Original research

Patients with symmetric Parkinson's disease do poorly with subthalamic stimulation

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ABSTRACT

Background Motor asymmetry is a hallmark of Parkinson's disease (PD), but ~20% of patients present with symmetric motor signs, which are associated with faster disease progression and poorer dopaminergic response. The impact of motor symmetry on activities of daily living (ADL) outcomes following subthalamic deep brain stimulation (STN-DBS) remains unclear. We hypothesised that patients with symmetric PD experience less ADL improvement post-STN-DBS than asymmetric PD patients.

Methods This was a prospective, quasi-experimental, non-randomised, controlled, international multicentre study with a 6-month follow-up. The primary outcome was the Scales for Outcomes in Parkinson's Disease-Motor ADL scale. Secondary outcomes included Unified Parkinson's Disease Rating Scale motor examination and Parkinson's Disease Questionnaire-8 (PDQ-8). We defined symmetric PD as a right-to-left hemibody motor score equalling 1. We analysed within-group longitudinal changes, between-group outcome differences, effect size and correlations between PDQ-8 and motor changes. We confirmed results in a propensity-score matched subcohort with well-balanced demographic and clinical parameters.

Results We included 200 patients with asymmetric and 54 with symmetric PD. In symmetric PD, ADL remained stable, which was not associated with the observed PDQ-8 improvement. In contrast, in asymmetric PD, ADL improved with a moderate effect size, which correlated moderately with PDQ-8 improvement. In symmetric PD, the absolute risk of experiencing no clinically relevant postoperative ADL improvement was 23.8% higher.

Conclusions This study provides class IIb evidence of worse ADL outcome of STN-DBS in patients with symmetric compared with asymmetric PD. Clinicians should counsel patients with symmetric PD on their elevated risk of ADL non-response when discussing STN-DBS as a treatment option.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Parkinson's disease (PD) is a heterogeneous condition, with most patients exhibiting asymmetric motor symptoms, while approximately 20% have a symmetric disease presentation. Symmetric PD is associated with faster disease progression and poorer response to dopaminergic therapy. Subthalamic deep brain stimulation (STN-DBS) improves quality of life, motor function and activities of daily living (ADL). ADL outcomes after STN-DBS are linked to the restoration of motor symmetry, but the impact of baseline motor symmetry on deep brain stimulation (DBS) outcomes has not been well-studied.

WHAT THIS STUDY ADDS

⇒ This prospective, multicentre study (n=254) provides class IIb evidence that patients with symmetric PD do not experience ADL improvements following STN-DBS, unlike those with asymmetric PD who show moderate ADL benefits. Patients with symmetric PD had a 23.8% higher absolute risk of not experiencing clinically relevant postoperative ADL improvement. ADL benefit correlated with quality of life improvement only in asymmetric PD, highlighting the differential effects of STN-DBS based on motor symmetry. Symmetric and asymmetric PD groups had comparable preoperative clinical characteristics, ruling out broad baseline differences as an explanation for the observed outcome disparity.

INTRODUCTION

Parkinson's disease (PD) is remarkably heterogeneous and while most patients with PD present with an asymmetric onset of motor symptoms starting contralateral to the nigrostriatal dopaminergic deficit, approximately 20% of patients display a symmetric disease onset.[1 2] Recent studies

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Clinical implications: preoperative motor symmetry assessments using a simple right-to-left hemibody motor score ratio (equal to 1 for symmetric PD) can help stratify ADL outcomes and refine patient selection criteria for STN-DBS. Patient counselling: clinicians should inform patients with symmetric PD about their higher risk of ADL non-response to STN-DBS, ensuring realistic expectations and personalised treatment planning. Future research: further studies are needed to investigate long-term DBS outcomes in symmetric PD and to explore whether alternative treatment strategies could improve ADL outcomes in this group.

have shown that in patients with symmetric PD, the progression of global non-motor and motor symptoms is faster than in patients with asymmetric PD.[3] Furthermore, fast-progressing patients with more symmetric PD respond worse to dopaminergic treatment.[3]

Subthalamic deep brain stimulation (STN-DBS) is a well-established treatment for patients with advanced PD, improving quality of life, motor impairment and activities of daily living (ADL).[4–7] Quality of life after subthalamic stimulation is influenced considerably by the ADL outcome,[6] which is in turn connected to the restoration of motor symmetry by STN-DBS.[8] Patients with symmetric PD have less potential to restore motor symmetry, so we hypothesised that they experience less ADL improvement following STN-DBS than patients with asymmetric PD. Additionally, we explored the relationship of clinical and demographic factors with motor symmetry to account for a potential confounding factor of differences in disease progression rates of the symmetric and asymmetric groups in our cohort.

