RESEARCH ARTICLE

Disentangling Bradykinesia and Rigidity in Parkinson's Disease: Evidence from Short- and Long-Term Subthalamic Nucleus Deep Brain Stimulation

Alessandro Zampogna, MD [1,2,3] Antonio Suppa, MD, PhD,[1,3†] Francesco Bove, MD, PhD [4] Francesco Cavallieri, MD, PhD [5] Anna Castrioto, MD, PhD,[2] Sara Meoni, MD, PhD [2] Pierre Pelissier, RA,[2] Emmanuelle Schmitt, PsyD,[2] Stephan Chabardes, MD,[6] Valerie Fraix, MD, PhD,[2] and Elena Moro, MD, PhD [2]

Objective: Bradykinesia and rigidity are considered closely related motor signs in Parkinson disease (PD), but recent neurophysiological findings suggest distinct pathophysiological mechanisms. This study aims to examine and compare longitudinal changes in bradykinesia and rigidity in PD patients treated with bilateral subthalamic nucleus deep brain stimulation (STN-DBS).

Methods: In this retrospective cohort study, the clinical progression of appendicular and axial bradykinesia and rigidity was assessed up to 15 years after STN-DBS in the best treatment conditions (ON medication and ON stimulation). The severity of bradykinesia and rigidity was examined using ad hoc composite scores from specific subitems of the Unified Parkinson's Disease Rating Scale motor part (UPDRS-III). Short- and long-term predictors of bradykinesia and rigidity were analyzed through linear regression analysis, considering various preoperative demographic and clinical data, including disease duration and severity, phenotype, motor and cognitive scores (eg, frontal score), and medication.

Results: A total of 301 patients were examined before and 1 year after surgery. Among them, 101 and 56 individuals were also evaluated at 10-year and 15-year follow-ups, respectively. Bradykinesia significantly worsened after surgery, especially in appendicular segments ($p < 0.001$). Conversely, rigidity showed sustained benefit, with unchanged clinical scores compared to preoperative assessment ($p > 0.05$). Preoperative motor disability (eg, composite scores from the UPDRS-III) predicted short- and long-term outcomes for both bradykinesia and rigidity ($p < 0.01$). Executive dysfunction was specifically linked to bradykinesia but not to rigidity ($p < 0.05$).

Interpretation: Bradykinesia and rigidity show long-term divergent progression in PD following STN-DBS and are associated with independent clinical factors, supporting the hypothesis of partially distinct pathophysiology.

ANN NEUROL 2024;00:1–13

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26961

Received Nov 28, 2023, and in revised form Apr 4, 2024. Accepted for publication Apr 7, 2024.

Address correspondence to Dr Moro, Division of Neurology, Grenoble Alpes University, Centre Hospitalier Universitaire de Grenoble, Grenoble Institute of Neuroscience, INSERM U1216, Boulevard de la Chantourne, Grenoble, 38700, France. E-mail: emoro@chu-grenoble.fr

†A.Z. and A.S. contributed equally to this work.

From the [1]Department of Human Neurosciences, Sapienza University of Rome, Rome, Italy; [2]Grenoble Alpes University, Division of Neurology, Centre Hospitalier Universitaire de Grenoble, Grenoble Institute of Neuroscience, INSERM U1216, Grenoble, France; [3]IRCCS Neuromed Institute, Pozzilli, Italy; [4]Neurology Unit, Department of Neuroscience, Sensory Organs and Chest, Fondazione Policlinico Universitario A. Gemelli IRCCS, Catholic University of the Sacred Heart, Rome, Italy; [5]Neurology Unit, Neuromotor and Rehabilitation Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; and [6]Division of Neurosurgery, Grenoble Alpes University, Centre Hospitalier Universitaire de Grenoble, Grenoble, France

Additional supporting information can be found in the online version of this article.

According to the International Parkinson's Disease and Movement Disorders Society consensus criteria, the clinical diagnosis of Parkinson disease (PD) can be achieved when bradykinesia occurs in combination with resting tremor and/or rigidity.[1] Resting tremor is considered an independent motor sign characterized by specific pathophysiology, course, and treatment response.[2] Resting tremor is not correlated with bradykinesia, rigidity, or dopamine depletion in the substantia nigra and shows a variable response to L-dopa.[2,3] By contrast, bradykinesia and rigidity are usually considered closely related motor signs that reflect the dopaminergic denervation in the nigrostriatal pathway.[3] A strong clinicopathological correlation exists between the severity of bradykinesia and rigidity, the neuronal loss of dopaminergic cells, and the volume reduction in the substantia nigra among patients with PD.[3] Accordingly, bradykinesia and rigidity show similar excellent improvements after the acute administration of L-dopa.[4] Furthermore, neurophysiological recordings reveal a close association between these signs and synchronized neuronal oscillations at beta band frequencies within the cortico-basal ganglia loops.[5] Additional evidence supporting the hypothesis that bradykinesia and rigidity share overlapping pathophysiological mechanisms comes from animal models based on nigrostriatal damage, mimicking the parkinsonian akinetic–rigid syndrome.[6] Notably, there are no animal PD models currently capable of disentangling bradykinesia and rigidity, thus indicating overlapping anatomic substrates.[6]

However, several recent observations suggest that bradykinesia and rigidity may reflect at least partly independent mechanisms. Whereas bradykinesia would prominently reflect a network dysfunction in the cortico-basal-ganglia–thalamocortical loop,[7–10] rigidity more likely arises from functional changes in specific brainstem circuits and descending neuronal pathways to the spinal cord.[11–13] Hence, to better clarify possible pathophysiological differences and thus disentangle bradykinesia and rigidity in people with PD, innovative ad hoc designed studies are crucially warranted. The use of methodologies able to differently modulate bradykinesia and rigidity in PD, like deep brain stimulation of the subthalamic nucleus (STN-DBS),[14–16] would help address this issue.

So far, no previous large cohort studies have specifically compared and analyzed differences in the short- and long-term pattern of the response of bradykinesia and rigidity to STN-DBS. Also, none has examined the progression of bradykinesia and rigidity following STN-DBS specifically focusing on body topography. Appendicular and axial segments may show differential responses to treatments and distinct prognostic implications in PD.[17,18] Lastly, no studies have investigated specific clinical predictors associated with short- and long-term bradykinesia and rigidity following STN-DBS. Filling these gaps would contribute to clarifying whether bradykinesia and rigidity reflect at least partly independent pathophysiological underpinnings in PD.

The present study aims to investigate the short- and long-term progression of bradykinesia and rigidity in a large cohort of PD patients with STN-DBS followed longitudinally up to 15 years. By employing a focused and systematic methodological approach, the study also aims to differentiate the progression of bradykinesia and rigidity according to body topography. Finally, the study investigates short- and long-term clinical predictors of bradykinesia and rigidity in PD.

Patients and Methods

This retrospective cohort study followed the guidelines provided in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) document, as detailed in Supplementary Materials S1. The study protocol was reviewed and approved by the institutional research center authority of Grenoble Alpes University Hospital before implementation. Informed consent was obtained from each subject.

Study Population

A retrospective evaluation of people with PD who underwent bilateral STN-DBS at Grenoble Alpes University Hospital (Grenoble, France) from 1993 to 2010 was conducted. To be eligible for surgery, patients had to meet the following criteria: a clinical diagnosis of idiopathic PD according to the UK Brain Bank criteria[19]; presence of motor complications (ie, fluctuations and/or L-dopa-induced dyskinesia) despite optimized antiparkinsonian medications; age younger than 75 years; absence of dementia, major ongoing psychiatric illness, or relevant structural abnormalities on brain magnetic resonance imaging, such as severe atrophy or diffuse cerebral ischemic lesions; and no surgical contraindications. Individuals who had undergone previous neurosurgical brain interventions or had DBS targets other than STN, surgical complications, implantation of more than two electrodes, or electrode misplacement requiring lead revision were excluded from the study. Tremor alone was not the main criterion for undergoing STN-DBS in patients with tremor-dominant phenotype.

