10.6 ± 6.8 at T0 and 11.3 ± 6.8 at T1 ($p = 0.183$).

3.2. Predictors of STN-DBS outcomes

Sex, PD duration, cognitive status, motor and axial response at the levodopa challenge test explained 12.9% of the motor improvement provided by STN-DBS ($R = 0.360$, p: 0.002), with pre-surgical levodopa response of axial symptoms (Beta = 0.203, p: 0.025) and disease duration (Beta = 0.205, p: 0.013) being the strongest predictors (Table 2).

Considering the daily Off time improvement as the dependent variable, motor and axial response at the levodopa challenge test and disease duration explained 10.6% of variance ($R = 0.326$, $p < 0.001$), with disease duration being the strongest predictor of improvement (Beta = 0.253, p: 0.001) and axial levodopa response showing a trend of significance in explaining the change (Beta = 0.173, p: 0.056) (Table 2).

Dyskinesia improvement was not significantly explained by the model (Table 2).

No signs of significant collinearity among variables were observed in the three models, confirming the quality of the analysis. Data from the univariate analyses that were used to feed the multivariate model are reported in the supplementary material (Supplementary Tables 1, 2, and 3).

Table 2
Multiple regression analysis for predictive factors of motor, daily Off, and dyskinesia improvement after STN-DBS.

	Pre vs. post STN-DBS MDS-UPDRS III improvement		Pre vs. post STN-DBS MDS-UPDRS 4.1 improvement		Pre vs. post STN-DBS MDS-UPDRS 4.3 improvement	
R^2	0.129		0.031		0.106	
Durbin-Watson	1.886		2.182		1.679	
p-value	0.002*		0.095		<0.001*	
	Beta	*p-value*	*Beta*	*p-value*	*Beta*	*p-value*
Sex	0.135	0.095	−0.127	0.120	NA	NA
Age at STN-DBS	NA	NA	NA	NA	NA	NA
PD duration at STN-DBS	0.205	0.013*	0.133	0.104	0.253	0.001*
Cognition	0.141	0.083	NA	NA	NA	NA
Presurgical LEDD	NA	NA	NA	NA	NA	NA
MDS-UPDRS III percentage levodopa response^	0.116	0.205	NA	NA	0.116	0.194
Presurgical axial subscore response to levodopa§	0.203	0.025*	NA	NA	0.173	0.056

STN-DBS: subthalamic Deep Brain Stimulation.
PD: Parkinson's disease.
LEDD: Levodopa equivalent daily dose.
MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale.
MDS-UPDRS III: motor score; MDS-UPDRS 4.1 = time spent with dyskinesia; MDS-UPDRS 4.3 = time spent in the OFF state.
NA: not applicable.
^ (MDS-UPDRS in OFF condition – MDS-UPDRS in ON condition) / (MDS-UPDRS in OFF condition). This % represents the percentage of score improvement after Levodopa testing before surgery.
§ (axial subscore in OFF condition – axial subscore in ON condition) / (axial subscore in OFF condition). This % represents the percentage of score improvement after Levodopa testing before surgery.

4. Discussion

In our large cohort of PD patients treated with STN-DBS, we identified a long disease duration and a large improvement on the axial subscore of the MDS-UPDRS part III as the most important predictors of motor symptoms and daily Off time improvement one year after surgery. Remarkably, these findings, obtained through a multivariate analysis, survived after covarying for multiple clinical and demographic confounders.

Previous studies, based on both retrospective analyses and data from clinical trials, aimed at analyzing the role played by specific clinical factors in favoring a good or excellent DBS outcome for PD. A younger age at onset, good/excellent levodopa response of motor symptoms, a longer disease duration, absence of levodopa-resistant symptoms, cumulative daily OFF time, and cognitive functions were identified as predictors of STN-DBS efficacy when using the UPDRS-III as the primary endpoint [7–9]. Still, the role of axial symptoms has been often overlooked. In fact, while a longer disease duration has been quite consistently found as a predictor of good DBS outcomes [9], the magnitude of axial symptoms improvement during the levodopa challenge test was not taken into account in most studies previously published. The presence of marked axial signs before surgery is considered a contraindication for surgery, but several grey areas exist, and there are no clear recommendations on a specific presurgical assessment of axial symptoms nor indications on the level of severity to predict a poor DBS outcome [2,10]. To our knowledge, only two studies (both including small sample size) suggested that the response of axial symptoms to levodopa, measured by a score derived from the 'axial' items of UPDRS, can be used as a predictor of DBS outcome [11,12]. In fact, it has been reported that levodopa-responsive axial signs of PD have an excellent response to STN-DBS, at least in the first years after surgery [10]. This aspect may reflect the strong correlation we found between the preoperative axial response and the motor DBS outcome.