MATERIALS AND METHODS

Design

In this prospective, quasi-experimental, non-randomised, controlled, international multicentre study with a 6-month follow-up, patients were consecutively enrolled in five deep brain stimulation (DBS) centres (Cologne, Marburg, London, Manchester and Toronto). Data were collected as part of the STN-DBS arm of the Non-motor International Longitudinal Study, an ongoing, prospective, international multicentre, longitudinal study in patients with PD.[9]

Participants

We diagnosed PD based on the UK Brain Bank and MDS clinical diagnostic criteria[10 11] and screened for DBS suitability following the Movement Disorders Society guidelines.[12] We determined DBS eligibility through multidisciplinary team assessments, including experts in movement disorders, stereotactic neurosurgeons, neuropsychologists, psychiatrists and speech therapists.[13 14] Patients with clinically relevant cognitive or mood disorders were considered unsuitable for DBS. DBS surgical procedures are described elsewhere.[15]

Classification of motor asymmetry

We classified motor asymmetry based on the asymmetry index developed by Cubo *et al*.[16] The asymmetry index was calculated by dividing the total score of SCOPA-M items for the dominant hemibody by the corresponding score of the non-dominant hemibody. Specifically, we used the following SCOPA-M motor items: (1) rest tremor, (2) postural tremor, (3) rapid alternating movements of the hands and (4) rigidity. Patients with an exact asymmetry index of 1 were classified as having symmetric PD, while all others (asymmetry index≠1) were classified as asymmetric PD. Cubo *et al* focused on gradations of asymmetry and excluded symmetric patients, whereas they included these patients. Additionally, we subdivided the asymmetric group into mild/moderate and severe asymmetry categories in a post hoc analysis to explore whether the degree of asymmetry influenced clinical outcomes.

Clinical assessment and outcome parameters

The following clinical assessments were conducted preoperatively in the MedON and at 6-month follow-up in the MedON and stimulation on state. The MedON was defined as at least 30 min after intake of dopaminergic medication, and after movement disorder neurologists and patients noted the best clinical improvement.[17] DBS settings with the largest therapeutic window were selected based on the highest threshold for side effects and the lowest threshold for improvement of tremor, rigidity and bradykinesia.[18]

Primary outcome parameter

- The primary outcome was the Scales for Outcomes in Parkinson's Disease-Motor scale (SCOPA-M) ADL score, which is recommended by the MDS for ADL assessments,[19] has been commonly used in STN-DBS studies[20–22] and ranges from 0 (no impairment) 21 (maximum impairment). In patients from the Toronto centre, SCOPA-M ADL items were extracted from the Unified Parkinson's Disease Rating Scale (UPDRS)-ADL scale (see online supplemental material) to ensure comparability with the other centres. The UPDRS-II is also commonly used in STN-DBS studies and both scales are highly correlated (r=0.88).[23–25]

Secondary outcome parameters

- Motor impairments and complications were assessed using the SCOPA-M motor examination scale.[26] The SCOPA-M is a well-established and validated short version of the UPDRS.[23] The SCOPA-M was chosen because its assessment time is approximately four times shorter than the MDS-UPDRS. Based on previously reported conversion methods,[23 27] the SCOPA-M motor examination results are reported as UPDRS-motor examination scores to enable comparisons with other studies. As published previously by our group,[28 29] we report the following SCOPA-M subscores: tremor, bradykinesia, axial symptoms, dysphagia and dysarthria, dyskinesia and motor fluctuations. This categorisation is based on a factor analysis by van Rooden *et al*,[30] which combines items from the motor examination and ADL sections of the SCOPA-M. Domain subscores were calculated by summing the relevant SCOPA-M items and dividing by the maximum possible score for the respective domain, resulting in percentage values (range: 0%–100%) to allow comparability across domains. Specifically, the tremor subscore included items 1 and 2 for both upper extremities; the bradykinesia subscore included items 3 and 4 for both sides; the axial symptoms score was composed of items 5, 6, 7, 9, 15 and 16. Dysarthria and dysphagia were based on items 8, 10 and 11; dyskinesia was derived from items 18 and 19; and motor fluctuations from items 20 and 21.

  Quality of life was measured using the Parkinson's Disease Questionnaire-8 (PDQ-8), a short form of the PDQ-39. Both versions produce strongly correlated results (r=0.96) when converted to a Summary Index.[31] Recommended for quality

of life evaluations by the Movement Disorders Society scales committee, the scale has been widely used in patients with PD[32] and those undergoing DBS.[33–36]

- The levodopa-equivalent daily dose (LEDD) was calculated using a method by Jost *et al*.[37]
- The total electrical energy delivered (TEED) was calculated according to a method by Koss *et al*,[38] with a standard impedance of 1000 Ω.[39]
- DBS lead locations were analysed based on preoperative MRI and postoperative CT scans referenced to the MNI space.[40 41]

Statistical analysis

Normal distribution was tested with the Shapiro-Wilk method. We categorised patients into the symmetric group when their asymmetry index was 1.[42 43] Differences in baseline characteristics between patients with symmetric and asymmetric PD were analysed using Mann-Whitney U tests and unpaired t-tests, when applicable. Within-group changes from baseline to 6-month follow-up were analysed using Wilcoxon signed-rank tests (or paired t-tests). Between-group differences of change scores (mean $test_{baseline}$ − mean $test_{follow\text{-}up}$) were tested using Mann-Whitney U tests and unpaired t-tests. P values were adjusted using the Benjamini-Hochberg procedure. Furthermore, to determine the strength of clinical responses, we calculated relative changes ((mean $test_{baseline}$ − mean $test_{follow\text{-}up}$)/mean $test_{baseline}$) and Cohen's d effect size with a method by Morris for pretest–post-test control group designs.[44] Also, we compared the proportion of patients who experience a clinically relevant improvement of ADL based on a previously published cohort-based cut-off (improvement by >1/2 $SD_{baseline}$)[45] and illustrated the postoperative ADL change of all patients' cumulative distribution functions as recommended by the US Food and Drug Administration.[46]