Clinical Assessments

All subjects underwent a detailed neuropsychiatric evaluation before surgery (baseline) as well as an L-dopa challenge, using established indications and procedures.[20]

At different time points (before surgery and at 1 year, 10 years, and 15 years after surgery), patients were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) up to 2011 and the Movement Disorder Society-sponsored revision of the UPDRS (MDS-UPDRS) after 2011; the axial score (sum of items 27 or 3.9, 28 or 3.13, 29 or 3.10, and 30 or 3.12 of the UPDRS or MDS-UPDRS, respectively)[21,22]; the Hoehn and Yahr scale (H&Y); the Mattis Dementia Rating Scale (MDRS); and the frontal score (ie, up to 20 points derived from the Wisconsin Card Sorting Test criteria multiplied by 3, with an additional +2 points if the responses needed are <43; up to 10 points from the scores of the Verbal Fluency Test divided by 3; and up to 20 points from the Graphic and Motor Series, for a maximal score of 50 points).[23] To ensure comparability, we converted available MDS-UPDRS-III scores to UPDRS-III scores using standardized formulas.[24]

Whereas at baseline patients were evaluated in both the OFF and ON medication conditions, postoperative assessments at 1, 10, and 15 years after STN-DBS surgery were conducted in the optimized treatment condition, that is, in the chronic ON medication and ON stimulation condition.

Statistical Analysis

Data were collected at baseline and 1, 10, and 15 years after STN-DBS surgery. Information was manually extracted from medical records and entered in a customized database for statistical analysis. The study collected demographic and clinical information at baseline, including age, sex, age at disease onset, age at surgery, disease duration at surgery, PD phenotype (calculated through published clinical algorithms[25]), dopaminergic medication using L-dopa equivalent daily doses (LEDDs), and the above cited standardized scales and scores.

The primary outcome was the longitudinal evaluation of bradykinesia and rigidity at the appendicular and axial regions, as assessed at baseline and 1, 10, and 15 years after STN-DBS in the best treatment conditions (ie, ON medication and ON medication/ON stimulation before and after surgery, respectively).

The severity of appendicular bradykinesia and rigidity was measured at baseline and follow-up visits, at the more and less affected sides, using specific composite scores including the sum of the following UPDRS/MDS-UPDRS part III items: items 23/3.4 (ie, "finger tapping") and 26/3.8 (ie, "leg agility") for appendicular bradykinesia (range = 0–8); and items 22/3.3 (ie, "rigidity of the upper limb") and 22/3.3 (ie, "rigidity of the lower limb") for appendicular rigidity (range = 0–8). The choice of using a single item ("finger tapping") to represent upper limb bradykinesia was made because of its already proven high sensitivity and accuracy in bradykinesia evaluation.[26] The more and less affected sides were determined based on the onset side and severity of symptoms at baseline. Concerning axial bradykinesia and rigidity, items 19/3.2 (ie, amimia) and 22/3.3 (ie, neck rigidity) of the UPDRS/MDS-UPDRS part III were respectively used (range = 0–4). While strictly connected to the craniocervical region, amimia and neck hypertonia effectively mirror the axial distribution of bradykinesia and rigidity. These signs are notably associated with additional axial disorders, including speech, swallowing, posture, gait, and balance issues.[27,28] However, in this study, only amimia and neck rigidity have been considered. Due to the non-normal distribution of data and censored data at the long-term follow-up (ie, 10 and 15 years after surgery), the Skillings–Mack test and the Wilcoxon test were used to compare composite scores of bradykinesia and rigidity over time (ie, repeated measures), at both the appendicular and axial regions. To assess the degree of change between bradykinesia and rigidity at different time points, the percentage variation of these signs from baseline at 1-, 10-, and 15-year follow-ups was analyzed with the Kruskal–Wallis test and the Mann–Whitney test. Specifically, we compared the percentage changes of bradykinesia to those of rigidity at each time point. The Kruskal–Wallis test and the Mann–Whitney test were also adopted to examine the evolution of symptoms with respect to body segments by comparing the percentage variation of bradykinesia and rigidity between appendicular and axial regions.

The secondary outcome consisted of the preoperative predictors of appendicular and axial bradykinesia and rigidity (ie, dependent variables) at 1, 10, and 15 years after STN-DBS surgery. Given the continuous nature of composite scores, which reflect a spectrum of severity (ie, higher values indicate greater motor impairment), a multiple linear regression was used to evaluate the relationship between dependent and independent variables. More in detail, univariate linear regression analysis was first applied to identify baseline independent factors potentially associated with bradykinesia and rigidity at appendicular and axial levels in the short (ie, 1 year after STN-DBS surgery) and long term (ie, 10 and 15 years after STN-DBS surgery).[29] Then, baseline variables showing significance at $p < 0.20$ in the univariate analysis entered the stepwise selection process for the final building of the multivariate model reporting the optimal combination of variables, following standardized procedures.[30] The preoperative covariates considered as independent variables for regression modeling included age at disease onset, disease duration at surgery, age at surgery, phenotype (ie, akinetic/rigid, tremor-dominant, and mixed types),

UPDRS part III in the OFF and ON medication conditions, H&Y in the OFF and ON medication conditions, composites scores of appendicular and axial bradykinesia and rigidity in the OFF and ON medication conditions, axial score in the OFF and ON medication conditions, L-dopa responsiveness of appendicular and axial bradykinesia and rigidity, MDRS, frontal score, and LEDDs. Independent preoperative variables with strict reciprocal correlations (ie, >0.7) were excluded from the model to prevent multicollinearity and lack of independence (Supplementary Materials S2). Missing data were handled by using a pairwise deletion method. The coefficient estimates for each independent variable were reported as standardized β coefficient followed by 95% confidence interval of β coefficient and *p* values.

Statistical analysis was performed using the SPSS package (IBM, Armonk, NY). For all statistical tests, the significant level was set at 0.05 (2-tailed).

Results

Of 417 people with PD who underwent bilateral STN-DBS between 1993 and 2010 and were assessed for eligibility, 116 were excluded due to being lost to follow-up, incomplete medical records, or unmet inclusion criteria. The study ultimately included data from 301 patients at 1-year follow-up after surgery, and 101 patients at 10-year and 56 patients at 15-year follow-ups.

The main demographic and clinical characteristics of PD patients at baseline and follow-up visits after STN-DBS surgery are presented in Table 1.

Short- and Long-Term Progression of Bradykinesia and Rigidity

Appendicular Measures. Appendicular bradykinesia exhibited significant changes between baseline, and 1, 10, and 15 years after surgery, at both the more and less affected sides. Notably, both the more and less affected sides displayed comparable levels of appendicular bradykinesia at baseline and at 1-year follow-up, but progressive deterioration at 10- and 15-year follow-ups (Table 2, Fig 1A).

Concerning appendicular rigidity, composite scores were significantly different at baseline and 1, 10, and 15 years after surgery, at both the more and less affected sides. At both the more and less affected sides, appendicular rigidity improved at 1 year after surgery but subsequently reverted to preoperative severity levels at 10- and 15-year follow-ups (see Table 2, Fig 1B).