One study on 36 PD patients used linear regression models to analyze whether gender, age, preoperative MMSE score, Hoehn and Yahr stage, disease duration, and magnitude of levodopa response, including UPDRS tremor, rigidity, bradykinesia, axial subscores, and total part III scores, could predict motor benefit from STN-DBS 3 and 31 months after surgery [11]. The authors found that the magnitude of preoperative levodopa responsiveness to tremor and axial symptoms could predict the effect of DBS during long-term follow-up [11]. A more recent study evaluated the predictive role of presurgical levodopa challenge test on motor outcome of DBS targeting either globus pallidus pars interna or STN [12]. The authors found that in the 18 STN-DBS treated patients, the stimulation efficacy 7 months after surgery was positively correlated with preoperative levodopa challenge responsiveness on the non-tremor total score of MDS UPDRS-III, including bradykinesia, rigidity and axial symptoms [12].

To date, no guidelines or expert consensus recommendations are helpful in defining a cut-off (for example, using the MDS-UPDRS III axial subscore) to inform the selection process, nor even in deciding the best way to assess axial symptoms in PD candidates [13]. Given the recognized relevance of axial symptoms in determining outcomes, disease progression, and also mortality in DBS-treated cohorts [10,14], we believe that it is important to explore the predictive role of a simple score for measuring axial symptoms in patients who have been considered good candidates for DBS according to the classical CAPSIT-PD and consensus-based recommendations for DBS surgery in PD [1,2]. Our findings indicate that the response of axial symptoms to levodopa, rather

than the total motor response, might be critical in selecting candidates for DBS, and it is worth being better investigated to support the critical decision on whether or not to suggest patients undergo neurosurgery.

Another relevant finding is that longer disease duration was a favorable prognostic factor. While this observation has already been found in previous studies, it is important to point out that early DBS may be a reasonable option for patients with motor complications and drug-resistant tremor disorders [15,16]. However, an excessively early approach has been argued considering that i) the shorter disease duration at the time of surgery might pose the risks of including subjects with atypical parkinsonism; ii) a shorter disease duration at the time of surgery might lead to treating more patients with greater and faster burden of disability, like carriers of severe glucocerobrosidase gene variants; and iii) it can be difficult to predict the trajectory of disease progression at an early stage [13,17].

These two latter aspects, in particular, may be implicated because, in a large retrospective cohort of DBS patients, we found a higher disease duration at surgery as a favorable prognostic factor. Indeed, patients with slower disease trajectories may be referred later to DBS and still obtain an excellent DBS outcome.

This study has some limitations, the main one being its single-center and retrospective design. Another potential limitation is the ceiling effect of some assessments for DBS eligibility. Nonetheless, this intrinsic lack of sample variability in certain measures already regarded as DBS selection criteria might have enhanced other parameters that are currently neglected. Moreover, our patients were not screened for PD-related genetic mutations that might affect the DBS clinical outcome. Finally, the apparent absence of ADL improvement after DBS we observed might be due to the use of the MDS-UPDRS part II, which includes non-motor symptoms and, in contrast to the old version of UPDRS-II, does not distinguish between On and Off periods, thus diluting the possibility of capturing Off-On differences in ADL after DBS. In fact, as proven in most randomized controlled trials, the ADL activities evaluated by the UPDRS part II significantly improved after DBS when considering the preoperative medication Off therapeutic condition [18].

4.1. Conclusions

The abovementioned limitations notwithstanding, and awaiting confirmatory studies in other cohorts, we believe that axial symptoms should be carefully analyzed during the selection phases for DBS, not necessarily considering their presence and severity as a contraindication but rather evaluating their responsiveness to levodopa as a predictor of a good DBS outcome. The development, validation, and use of specific scales to comprehensively assess axial symptoms in PD would be of great importance for future studies.

Author's contributions

Carlo Alberto Artusi and Marco Bozzali contributed to the study conception and design. Material preparation, data collection and analysis were performed by Carlo Alberto Artusi, Claudia Ledda, Domiziana Rinaldi, Elisa Montanaro, Alberto Romagnolo, Gabriele Imbalzano, Mario Giorgio Rizzone, Maurizio Zibetti, Leonardo Lopiano. The first draft of the manuscript was written by Carlo Alberto Artusi and Claudia Ledda, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics

The authors confirm that they have received the approval of an institutional review board of the University of Turin for this work. Written informed consent was obtained from the patients.

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Declaration of Competing Interest

Carlo Alberto Artusi: received travel grants from Zambon and AbbVie, and speaker grants from Zambon, Bial and Lusofarmaco.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Appendix A. Supplementary data

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References

[1] G.L. Defer, H. Widner, R.M. Marié, et al., Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD), Mov. Disord. 14 (1999) 572–584, https://doi.org/10.1002/1531-8257(199907)14:4<572::aid-mds1005>3.0.co;2-c.