Additionally, we explored the relationship between change scores of the PDQ-8 Summary Index and changes in the motor aspect using Spearman correlations and partial correlations. The following parameters defined the correlation coefficient (r_s): very strong (≥0.70), strong (0.50–0.70), moderate (0.30–0.50) and weak (0.10–0.30).[47] To confirm the results of the asymmetric group, we explored categorising asymmetric patients into mildly/moderately and extremely asymmetric patients using an established classification method.[16]

Furthermore, we repeated analyses after excluding patients with ADL scores extracted from the UPDRS-ADL scale and reported both the full cohort and sensitivity analyses. Additionally, to corroborate the overall cohort results, we identified a subcohort of patients with well-balanced demographic and preoperative clinical parameters. We computed propensity score matching, implementing a 1:3 ratio for symmetric:asymmetric patients using optimal pair matching (package 'MatchIt' in R-studio, V.4.2.3) with the following baseline matching parameters: age at intervention, disease duration, UPDRS-motor examination, LEDD and SCOPA-M tremor score. We have published the matching method applied here previously.[5 28 48] The grade of evidence was rated following the classification used in the practice guidelines by the National Guideline Clearinghouse of the US Department of Health and Human Services,[49] which is commonly used in the field of PD and DBS research.[5 6 28 29 50]

RESULTS

Baseline characteristics in the overall cohort

We screened 293 consecutive patients undergoing STN-DBS for PD between July 2011 and October 2022 (see figure 1). Of these, 254 patients were included in the final analysis (90 female; mean age: 61.2 years±8.4, mean disease duration: 10.0 years±4.6). These patients were recruited from five DBS centres: Cologne (n = 153), Manchester (n = 30), Marburg (n = 28), London (n = 26) and Toronto (n = 17). The mean time to follow-up was 0.5 years±0.2 and the between-centre difference in time to follow-up was not significant (p>0.5). 54 patients (21.3%) were classified as symmetric, 200 as asymmetric (78.7%). In the asymmetric group, 99 patients had predominantly left-sided motor symptoms, and 101 had right-sided motor symptoms. In a subsample of 115 patients with available motor scores in the medication-off state at the preoperative baseline, patient classification did not differ significantly from classification results in the medication-on state (p=0.607).

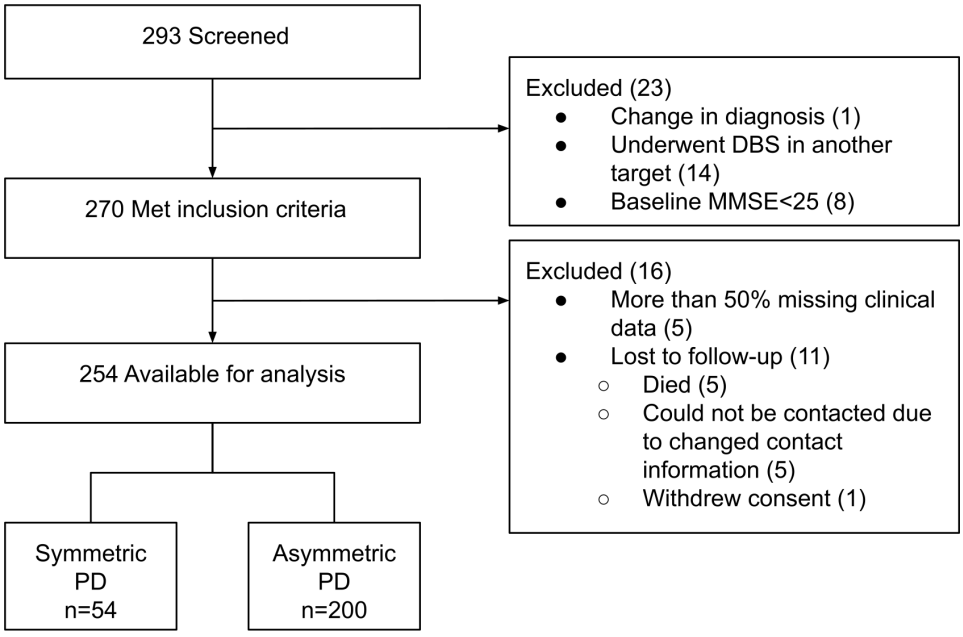

Figure 1 Enrolment. DBS, deep brain stimulation; MMSE, mini-mental state examination; PD, Parkinson's disease.