Given comparable changes over time in bradykinesia and rigidity at both sides, only the more affected side was considered for subsequent analyses, including the longitudinal differences in symptom severity, the variations based on body topography, and the identification of predictive factors (ie, univariate and multivariate regression analyses).

The extent of longitudinal changes in appendicular bradykinesia and rigidity differed significantly at 1, 10, and 15 years after surgery. Appendicular bradykinesia showed a greater percentage of variation than appendicular rigidity at 1, 10, and 15 years after surgery (Table 3, Fig 1C,D).

Axial Measures. Significant differences in axial bradykinesia were observed at baseline and 1-, 10-, and 15-year follow-ups after surgery. More in detail, composite scores of axial bradykinesia progressively increased from the first year after surgery up to the 15-year follow-up (see Table 2, Fig 2A).

Axial rigidity also significantly changed over time, showing a short-term improvement 1 year after surgery, followed by a long-term deterioration at 10- and 15-year follow-ups (see Table 2, Fig 2B).

Finally, the extent of longitudinal changes in axial bradykinesia and rigidity was significantly different at 1, 10, and 15 years after surgery. Notably, axial bradykinesia exhibited a higher percentage variation than axial rigidity at 1 and 15 years after surgery (see Table 3, Fig 2C).

Appendicular versus Axial Measures. Appendicular and axial bradykinesia showed a different extent of longitudinal changes at 1, 10, and 15 years after surgery. Appendicular bradykinesia improved at 1 year after surgery, and worsened at 10- and 15-year follow-ups to a greater extent compared to axial bradykinesia (see Table 3, Fig 3A).

Axial rigidity exhibited a less pronounced improvement at 1 year and a more significant worsening at 10 years following surgery when compared to appendicular rigidity. No statistical differences were found when comparing axial and appendicular rigidity at the 15-year follow-up (see Table 3, Fig 3B).

Predictive Factors of Bradykinesia and Rigidity

Appendicular Measures. The preoperative independent variables selected through the univariate analysis for subsequent stepwise selection processes in regression modeling of appendicular bradykinesia and rigidity are reported in Supplementary Materials S2.

The multivariate linear regression models showed that the UPDRS-III scores in the ON medication condition and the frontal scores were independent preoperative predictors of appendicular bradykinesia 1 year after surgery. The frontal scores also predicted appendicular bradykinesia at 10 and 15 years after surgery, along with

TABLE 1. Demographic and Clinical Characteristics of Parkinson Disease Patients at Baseline and Follow-up Visits after Bilateral Deep Brain Stimulation of the Subthalamic Nucleus

Characteristic	Baseline, n = 301[a]	1-year follow-up, n = 301[a]	10-year follow-up, n = 101	15-year follow-up, n = 56
Female sex	119 (39.5%)	119 (39.5%)	40 (39.6%)	20 (35.7%)
Age, yr	55.65 ± 8.41	56.69 ± 8.41	62.84 ± 8.39	65.03 ± 8.26
Age at disease onset, yr	43.98 ± 8.18	43.98 ± 8.18	40.7 ± 7.69	39.77 ± 7.18
Disease duration, yr	11.77 ± 4.27	12.76 ± 4.33	22.90 ± 4.37	26.50 ± 3.79
Clinical phenotype	109 AR (36.21%)	109 AR (36.21%)	37 AR (36.63%)	18 AR (32.1%)
	41 T (13.62%)	41 T (13.62%)	10 T (9.90%)	6 T (10.7%)
	151 mixed (50.17%)	151 mixed (50.17%)	54 mixed (53.47%)	32 mixed (57.1%)
Hoehn and Yahr	OFF 3.35 ± 0.99	ON med/ON stim	ON med/ON stim	ON med/ON stim
	ON 1.86 ± 0.76	1.97 ± 0.71	2.96 ± 0.91	2.99 ± 0.90
UPDRS-III[b]	OFF 45.29 ± 15.42	ON med/ON stim	ON med/ON stim	ON med/ON stim
	ON 13.78 ± 7.98	12.77 ± 9.46	29.63 ± 15.25	35.93 ± 17.35
Axial score	OFF 6.83 ± 3.94	ON med/ON stim	ON med/ON stim	ON med/ON stim
	ON 1.95 ± 1.80	1.99 ± 2.14	6.11 ± 4.24	7.39 ± 4.73
Stimulation parameters	NA	L: 2.84 V (±0.60); 130 Hz (60–185); 60 μs (60–90)	L: 2.96 V (±0.53); 130 Hz (60–185); 60 μs (60–90)	L: 2.96 V (±0.61); 130 Hz (60–185); 60 μs (60–90)
		R: 2.85 V (±0.57); 130 Hz (60–185); 60 μs (60–90)	R: 2.91 V (±0.68); 130 Hz (60–185); 60 μs (60–90)	R: 2.97 V (±0.60); 130 Hz (60–185); 60 μs (60–90)
LEDD	1,347.02 ± 506.68	390.68 ± 400	660.04 ± 377.51	650.61 ± 315.14

AR = akinetic-rigid type; L = left; LEDD = L-dopa equivalent daily dose; med = medication; NA = not applicable; R = right; stim = stimulation; T = tremor-dominant type; UPDRS-III = Unified Parkinson's Disease Rating Scale part III.

[a]All participants enrolled at baseline were also included in the 1-year follow-up.

[b]To ensure comparability and for descriptive purposes only, available Movement Disorder Society-sponsored revision of the UPDRS-III scores were converted to UPDRS-III scores.

the preoperative severity of bradykinesia in the ON medication condition (Table 4).

Preoperative appendicular rigidity in the ON medication and axial scores in the OFF medication conditions predicted appendicular rigidity at 1 year after surgery. Appendicular rigidity was also associated with preoperative scores of appendicular rigidity in the ON medication condition and the MDRS at 10 years, and with the UPDRS-III scores in the ON medication condition at 15 years after surgery (see Table 4).

Axial Measures. The preoperative independent variables selected through the univariate analysis for subsequent stepwise selection processes in regression modeling of axial bradykinesia and rigidity are reported in Supplementary Materials S2.

The multivariate linear regression models showed that the preoperative severity of axial bradykinesia in the ON and OFF medication condition, the frontal scores, and the H&Y scores in the ON medication condition predicted axial bradykinesia 1 year after surgery. Axial scores in the OFF medication condition and frontal scores were associated with axial bradykinesia at 10- and 15-year follow-ups, respectively (see Table 4).

The preoperative predictors of axial rigidity included the severity of axial rigidity and the UPDRS-III scores in the ON medication condition at 1 year after surgery, the severity of axial rigidity in the OFF medication condition

TABLE 2. Short- and Long-Term Progression of Bradykinesia and Rigidity in Parkinson Disease