[2] J.M. Bronstein, M. Tagliati, R.L. Alterman, et al., Deep brain stimulation for Parkinson disease: an expert consensus and review of key issues, Arch. Neurol. 68 (2011) 165, https://doi.org/10.1001/archneurol.2010.260.

[3] M.M. Lanotte, M. Rizzone, B. Bergamasco, et al., Deep brain stimulation of the subthalamic nucleus: anatomical, neurophysiological, and outcome correlations with the effects of stimulation, J. Neurol. Neurosurg. Psychiatry 72 (2002) 53–58, https://doi.org/10.1136/jnnp.72.1.53.

[4] P. Perozzo, M. Rizzone, B. Bergamasco, et al., Deep brain stimulation of the subthalamic nucleus in Parkinson's disease: comparison of pre- and postoperative neuropsychological evaluation, J. Neurol. Sci. 192 (2001) 9–15, https://doi.org/10.1016/s0022-510x(01)00575-5.

[5] C.G. Goetz, G.T. Stebbins, B.C. Tilley, Calibration of unified Parkinson's disease rating scale scores to Movement Disorder Society-unified Parkinson's disease rating scale scores, Mov. Disord. 27 (2012) 1239–1242, https://doi.org/10.1002/mds.25122.

[6] I. Litvan, D. Aarsland, C.H. Adler, et al., MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI, Mov. Disord. 26 (2011) 1814–1824, https://doi.org/10.1002/mds.23823.

[7] M.L. Welter, J.L. Houeto, S. Tezenas du Montcel, et al., Clinical predictive factors of subthalamic stimulation in Parkinson's disease, Brain 125 (2002) 575–583, https://doi.org/10.1093/brain/awf050.

[8] A. Shalash, A. Alexoudi, K. Knudsen, et al., The impact of age and disease duration on the long term outcome of neurostimulation of the subthalamic nucleus,

Parkinsonism Relat. Disord. 20 (2014) 47–52, https://doi.org/10.1016/j.parkreldis.2013.09.014.
[9] F. Cavallieri, V. Fraix, F. Bove, et al., Predictors of long-term outcome of subthalamic stimulation in Parkinson disease, Ann. Neurol. 89 (2012) 587–597, https://doi.org/10.1002/ana.25994.
[10] A. Fasano, C.C. Aquino, J.K. Krauss, et al., Axial disability and deep brain stimulation in patients with Parkinson disease, Nat. Rev. Neurol. 11 (2015) 98–110, https://doi.org/10.1038/nrneurol.2014.252.
[11] S.T. Tsai, S.H. Lin, Y.C. Chou, et al., Prognostic factors of subthalamic stimulation in Parkinson's disease: a comparative study between short- and long-term effects, Stereotact. Funct. Neurosurg. 87 (2009) 241–248, https://doi.org/10.1159/000225977.
[12] Z. Lin, X. Zhang, L. Wang, et al., Revisiting the L-Dopa response as a predictor of motor outcomes after deep brain stimulation in Parkinson's disease, Front. Hum. Neurosci. 15 (2021) 604433, https://doi.org/10.3389/fnhum.2021.604433.
[13] C.A. Artusi, L. Lopiano, F. Morgante, Deep brain stimulation selection criteria for Parkinson's disease: time to go beyond CAPSIT-PD, J. Clin. Med. 9 (2020) 3931, https://doi.org/10.3390/jcm9123931.
[14] B. Lau, N. Meier, G. Serra, et al., Axial symptoms predict mortality in patients with Parkinson disease and subthalamic stimulation, Neurology. 92 (2019) e2559–e2570, https://doi.org/10.1212/WNL.0000000000007562.
[15] W.M. Schuepbach, J. Rau, K. Knudsen, et al., Neurostimulation for Parkinson's disease with early motor complications, N. Engl. J. Med. 368 (2013) 610–622, https://doi.org/10.1056/NEJMoa1205158.
[16] G. Deuschl, A. Antonini, J. Costa, et al., European academy of neurology/movement disorder society-European section guideline on the treatment of Parkinson's disease: I. Invasive therapies, Mov. Disord. 37 (2022) 1360–1374, https://doi.org/10.1002/mds.29066.
[17] T.A. Mestre, A.J. Espay, C. Marras, et al., Subthalamic nucleus-deep brain stimulation for early motor complications in Parkinson's disease-the EARLYSTIM trial: early is not always better, Mov. Disord. 29 (2014) 1751–1756, https://doi.org/10.1002/mds.26024.
[18] G. Deuschl, C. Schade-Brittinger, P. Krack, et al., A randomized trial of deep-brain stimulation for Parkinson's disease [published correction appears in N Engl J Med. 2006 Sep 21;355(12):1289], N. Engl. J. Med. 355 (2006) 896–908, https://doi.org/10.1056/NEJMoa060281.