Table 1 Baseline characteristics in the overall cohort

Characteristic	Baseline		
	n	Mean	SD
Age at intervention	254	61.2	8.4
Disease duration	253	10.0	4.6
Sex (male/female) (%)	254	(164/90)	(64.6/35.4)
SCOPA-M			
Activities of daily living	251	6.9	3.4
Tremor (%)	254	14.8	18.6
Bradykinesia (%)	254	35.6	20.0
Axial symptoms (%)	252	27.4	17.1
Dysphagia and dysarthria (%)	251	21.7	16.0
Dyskinesia (%)	232	35.7	29.9
Fluctuations (%)	251	44.2	25.1
UPDRS-motor examination	254	24.6	12.0
PDQ-8 Summary Index	226	31.6	16.9
LEDD	252	1131.6	502.8

LEDD, levodopa-equivalent daily dose; PDQ-8, 8-item Parkinson's Disease Questionnaire; SCOPA-M, Scales for Outcomes in Parkinson's disease-Motor scale; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 1 presents clinical characteristics at preoperative baseline in the overall cohort. In the primary outcome analysis, SCOPA-M ADL improved from baseline to 6-month follow-up by 21.7% (SCOPA-M ADL $_{\text{baseline}}$: 6.9±3.4; SCOPA-M ADL $_{\text{follow-up}}$: 5.4±3.5; p<0.001). However, Cohen's d effect size was small (Cohen's d=0.44) and only 48.1% (116/241) of patients experienced a clinically relevant ADL improvement in the overall cohort (see online supplemental tables 1 and 2). The secondary outcomes UPDRS-motor examination and PDQ-8 Summary Index improved, and LEDD was reduced at follow-up. Exploring SCOPA-M subscales, only dysphagia and dysarthria did not improve.

Baseline characteristics in symmetric and asymmetric PD

Table 2 presents clinical baseline characteristics in patients with symmetric and asymmetric PD. In the symmetric group, 54 patients (22 women, 40.7%) were aged 63.3 years±7.5 with 10.4 years±4.6 disease duration. In the asymmetric group, 200 patients (68 women, 34.0%) were aged 60.7 years±8.5 with 9.9 years±4.7 disease duration. The asymmetry index was 1.0 for all patients in the symmetric PD group and ranged from 1.1 to 14.0 in the asymmetric PD group.

Comparing baseline characteristics between both groups, we observed a 6.2% more severe tremor score in the asymmetric group (p=0.006). All other clinical baseline characteristics and SCOPA-M subscores did not differ significantly between groups.

Clinical outcomes at 6-month follow-up

Table 3 reports longitudinal within-group changes and between-group differences. In the within-group analysis, the primary outcome, that is, the SCOPA-M ADL score, remained stable in the symmetric group. In contrast, it improved with a moderate effect size in the asymmetric group. In the between-group analysis, SCOPA-M ADL outcome was unfavourable in the symmetric group (change score of the symmetric group 0.3±3.4 and asymmetric group 1.8±3.5, p=0.007, see also online supplemental table 3). This effect was driven by the between-group outcome difference of the ADL items 'feeding' and 'walking' (see online supplemental table 4, 'feeding' change score of the symmetric group −0.06±0.79 and asymmetric group 0.41±0.78, p=0.001, and 'walking' change score symmetric group −0.10±0.83 and asymmetric group 0.15±0.84, p=0.034, see online supplemental table 4). In 17 patients from Toronto, ADL scores were extracted from the UPDRS-ADL scale. In a sensitivity analysis, we excluded these 17 patients and we confirmed the result of the overall cohort that ADL did not improve in the symmetric group, whereas it improved in the asymmetric group (see online supplemental table 5).

Table 2 Baseline characteristics in patients with symmetric and asymmetric motor symptoms of Parkinson's disease

Characteristic	Symmetric (n=54)			Asymmetric (n=200)			Symmetric vs asymmetric
	n	Mean	SD	n	Mean	SD	P value*
Age at intervention	54	63.3	7.5	200	60.7	8.5	0.051
Disease duration	54	10.4	4.6	200	9.9	4.7	0.462
Sex (male/female) (%)	54	(32/22)	(59.3/40.7)	200	132/68	(66.0/34.0)	0.358
SCOPA-M							
Activities of daily living	53	6.5	3.6	198	7.0	3.3	0.292
Tremor (%)	54	9.9	15.6	200	16.1	19.1	**0.006**
Bradykinesia (%)	54	35.5	22.0	200	35.7	19.5	0.991
Axial symptoms (%)	53	29.5	19.3	199	26.8	16.5	0.511
Dysphagia and dysarthria (%)	53	22.9	16.1	198	21.4	16.0	0.553
Dyskinesia (%)	50	36.0	29.6	182	35.6	30.1	0.988
Fluctuations (%)	53	45.6	24.9	198	43.8	25.1	0.721
UPDRS-motor examination	54	23.3	12.7	200	24.9	11.8	0.359
PDQ-8 Summary Index	49	33.0	18.5	177	31.2	16.5	0.690
LEDD	54	1158.4	526.5	198	1124.3	497.2	0.715

Symptom asymmetry was quantified using each patient's SCOPA-M subscores. The following items were used: (1) rest tremor, (2) postural tremor, (3) rapid alternating movement of hands, (4) rigidity. Right asymmetry was defined as having a quotient >1 after dividing the total score of right SCOPA-M subscores by the score of the left side. The same formula with the left motor scores was used to define left asymmetry. Right and left-sided Parkinson's disease patients were grouped as asymmetric. Patients with a quotient =1 were defined as symmetric. Statistically significant p-values are highlighted in bold.

*Mann-Whitney U tests between symmetric versus asymmetric patients.