		Time point				Skilling–Mack Test (Q_3; p)	Wilcoxon Signed-Rank Test (Z; p)					
		PRE	1-Y	10-Y	15-Y		PRE vs 1-Y	PRE vs 10-Y	PRE vs 15-Y	1-Y vs 10-Y	1-Y vs 15-Y	10-Y vs 15-Y
Bradykinesia	More affected	1.43 ± 0.61	1.30 ± 0.67	3.18 ± 0.95	3.59 ± 0.92	132.390; **<0.001**	−1.617; 0.106	−7.258; **<0.001**	−6.062; **<0.001**	−7.863; **<0.001**	−6.214, **<0.001**	−2.266; **0.023**
	Less affected	0.82 ± 0.49	0.90 ± 0.58	2.79 ± 0.94	3.22 ± 0.90	148.000; **<0.001**	−0.776; 0.438	−7.966; **<0.001**	−6.230; **<0.001**	−8.076; **<0.001**	−6.416; **<0.001**	−2.873; **0.004**
	Axial	1.01 ± 0.33	1.16 ± 0.41	1.85 ± 0.48	2.28 ± 0.39	98.325; **<0.001**	−2.884; **0.004**	−6.625; **<0.001**	−6.250; **<0.001**	−6.126; **<0.001**	−5.936; **<0.001**	−3.788; **0.001**
Rigidity	More affected	1.45 ± 0.67	0.82 ± 0.54	1.42 ± 0.85	1.63 ± 0.93	29.545; **<0.001**	−7.126; **<0.001**	−0.899; 0.369	−1.175; 0.240	−3.482; **<0.001**	−2.736; **0.006**	−0.877; 0.381
	Less affected	1.06 ± 0.58	0.58 ± 0.47	1.01 ± 0.75	1.15 ± 0.87	28.995; **<0.001**	−6.526; **<0.001**	−0.141; 0.888	−1.094; 0.274	−3.444; **0.001**	−3.179; **0.001**	−0.128; 0.898
	Axial	0.90 ± 0.46	0.64 ± 0.40	1.33 ± 0.62	1.37 ± 0.61	39.380; **<0.001**	−4.291; **<0.001**	−2.799; **0.005**	−2.770; **0.006**	−5.292; **<0.001**	−4.473; **<0.001**	−0.156; 0.876

Bold font indicates statistical significance.
10-Y = 10-year postoperative follow-up; 15-Y = 15-year postoperative follow-up; 1-Y = 1-year postoperative follow-up; PRE = preoperative period.

and the UPDRS-III scores in the ON medication condition at 10 years, and the UPDRS-III scores in the ON medication condition at 15 years (see Table 4).

Discussion

In this retrospective cohort study including a large sample of PD patients with bilateral STN-DBS, bradykinesia and rigidity showed a divergent and complex progression over the long-term follow-up. Moreover, different preoperative predictive factors for bradykinesia and rigidity outcomes could be identified. These findings challenge the commonly accepted notion that bradykinesia and rigidity follow a similar clinical evolution over time in patients with PD, suggesting not only nonidentical anatomic substrates but also distinct pathophysiological mechanisms.

Bradykinesia and Rigidity Differently Progress after STN-DBS

Appendicular bradykinesia remained unchanged 1 year after surgery, whereas it significantly worsened at 10- and 15-year follow-ups. By contrast, appendicular rigidity drastically improved 1 year after STN-DBS, and then returned to preoperative levels only 10 and 15 years afterward. Nonetheless, axial bradykinesia and rigidity manifested a similar pattern of progression following STN-DBS, except for an early deterioration of axial bradykinesia (at 1-year postsurgery). Overall, these findings suggest that STN-DBS in PD may not provide supplementary benefits for improving bradykinesia compared to L-Dopa alone. By contrast, STN-DBS may offer additional and sustained relief for rigidity over time.

The divergent progression of bradykinesia and rigidity, in the short and long term after STN-DBS, fits in well with previous studies using whole-body measures of both motor signs in PD.[31–33] Several pathophysiological interpretations could explain our observations. The sensorimotor region of the STN (usually targeted by DBS) may include independent "sweet spots" for bradykinesia and rigidity, as suggested by recent symptom-stimulation mapping studies.[34–38] In theory, because the intraoperative assessment of rigidity is a relevant maneuver in guiding the optimal placement of the macroelectrode (when patients are operated on under local anesthesia), a preferential targeting for rigidity sweet spots could be responsible for our findings. However, the intrinsic variability in DBS electrode placement in the STN and the high number of subjects enrolled in this study make the hypothesis of a preferential targeting for rigidity sweet spot rather weak. Furthermore, the consistent overlap in the progression of bradykinesia and rigidity when comparing the more and less affected body sides also strongly argues against this hypothesis. As a second scenario, bradykinesia and rigidity in PD would show different response thresholds to STN-DBS parameters (ie, frequency and pulse width). Early seminal studies have reported that bradykinesia requires higher frequencies (ie, from 50 Hz)

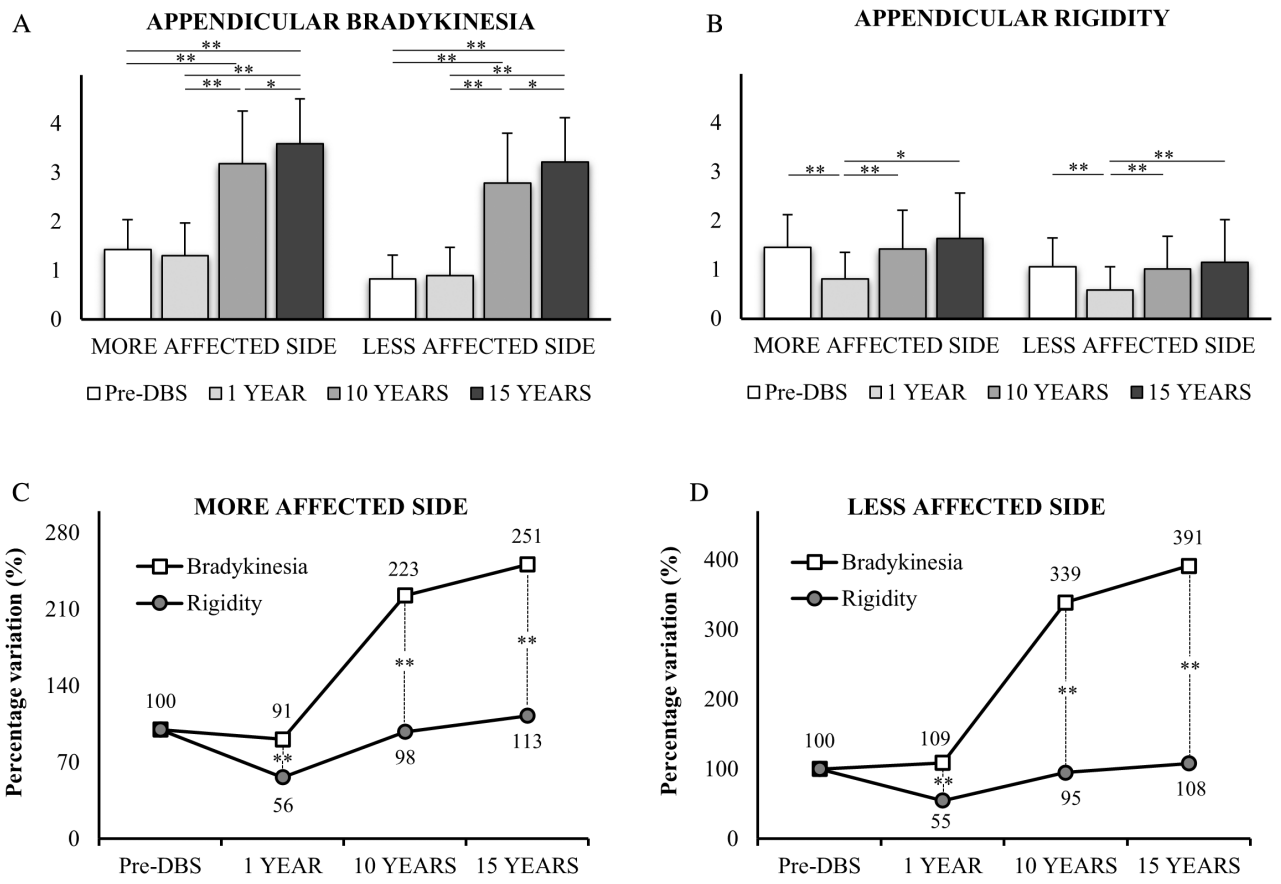

FIGURE 1: Appendicular bradykinesia and rigidity in the cohort of Parkinson disease patients with bilateral deep brain stimulation (DBS) of the subthalamic nucleus. Longitudinal changes of appendicular bradykinesia (A) and rigidity (B) are displayed for the more and less affected sides through histograms. The comparison of percentage variations of appendicular bradykinesia and rigidity is also shown for the more (C) and less affected side (D) at each time point. Asterisks indicate the main differences (*$p < 0.05$, **$p < 0.001$).