LEDD, levodopa-equivalent daily dose; PDQ-8, 8-item Parkinson's Disease Questionnaire; SCOPA-M, Scales for Outcomes in Parkinson's disease-Motor scale; UPDRS, Unified Parkinson's Disease Rating Scale.

Table 3 Change in outcome parameters from baseline to 6-month follow-up in symmetric and asymmetric Parkinson's disease

	Symmetric			Asymmetric			Between-group differences
	Baseline vs 6-MFU			Baseline vs 6-MFU			Symmetric vs asymmetric*
Characteristic	n	Δmean	P value	n	Δmean	P value	P value
SCOPA-M							
Activities of daily living	52	−0.3	0.503	192	−1.9	**<0.001**	**0.007**
Tremor (%)	51	−1.9	0.404	186	−5.5	**<0.001**	0.092
Bradykinesia (%)	51	−6.6	**0.049**	186	−8.5	**<0.001**	0.437
Axial symptoms (%)	51	−5.0	0.073	184	−4.8	**<0.001**	0.945
Dysphagia and dysarthria (%)	51	0.0	0.880	184	−1.3	0.126	0.513
Dyskinesia (%)	50	−16.7	**<0.001**	184	−17.9	**<0.001**	0.764
Fluctuations (%)	53	−18.7	**<0.001**	190	−22.4	**<0.001**	0.303
UPDRS-motor examination	52	−3.7	**0.014**	186	−5.7	**<0.001**	0.173
PDQ-8 Summary Index	50	−5.3	**0.014**	175	−8.0	**<0.001**	0.330
LEDD	54	−590.2	**<0.001**	199	1124.3	**<0.001**	0.584

SCOPA-M ADL outcome differed between the symmetric and asymmetric group, with stable scores in the symmetric and improved outcome in the asymmetric group. Statistically significant p-values are highlighted in bold.
*Mann-Whitney U tests between outcome change scores in symmetric versus asymmetric PParkinson's disease.
ADL, activities of daily living; LEDD, levodopa-equivalent daily dose; 6-MFU, 6-month follow-up; PDQ-8, 8-item Parkinson's Disease Questionnaire; SCOPA-M, Scales for Outcomes in Parkinson's disease-Motor scale; UPDRS, Unified Parkinson's Disease Rating Scale.

To define a clinically relevant improvement in SCOPA-M ADL, we applied the distribution-based approach of 1/2 SD at baseline, resulting in a >1.7 point threshold for a clinically relevant ADL change (SD=3.4).[45] Figure 2 and online supplemental table 2 show that, based on this threshold for clinically relevant ADL improvement, only 29.4% (15/51) of patients in the symmetric group were classified as 'ADL responders', whereas this proportion was 53.2% (101/190) in the asymmetric group. Therefore, the absolute risk of ADL non-response was 23.8% lower in the asymmetric group compared with the symmetric PD group.

Regarding secondary outcomes, we observed improvements in the UPDRS-motor examination and PDQ-8 Summary Index and reductions of LEDD in both groups.