TABLE 3. Longitudinal Changes of Bradykinesia and Rigidity in Parkinson Disease

		Bradykinesia vs Rigidity, Appendicular[a]	Bradykinesia vs Rigidity, Axial	Bradykinesia, Appendicular[a] vs Axial	Rigidity, Appendicular[a] vs Axial
Kruskal–Wallis (χ^2_5; p)		200.6; **<0.001**	57.7; **<0.001**	221.3; **<0.001**	58.1; **<0.001**
Mann–Whitney (U; p)[b]	I-Y	37,088.5; **<0.001**	35,125.5; **<0.001**	39,849.0; **0.009**	40,702.0; **0.025**
	10-Y	2,412.0; **<0.001**	3,856.0; **0.002**	4,012.5; **0.008**	4,049.5; **0.009**
	15-Y	754.5; **<0.001**	940.5; **<0.001**	1,226.0; **0.042**	1,318.5; 0.132

Bold font indicates statistical significance.
10-Y = 10-year postoperative follow-up; 15-Y = 15-year postoperative follow-up; 1-Y = 1-year postoperative follow-up.
[a]More affected side.
[b]Bradykinesia and rigidity comparison was performed exclusively at the same time point.

and a narrower pulse width (ie, 60 μs) than rigidity. By contrast, rigidity ameliorates starting at 33 Hz and responds to a wider range of pulse widths (ie, between 60 and 210 μs).[39] In the present study, the vast majority of patients received ranges of STN-DBS parameters reasonably effective for both motor signs (ie, stimulation frequency ≥ 60 Hz and pulse width = 60 μs). Biophysical models have demonstrated that electric stimulation can

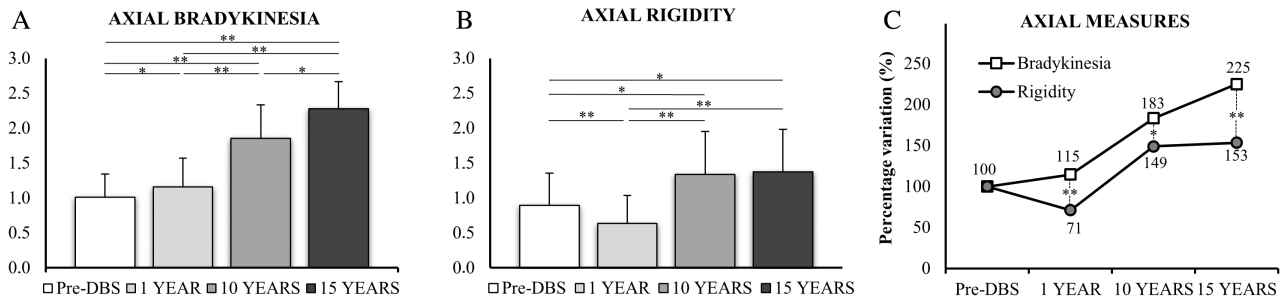

FIGURE 2: Axial bradykinesia and rigidity in in the cohort of Parkinson disease patients with bilateral deep brain stimulation (DBS) of the subthalamic nucleus. Longitudinal changes of axial bradykinesia (A) and rigidity (B) are displayed through histograms. The comparison of percentage variations of axial bradykinesia and rigidity is also shown (C) at each time point. Asterisks indicate the main differences (*$p < 0.05$, **$p < 0.001$).

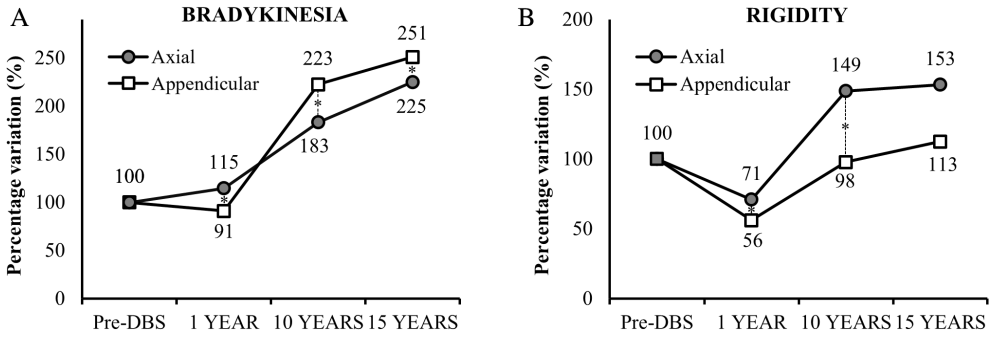

FIGURE 3: Body topography of bradykinesia and rigidity in the cohort of Parkinson disease patients with bilateral deep brain stimulation (DBS) of the subthalamic nucleus. The comparison of percentage variations of bradykinesia (A) and rigidity (B) according to body topography (ie, appendicular vs axial) is displayed at each time point. Asterisks indicate the main differences (*$p < 0.05$).

induce varying activation patterns based on axon features (ie, diameter and orientation)[40–42] and structural connectivity of the STN.[34,38] Hence, a third hypothesis implies that STN-DBS differently activates neural networks contributing to bradykinesia and rigidity in PD according to separate neuronal pathways. This hypothesis fully agrees with recent neuroimaging findings demonstrating distinct structural connectivity profiles of the STN for bradykinesia and rigidity.[43] The hypothesis of distinct neuronal pathways for bradykinesia and rigidity is also supported by other studies in PD as well as in parkinsonian nonhuman primates showing divergent motor outcomes following DBS of the globus pallidus pars interna (GPi).[44] The stimulation of the most ventral part of GPi significantly ameliorates rigidity although it exerts an antikinetic effect. Conversely, stimulation of the dorsal GPi or the globus pallidus pars externa reduces akinesia but yields far less pronounced effects on rigidity.[44] Bradykinesia in PD is currently thought to reflect a corticosubcortical network disorder implying abnormal functional connections among the fronto-basal-ganglia–thalamocortical motor loop and the cerebellum.[7–10,45] By contrast, parkinsonian rigidity likely arises from abnormal inputs from GPi and substantia nigra pars reticulata to the pontobulbar reticular formation, leading to hyperactive descending projections (dorsal and medial reticulospinal tracts) directed to propriospinal as well as spinal Ia and Ib interneurons.[11–13] This in turn results in hyperexcitability of gamma and alpha motoneurons responsible for increased muscle tone.[11–13] Accordingly, a more reasonable interpretation of our findings would point to the preferential interaction of STN-DBS with neural networks responsible for rigidity compared with those contributing to bradykinesia. Degenerative changes impacting these neural networks may progress independently or at varying rates, potentially exacerbating the dissociation between bradykinesia and rigidity in PD as the disease advances. Although rather speculative, we suggest that the preferential effect of STN-DBS on parkinsonian rigidity reflects the prominent activation of basal ganglia projections to brainstem nuclei such as the pedunculopontine nucleus and the pontobulbar reticular formation. This preferential interaction could result in sustained relief for rigidity. Conversely, bradykinesia may deteriorate over time as neural circuits unaffected by STN-DBS become increasingly involved, thereby constraining the efficacy of parameter adjustments for addressing this sign in the long-term period.