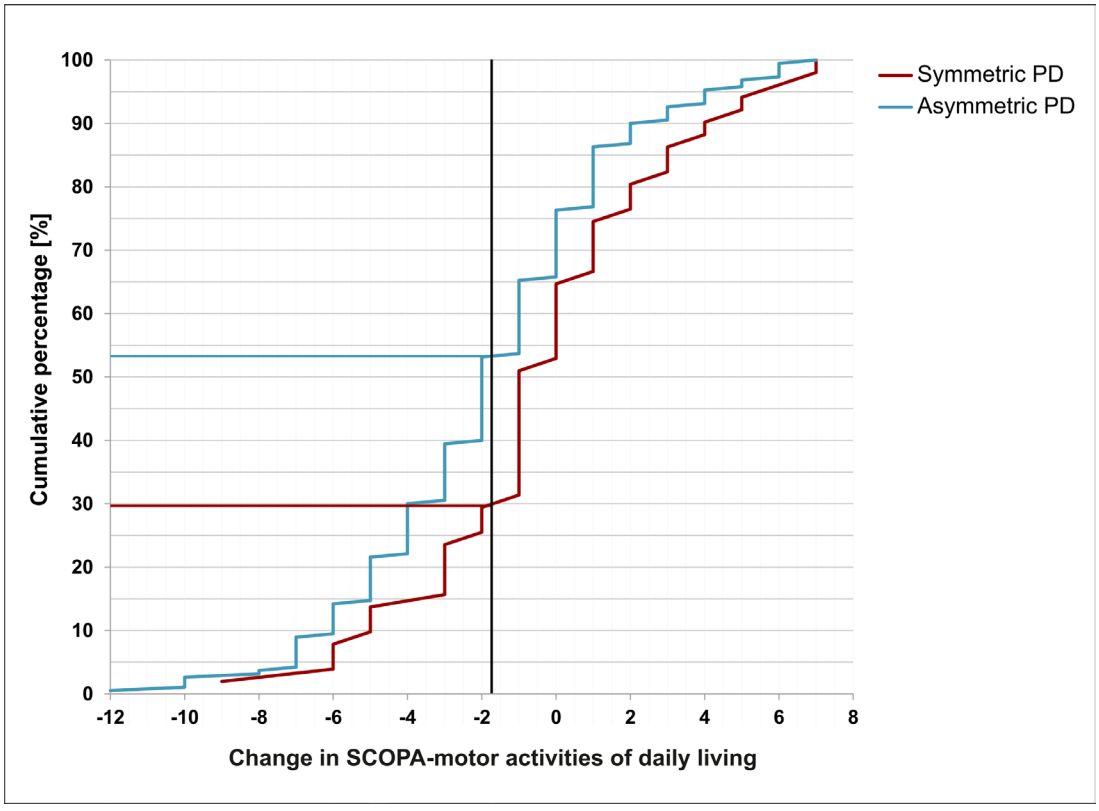

Figure 2 Cumulative distribution curves for SCOPA-M activities of daily living change following subthalamic stimulation stratified by motor symmetry/asymmetry. In cumulative distribution curves, negative values indicate improvement of SCOPA-M ADL from baseline to 6-month follow-up. The vertical black line marks the 1.7 point threshold for a clinically relevant change. ADL, activities of daily living; PD, Parkinson's disease; SCOPA-M, Scales for Outcomes in Parkinson's disease-Motor scale.

Post-hoc analysis of the SCOPA-M domains (see figure 3) showed that tremor and axial symptoms did not improve in the symmetric group, whereas they improved in the asymmetric group. In both groups, bradykinesia, dyskinesia and motor fluctuations improved, while dysarthria and dysphagia remained stable.

The magnitude of clinical changes at 6-month follow-up is presented in table 4. SCOPA-M ADL and tremor outcomes were unfavourable in the symmetric group with a small effect size difference. Other effect size differences were negligible.

Table 5 displays Spearman correlations between change scores of the PDQ-8 Summary Index and motor aspects of PD (see also online supplemental table 6). In the symmetric group, changes in the PDQ-8 Summary Index were not correlated with SCOPA-M ADL or other motor aspects. In contrast, in the asymmetric group, PDQ-8 Summary Index and SCOPA-M ADL changes correlated moderately (r_s=0.37, p<0.001), and this relationship was still observed when controlling for changes of the SCOPA-M tremor subscore in partial correlations (r_s=0.35, p<0.001). Of note, changes in the PDQ-8 Summary Index and motor fluctuations and dyskinesia were not correlated in the symmetric and asymmetric groups.

Furthermore, changes of ADL and UPDRS-motor examination changes and SCOPA-M motor fluctuations were not associated in the symmetric group, whereas they weakly correlated in the asymmetric group (changes of ADL and UPDRS-motor examination: r_s=0.21, p=0.005; changes of ADL and motor fluctuations: r_s=0.25, p<0.001).

The mean TEED at 6-month follow-up was 42.0 μJ/s±28.6 in the symmetric group and 54.5 μJ/s±46.9 in the asymmetric group. The TEED did not differ significantly between groups (p=0.292). DBS electrode tip position coordinates for the left and right electrodes did not differ significantly in x, y and z axis between groups (all p>0.05, see online supplemental table 7).

Baseline tremor scores differed between the symmetric and asymmetric groups in the overall cohort. Therefore, we explored outcomes after propensity score matching, which resulted in a subcohort with well-balanced demographic and preoperative clinical parameters, including tremor scores (symmetric n=54; asymmetric n=162). The results of the propensity score-matched subcohort confirmed the observation in the overall cohort that ADL did not improve in the symmetric group. In contrast, it improved in the asymmetric group (see online supplemental tables 8 and 9).

In an additional explorative analysis, we categorised patients with asymmetric PD based on their asymmetry index into the groups mildly/moderately and extremely asymmetric and observed that ADL improved in both groups (mild-moderate asymmetric: baseline 7.1±3.5, 6-month follow-up 5.1±3.4, p<0.001; extreme asymmetric: baseline 6.6±2.8, 6-month follow-up 5.2±3.4, p=0.006; see online supplemental tables 10 and 11).

DISCUSSION

This prospective, quasi-experimental, non-randomised, controlled, international multicentre study with 254 patients undergoing STN-DBS for PD provides class IIb evidence that patients with symmetric PD show no improvement in ADL, whereas those with asymmetric PD experience ADL benefits. Furthermore, in patients with symmetric PD, the postoperative ADL change was not associated with the observed quality of life improvement. In contrast, in asymmetric PD, the improvements in these outcomes were moderately correlated, highlighting this finding's clinical relevance.

In our cohort of advanced PD, 54 of 254 patients (21.3%) were categorised into the symmetric motor symptoms group, which is well in line with the literature (19.7%–29.3%).[1 51] Following STN-DBS, ADL improved by 21.7% in our overall cohort, which aligns well with previous studies ranging from 17.0% to 82.0%.[52 53]

The main result of our study, no postoperative ADL improvement in patients with symmetric PD, adds to the findings of a previous study, which reported beneficial DBS motor outcomes due to a restoration of symmetry.[8] The restoration of symmetry can only be assessed a posteriori for individual patients, whereas our present study compared ADL outcomes in patients categorised into a symmetric or asymmetric group at baseline based on a predefined and well-established cut-off (asymmetry index=1 indicating symmetric motor signs of PD).