TABLE 4. Predictive Factors of Bradykinesia and Rigidity in Parkinson Disease

		Selected variables	I-Y	10-Y	15-Y
Bradykinesia	Appendicular[a]	UPDRS-III ON	β = 0.301, CI 0.029 to 0.072, ***p* < 0.001**	ns	ns
		Frontal score	β = −0.301, CI 0.029 to 0.072, ***p* < 0.001**	β = −0.359, CI −0.138 to −0.035, ***p* = 0.001**	β = −0.375, CI −0.146 to −0.029, ***p* = 0.004**
		Bradykinesia score ON	ns	β = 0.314, CI 0.157 to 0.816, ***p* = 0.004**	β = 0.303, CI 0.078 to 0.828, ***p* = 0.019**
	Axial	Bradykinesia score ON	β = 0.191, CI 0.074 to 0.403, ***p* = 0.005**	ns	ns
		Bradykinesia score OFF	β = 0.193, CI 0.071 to 0.363, ***p* = 0.004**	ns	ns
		Frontal score	β = −0.204, CI −0.034 to −0.009, ***p* = 0.001**	ns	β = −0.290, CI −0.055 to −0.002, ***p* = 0.035**
		H&Y ON	β = 0.165, CI 0.050 to 0.305, ***p* = 0.007**	ns	ns
		Axial score OFF	ns	β = 0.223, CI 0.026 to 0.400, ***p* = 0.026**	ns
Rigidity	Appendicular[a]	Rigidity score ON	β = 0.289, CI 0.137 to 0.333, ***p* < 0.001**	β = 0.324, CI 0.136 to 0.686, ***p* = 0.004**	ns
		Rigidity score OFF	β = 0.135, CI 0.004 to 0.070, ***p* = 0.028**	ns	ns
		MDRS	ns	β = −0.306, CI −0.176 to −0.030, ***p* = 0.006**	ns
		UPDRS-III ON	ns	ns	β = 0.277, CI 0.004 to 0.126, ***p* = 0.039**
	Axial	Rigidity score ON	β = 0.257, CI 0.111 to 0.336, ***p* < 0.001**	ns	ns
		UPDRS-III ON	β = 0.251, CI 0.012 to 0.038, ***p* < 0.001**	β = 0.239, CI 0.001 to 0.073, ***p* = 0.045**	β = 0.372, CI 0.017 to 0.096, ***p* = 0.006**
		Rigidity score OFF	ns	β = 0.242, CI 0.009 to 0.521, ***p* = 0.043**	ns

Bold font indicates statistical significance.
10-Y = 10-year postoperative follow-up; 15-Y = 15-year postoperative follow-up; 1-Y = 1-year postoperative follow-up; CI = 95% confidence interval; H&Y = Hoehn and Yahr; MDRS = Mattis Dementia Rating Scale; ns = not significant; UPDRS-III = Unified Parkinson's Disease Rating Scale part III.
[a]More affected side.

Further supporting this pathophysiological interpretation, our study discloses the opposite trend of bradykinesia and rigidity following STN-DBS according to body topography. When directly comparing the progression of motor signs in appendicular and axial regions, bradykinesia deteriorated prominently at the appendicular level compared with axial regions, and vice versa for rigidity. The opposite progression of bradykinesia and rigidity in PD, according to body topography, may be explained by the distinct neural control and primary actions of axial and appendicular regions. Notably, the phylogenetically old medial system, involving descending brainstem

pathways, is responsible for the resting sustained regulation of muscle tone underlying postural maintenance in axial muscles.[46] Conversely, the phylogenetically more recent lateral system allows the fine motor control of hands and fingers.[46] Accordingly, the observation of prominent rigidity in axial regions and prevalent bradykinesia in appendicular regions further corroborates the hypothesis that rigidity would originate from changes in the brainstem pathways, while bradykinesia is linked to a corticosubcortical dysfunction.

Predictive Factors of Bradykinesia and Rigidity

Bradykinesia and rigidity showed similar short- and long-term predictive factors in our STN-DBS cohort of PD patients at the appendicular and axial levels. Predictive factors included the preoperative severity of motor impairment, as measured by the UPDRS-III, the composite scores of bradykinesia and rigidity, the H&Y, and the axial scores, especially in the ON medication condition. The reported findings are fully in line with previous studies demonstrating baseline motor disability as a crucial prognostic factor affecting the outcome of STN-DBS in PD.[22,47] Furthermore, the greater impact of motor impairment at baseline, especially in the ON medication condition, confirms and further expands previous observations on the prognostic value of preoperative response of motor symptoms to L-dopa in the short- and long-term follow-up.[48] Besides the preoperative severity of motor impairment, the analysis of predictive factors demonstrated that the baseline severity of frontal dysfunction (ie, the frontal score) was consistently associated with bradykinesia but not with rigidity. This observation agrees with the well-known impact of frontal functions on STN-DBS outcomes in PD.[49,50] PD patients with cognitive dysfunction, especially those with executive deficits, exhibit poorer motor function and experience a more rapid motor deterioration.[49,50] Moreover, cortical atrophy in the frontal lobe is associated with unfavorable motor outcomes following STN-DBS.[51] The frontostriatal network is actively engaged in various cognitive processes, such as attention and decision-making, which are crucial for motor planning and the proper execution of sequential movements.[52] Accordingly, a frontal impairment may significantly contribute to the progressive deterioration and decremental response of bradykinesia to STN-DBS but not rigidity, by impairing motor planning and, consequently, the ability to voluntarily initiate and execute repetitive movements in PD. In summary, baseline motor impairment and frontal dysfunction emerge as primary clinical factors for predicting both short- and long-term outcomes of bradykinesia and rigidity in PD patients undergoing STN-DBS. The subgroup of patients with a more favorable prognosis in terms of rigidity and bradykinesia, therefore, consists of those with milder motor signs and more preserved executive abilities before surgery.

When considering the present findings, it is important to acknowledge some limitations. First, like previous longitudinal analyses,[21,53] our study lacks a control group of subjects under the best medical treatment and without STN-DBS, thus precluding clarification of the isolated effects of STN-DBS on bradykinesia and rigidity. Second, we only considered the optimized treatment conditions (ie, the ON medication condition before surgery and the ON medication/ON stimulation condition after surgery) in our cohort of patients, thus preventing the possibility of clearly separating the effects of pharmacological and surgical treatments as well as disease progression per se. Yet, it would have been highly challenging to expose our patients with advanced PD to the poorly tolerated condition of OFF medication and/or OFF stimulation (considering also the lack of consensus about the duration of OFF time needed before evaluation, and the risk of severe STN-DBS withdrawal syndrome[54]). Nevertheless, we are confident that the prominent postoperative LEDD reduction and the known dopamine receptor desensitization following continuous STN stimulation limited the impact of this possible confounding, thus enhancing the reliability of our results. Lastly, a "floor effect" may have statistically biased the identification of accurate predictors for rigidity, resulting in reduced variability. This may have limited the ability to uncover significant relationships between variables and potentially led to under- or overestimated associations (eg, the MDRS). Nevertheless, the inclusion of a relevant number of subjects enrolled from the same clinical center increased the generalizability of the observations and reduced possible methodological heterogeneity in clinical and experimental procedures. The long-term longitudinal assessment also allowed a clear investigation of time-related changes in bradykinesia and rigidity, thus controlling for inter-subject variability. Lastly, the independent examination of bradykinesia and rigidity in appendicular and axial regions prevented possible confounding related to the different rates of symptom progression according to body topography.

Conclusions

Bradykinesia and rigidity in PD have long been regarded as closely linked motor signs that share similar neural substrates, clinical evolution, and responses to treatments. This study demonstrates divergent clinical trajectories and distinct predictive factors of bradykinesia and rigidity in PD, suggesting partially different underlying mechanisms.

The observation of diverse clinical progression and predictors prompts a reevaluation of the involved neural networks, potentially leading to personalized treatment strategies tailored to specific motor signs. This hypothesis requires further longitudinal investigations also comparing implanted and nonimplanted PD patients tested in various pharmacological conditions. Future studies should also consider postoperative factors associated with therapeutic outcomes, including changes in the total electrical energy delivered as well as current steering. Coupling model predictions of the volume of tissue activated in the brain to symptom outcomes could help further clarify the specific pathophysiology underlying rigidity and bradykinesia in PD. Moreover, the potential impact of disease progression on brain structure and DBS efficacy should not be overlooked. If atrophy increases over time, coupled with increased stimulation parameters, it may lead to a broader spread of current to surrounding areas, thus affecting different neural pathways and potentially contributing to differential effects on symptoms. Hence, exploring the interplay between disease progression, structural changes, and stimulation parameters is a crucial perspective for a comprehensive understanding of the observed outcomes. Lastly, the potential implication of specific genetic profiles for bradykinesia and rigidity outcomes should be evaluated by considering large cohorts of patients carrying known genetic mutations. This approach could provide valuable insights into the differential responses to STN-DBS and inform personalized treatment strategies by tailored interventions.

Acknowledgments

The authors extend their sincere gratitude to P. Pollak, P. Limousin, C. Ardouin, P. Krack, and A. L. Benabid for their invaluable contributions to the medical care provided to the participants involved in this study. There was no funding for the present study.

Author Contributions

A.Z., A.S., and E.M. contributed to the conception and design of the study. A.Z., F.B., F.C., A.C., S.M., P.P., E.S., S.C., and V.F. contributed to the acquisition and analysis of data. All authors contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

E.M. has received honoraria for consulting services from Medtronic and Abbott, as well as grant support from France Parkinson, Ipsen, and Boston Medical. A.C. has received research grants from France Parkinson. V.F. has received honoraria from AbbVie and Medtronic for consulting services and lecturing.

Data Availability

The dataset used in this study can be obtained from the corresponding author upon reasonable request. Access to sensitive data will be restricted to preserve privacy.

References

1. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 2015;30:1591–1601. https://doi.org/10.1002/mds.26424.
2. Abusrair AH, Elsekaily W, Bohlega S. Tremor in Parkinson's disease: from pathophysiology to advanced therapies. Tremor Other Hyperkinet Mov 2022;12:29. https://doi.org/10.5334/tohm.712.
3. Poston KL, Ua Cruadhlaoich MAI, Santoso LF, et al. Substantia Nigra volume dissociates bradykinesia and rigidity from tremor in Parkinson's disease: a 7 tesla imaging study. J Parkinsons Dis 2020; 10:591–604. https://doi.org/10.3233/JPD-191890.
4. Frequin HL, Schouten J, Verschuur CVM, et al. Levodopa response in patients with early Parkinson disease: further observations of the LEAP study. Neurology 2023;100:e367–e376. https://doi.org/10.1212/WNL.0000000000201448.
5. Kühn AA, Tsui A, Aziz T, et al. Pathological synchronisation in the subthalamic nucleus of patients with Parkinson's disease relates to both bradykinesia and rigidity. Exp Neurol 2009;215:380–387. https://doi.org/10.1016/j.expneurol.2008.11.008.
6. Pingale T, Gupta GL. Classic and evolving animal models in Parkinson's disease. Pharmacol Biochem Behav 2020;199:173060. https://doi.org/10.1016/j.pbb.2020.173060.
7. de Hemptinne C, Swann NC, Ostrem JL, et al. Therapeutic deep brain stimulation reduces cortical phase-amplitude coupling in Parkinson's disease. Nat Neurosci 2015;18:779–786. https://doi.org/10.1038/nn.3997.
8. Michely J, Volz LJ, Barbe MT, et al. Dopaminergic modulation of motor network dynamics in Parkinson's disease. Brain 2015;138:664–678. https://doi.org/10.1093/brain/awu381.
9. Moënne-Loccoz C, Astudillo-Valenzuela C, Skovgård K, et al. Cortico-striatal oscillations are correlated to motor activity levels in both physiological and parkinsonian conditions. Front Syst Neurosci 2020;14. https://doi.org/10.3389/fnsys.2020.00056.
10. Wilkins KB, Kehnemouyi YM, Petrucci MN, et al. Bradykinesia and its progression are related to interhemispheric Beta coherence. Ann Neurol 2023;93:1029–1039. https://doi.org/10.1002/ana.26605.
11. Asci F, Falletti M, Zampogna A, et al. Rigidity in Parkinson's disease: Evidence from biomechanical and neurophysiological measures. Brain 2023;146(9):3705–3718. https://doi.org/10.1093/brain/awad114.
12. Delwaide PJ, Pepin JL, De Pasqua V, de Noordhout AM. Projections from basal ganglia to tegmentum: a subcortical route for explaining the pathophysiology of Parkinson's disease signs? J Neurol 2000; 247 Suppl 2:II75–II81. https://doi.org/10.1007/pl00007765.
13. Linn-Evans ME, Petrucci MN, Amundsen Huffmaster SL, et al. REM sleep without atonia is associated with increased rigidity in patients with mild to moderate Parkinson's disease. Clin Neurophysiol 2020; 131:2008–2016. https://doi.org/10.1016/j.clinph.2020.04.017.
14. Boutet A, Germann J, Gwun D, et al. Sign-specific stimulation "hot" and "cold" spots in Parkinson's disease validated with machine learning. Brain Commun 2021;3:fcab027. https://doi.org/10.1093/braincomms/fcab027.

15. Hilliard JD, Frysinger RC, Elias WJ. Effective subthalamic nucleus deep brain stimulation sites may differ for tremor, bradykinesia and gait disturbances in Parkinson's disease. Stereotact Funct Neurosurg 2011;89:357–364. https://doi.org/10.1159/000331269.

16. Neumann WJ, Horn A, Kühn AA. Insights and opportunities for deep brain stimulation as a brain circuit intervention. Trends Neurosci 2023;46:472–487. https://doi.org/10.1016/j.tins.2023.03.009.

17. Wright WG, Gurfinkel VS, Nutt J, et al. Axial hypertonicity in Parkinson's disease: direct measurements of trunk and hip torque. Exp Neurol 2007;208:38–46. https://doi.org/10.1016/j.expneurol.2007.07.002.

18. Zampogna A, Mileti I, Martelli F, et al. Early balance impairment in Parkinson's disease: evidence from robot-assisted axial rotations. Clin Neurophysiol 2021;132:2422–2430. https://doi.org/10.1016/j.clinph.2021.06.023.

19. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–184. https://doi.org/10.1136/jnnp.55.3.181.

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

21. Lau B, Meier N, Serra G, et al. Axial symptoms predict mortality in patients with Parkinson disease and subthalamic stimulation. Neurology 2019;92:e2559–e2570. https://doi.org/10.1212/WNL.0000000000007562.

22. Zampogna A, Cavallieri F, Bove F, et al. Axial impairment and falls in Parkinson's disease: 15 years of subthalamic deep brain stimulation. NPJ Parkinsons Dis 2022;8:121. https://doi.org/10.1038/s41531-022-00383-y.

23. Pillon B, Gouider-Khouja N, Deweer B, et al. Neuropsychological pattern of striatonigral degeneration: comparison with Parkinson's disease and progressive supranuclear palsy. J Neurol Neurosurg Psychiatry 1995;58:174–179.