At the preoperative baseline, we observed no differences between patients with symmetric and asymmetric PD in the demographic parameters age, disease duration and sex, and in the clinical parameters ADL, quality of life, motor impairment, motor complications and medication requirements. This finding indicates that their total motor disease progression was similar at the time of surgery. Motor complications, as the most common indication for DBS, were comparable at baseline in both groups. In a previous study examining a general PD population without DBS treatment, a symmetrical distribution was associated with worse severity of motor and non-motor symptoms and higher medication requirements.[54] However, this was explained by confounding factors, such as a higher age and longer disease duration in the symmetric group.[54] In this context, age and disease duration were comparable in the symmetric and asymmetric PD groups. This probably results from our DBS cohort being highly selected through strict preoperative indication evaluations. Therefore, the results of our DBS cohort cannot be applied to other device-aided therapies, for example, infusion therapies, as these typically apply other inclusion criteria.[55]

The only observed baseline difference in our cohort was a more severe tremor score in the asymmetric group, which aligns with the general PD and DBS literature.[8 54]

At the 6-month follow-up, we observed unfavourable DBS outcomes in the symmetric group with less beneficial effects on ADL, tremor and axial symptom score. In contrast, these symptoms improved in the asymmetric group. Additionally, we observed smaller effect sizes in the symmetric group for improvements in the UPDRS-motor examination and SCOPA-M fluctuations scores. The greater clinical efficacy of DBS on motor examination and motor fluctuations in asymmetric PD may explain that only in this group, improvements of these motor aspects were related to ADL improvements, which in turn were moderately associated with quality of life improvement.

In symmetric PD, quality of life gains were not linked to motor improvements (dyskinesia, motor fluctuations and UPDRS-motor examination), suggesting that non-motor effects may contribute and warrant targeted evaluation in future studies. In this context, it is important to emphasise that quality of life improved in both groups, with no statistically significant difference between patients with symmetric and asymmetric PD. This highlights that motor symmetry should be seen as one component in the multifactorial evaluation of DBS outcomes. Notably, only 53.2% of patients in our asymmetric PD group, respectively, only 48.1% in our overall cohort, experienced a clinically important postoperative ADL improvement. These findings