24. Goetz CG, Stebbins GT, Tilley BC. Calibration of unified Parkinson's disease rating scale scores to Movement Disorder Society-unified Parkinson's disease rating scale scores. Mov Disord 2012;27:1239–1242. https://doi.org/10.1002/mds.25122.

25. Schiess MC, Zheng H, Soukup VM, et al. Parkinson's disease subtypes: clinical classification and ventricular cerebrospinal fluid analysis. Parkinsonism Relat Disord 2000;6:69–76. https://doi.org/10.1016/s1353-8020(99)00051-6.

26. Agostino R, Berardelli A, Currà A, et al. Clinical impairment of sequential finger movements in Parkinson's disease. Mov Disord 1998;13:418–421. https://doi.org/10.1002/mds.870130308.

27. Ricciardi L, De Angelis A, Marsili L, et al. Hypomimia in Parkinson's disease: an axial sign responsive to levodopa. Eur J Neurol 2020;27:2422–2429. https://doi.org/10.1111/ene.14452.

28. Franzén E, Paquette C, Gurfinkel VS, et al. Reduced performance in balance, walking and turning tasks is associated with increased neck tone in Parkinson's disease. Exp Neurol 2009;219:430–438. https://doi.org/10.1016/j.expneurol.2009.06.013.

29. Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. Fam Med Community Health 2020;8:e000262. https://doi.org/10.1136/fmch-2019-000262.

30. Hosmer D, Lemeshow S, Sturdivant R. Applied Logistic Regression, 2013. https://onlinelibrary.wiley.com/doi/epub/10.1002/9781118548387. Accessed September 7, 2023.

31. Aviles-Olmos I, Kefalopoulou Z, Tripoliti E, et al. Long-term outcome of subthalamic nucleus deep brain stimulation for Parkinson's disease using an MRI-guided and MRI-verified approach. J Neurol Neurosurg Psychiatry 2014;85:1419–1425. https://doi.org/10.1136/jnnp-2013-306907.

32. Golfrè Andreasi N, Romito LM, Telese R, et al. Short- and long-term motor outcome of STN-DBS in Parkinson's disease: focus on sex differences. Neurol Sci 2022;43:1769–1781. https://doi.org/10.1007/s10072-021-05564-w.

33. Lilleeng B, Gjerstad M, Baardsen R, et al. Motor symptoms after deep brain stimulation of the subthalamic nucleus. Acta Neurol Scand 2015;131:298–304. https://doi.org/10.1111/ane.12342.

34. Akram H, Sotiropoulos SN, Jbabdi S, et al. Subthalamic deep brain stimulation sweet spots and hyperdirect cortical connectivity in Parkinson's disease. Neuroimage 2017;158:332–345. https://doi.org/10.1016/j.neuroimage.2017.07.012.

35. Averna A, Debove I, Nowacki A, et al. Spectral topography of the subthalamic nucleus to inform next-generation deep brain stimulation. Mov Disord 2023;38:818–830. https://doi.org/10.1002/mds.29381.

36. Dembek TA, Roediger J, Horn A, et al. Probabilistic sweet spots predict motor outcome for deep brain stimulation in Parkinson disease. Ann Neurol 2019;86:527–538. https://doi.org/10.1002/ana.25567.

37. Hacker ML, Rajamani N, Neudorfer C, et al. Connectivity profile for subthalamic nucleus deep brain stimulation in early stage Parkinson disease. Ann Neurol 2023;94:271–284. https://doi.org/10.1002/ana.26674.

38. Plantinga BR, Temel Y, Duchin Y, et al. Individualized parcellation of the subthalamic nucleus in patients with Parkinson's disease with 7T MRI. Neuroimage 2018;168:403–411. https://doi.org/10.1016/j.neuroimage.2016.09.023.

39. Moro E, Esselink RJA, Xie J, et al. The impact on Parkinson's disease of electrical parameter settings in STN stimulation. Neurology 2002;59:706–713. https://doi.org/10.1212/wnl.59.5.706.

40. Bingham CS, McIntyre CC. Subthalamic deep brain stimulation of an anatomically detailed model of the human hyperdirect pathway. J Neurophysiol 2022;127:1209–1220. https://doi.org/10.1152/jn.00004.2022.

41. Johansson JD. Estimation of electric field impact in deep brain stimulation from axon diameter distribution in the human brain. Biomed Phys Eng Express 2021;7:065033. https://doi.org/10.1088/2057-1976/ac2dd4.

42. Ranck JB. Which elements are excited in electrical stimulation of mammalian central nervous system: a review. Brain Res 1975;98:417–440. https://doi.org/10.1016/0006-8993(75)90364-9.

43. Strotzer QD, Anthofer JM, Faltermeier R, et al. Deep brain stimulation: connectivity profile for bradykinesia alleviation. Ann Neurol 2019;85:852–864. https://doi.org/10.1002/ana.25475.

44. Johnson MD, Zhang J, Ghosh D, et al. Neural targets for relieving parkinsonian rigidity and bradykinesia with pallidal deep brain stimulation. J Neurophysiol 2012;108:567–577. https://doi.org/10.1152/jn.00039.2012.

45. Panyakaew P, Duangjino K, Kerddonfag A, et al. Exploring the complex phenotypes of impaired finger dexterity in mild-to-moderate stage Parkinson's disease: a time-series analysis. J Parkinsons Dis 2023;13:977–990. https://doi.org/10.3233/JPD-230029.

46. Shinoda Y, Sugiuchi Y, Izawa Y, Hata Y. Long descending motor tract axons and their control of neck and axial muscles. Prog Brain Res 2006;151:527–563. https://doi.org/10.1016/S0079-6123(05)51017-3.

47. Cavallieri F, Fraix V, Bove F, et al. Predictors of long-term outcome of subthalamic stimulation in Parkinson disease. Ann Neurol 2021;89:587–597. https://doi.org/10.1002/ana.25994.

48. Lachenmayer ML, Mürset M, Antih N, et al. Subthalamic and pallidal deep brain stimulation for Parkinson's disease-meta-analysis of outcomes. NPJ Parkinsons Dis 2021;7:77. https://doi.org/10.1038/s41531-021-00223-5.

49. Clissold BG, McColl CD, Reardon KR, et al. Longitudinal study of the motor response to levodopa in Parkinson's disease. Mov Disord 2006;21:2116–2121. https://doi.org/10.1002/mds.21126.

50. Moustafa AA, Chakravarthy S, Phillips JR, et al. Interrelations between cognitive dysfunction and motor symptoms of Parkinson's disease: behavioral and neural studies. Rev Neurosci 2016;27:535–548. https://doi.org/10.1515/revneuro-2015-0070.

51. Muthuraman M, Deuschl G, Koirala N, et al. Effects of DBS in parkinsonian patients depend on the structural integrity of frontal cortex. Sci Rep 2017;7:43571. https://doi.org/10.1038/srep43571.

52. Haber SN. Corticostriatal circuitry. Dialogues Clin Neurosci 2016;18:7–21.

53. Bove F, Mulas D, Cavallieri F, et al. Long-term outcomes (15 years) after subthalamic nucleus deep brain stimulation in patients with Parkinson disease. Neurology 2021;97(3):e254–e262. https://doi.org/10.1212/WNL.0000000000012246.

54. Reuter S, Deuschl G, Falk D, et al. Uncoupling of dopaminergic and subthalamic stimulation: life-threatening DBS withdrawal syndrome. Mov Disord 2015;30:1407–1413. https://doi.org/10.1002/mds.26324.