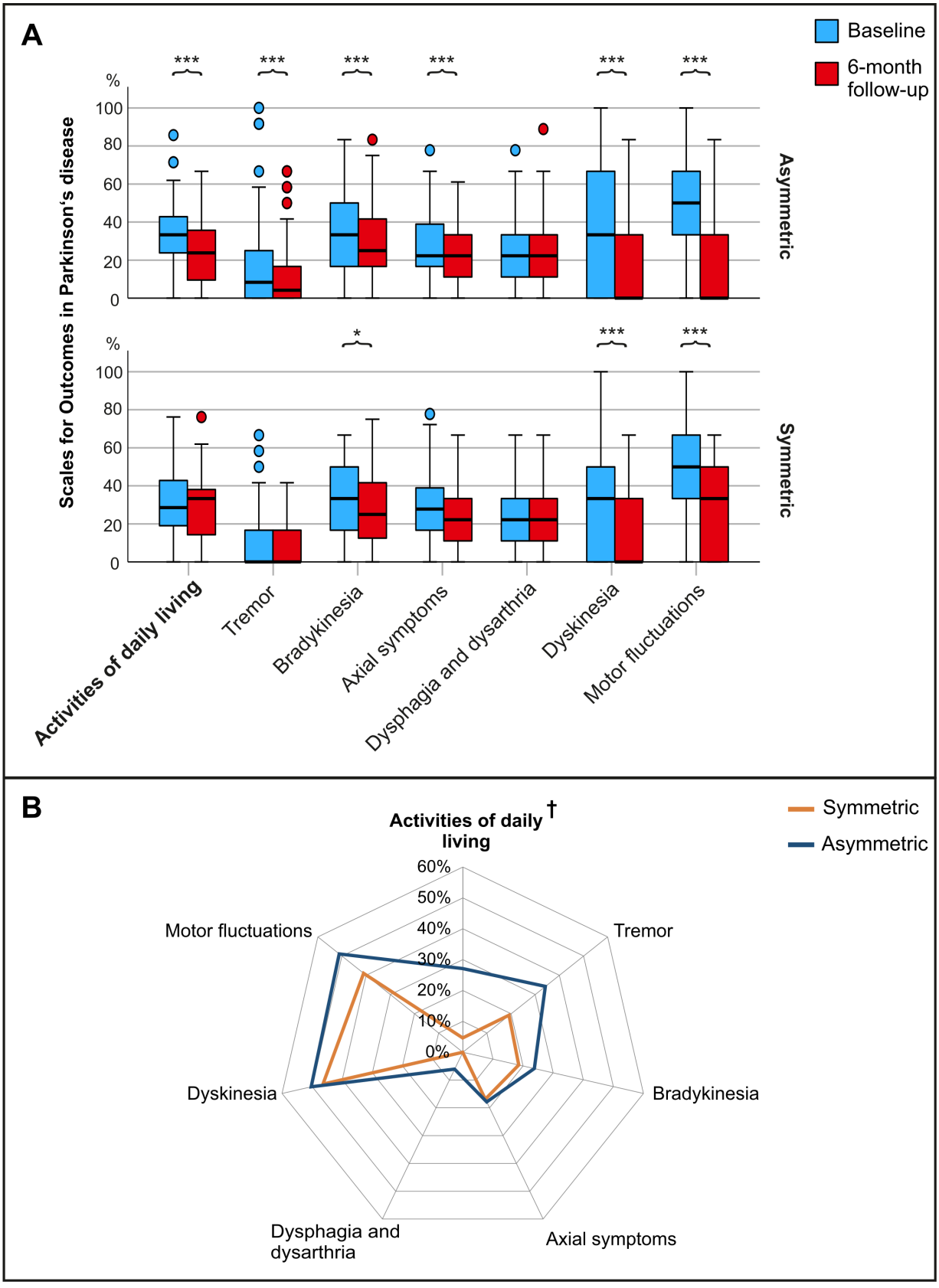

Figure 3 Scales for Outcomes in Parkinson's disease-Motor scale (SCOPA-M) domains at baseline and 6-month follow-up for symmetric and asymmetric Parkinson's disease (PD) in clustered boxplots (A) and relative changes of SCOPA-M domains in a radar chart (B). (A) SCOPA-M domains at baseline (blue) and 6-month follow-up (red) for symmetric and asymmetric PD in clustered boxplots. Significant within-group changes of SCOPA-M domains from baseline to 6-month follow-up are highlighted with asterisks. Outliers are illustrated with dots (2–3 SD). (B) Relative changes of SCOPA-M domains at 6-month follow-up. Bigger areas represent greater improvements. Significant between-group differences between symmetric and asymmetric patients are highlighted with a dagger.

Table 4 Relative changes and effect sizes from baseline to 6-month follow-up and differences between symmetric and asymmetric Parkinson's disease

	Within-group changes at 6-month follow-up						Between-group differences symmetric vs asymmetric	
	Relative change (%)		Symmetric		Asymmetric			
Characteristic	Symmetric	Asymmetric	ES	Classification	ES	Classification	ES	Classification
SCOPA-M								
Activities of daily living	4.6	27.1	0.08	–	0.75	Moderate	0.46	Small favouring asymmetric
Tremor (%)	19.2	34.2	0.14	–	0.31	Small	0.21	Small favouring asymmetric
Bradykinesia (%)	18.6	23.8	0.31	Small	0.45	Small	0.09	–
Axial symptoms (%)	16.9	17.9	0.27	Small	0.30	Small	0.01	–
Dysphagia and dysarthria (%)	0.0	6.1	0.00	–	0.08	–	0.08	–
Dyskinesia (%)	46.4	50.3	0.63	Moderate	0.65	Moderate	0.04	–
Fluctuations (%)	41.0	51.1	0.74	Moderate	0.90	Large	0.15	–
UPDRS-motor examination	15.9	22.9	0.33	Small	0.52	Moderate	0.16	–
PDQ-8 Summary Index	16.1	25.6	0.30	Small	0.48	Small	0.15	–
LEDD	50.9	47.7	1.33	Large	1.21	Large	0.10	–

Relative change=(mean $test_{baseline}$–mean $test_{follow\text{-}up}$)/mean $test_{baseline}$×100.
Cohen's effect size=(mean $test_{baseline}$–mean $test_{follow\text{-}up}$)/SD $test_{pooled}$.
Cohen's effect size for differences in change scores between symmetric and asymmetric Parkinson's disease=(mean pre-post $change_{symmetric}$–mean pre-post $change_{asymmetric}$)/SD $pretest_{pooled\ groups}$ calculated with the effect size d according to Morris.[44]
Cohen's effect size d can be classified as 'small' (0.20≥d<0.50), 'moderate' (0.50≥d<0.80) and 'large' (d≥0.80).
ES, effect size; LEDD, levodopa-equivalent daily dose; PDQ-8, 8-item Parkinson's Disease Questionnaire; SCOPA-M, Scales for Outcomes in Parkinson's diseaseMotor scale; UPDRS, Unified Parkinson's Disease Rating Scale.

underline the need for realistic expectations and nuanced counselling of all DBS candidates.

Since LEDD, TEED and electrode placements were comparable in both groups, the observed differences in clinical outcomes of patients with symmetric and asymmetric PD cannot be explained by pharmacological treatment and neurostimulation.

A possible explanation for the differential effects is that PD pathology could be more advanced globally in the symmetric group, which may decrease the stimulation effectiveness.[56] However, as clinical surrogate parameters for global disease progression, such as disease duration, age, UPDRS-motor examination and motor complications, were comparable between groups, this explanation seems less likely. Another possible reason may be that the damage specifically to the motor system in basal ganglia-thalamo-cortical loops is less extensive in asymmetric PD because the hemisphere ipsilateral to the more severely affected body side is relatively preserved.[56 57] Closely related, these differences in unihemispheric versus bihemispheric damage patterns could result in differences in brain network flexibility and responsiveness to network changes resulting from neuromodulation.

The neurophysiological basis of symptom asymmetry in PD is still not fully understood.[58] Possible mechanisms include genetic, structural or environmental causes for motor asymmetry.[59] For instance, inherent differences in the number of nigral dopaminergic neurons in each hemisphere might lead to an uneven dopamine distribution on both sides from birth.[59] Another plausible explanation is the body-first and brain-first PD hypothesis.[56] In body-first PD, it is proposed that the pathology in body-first patients originates in the enteric nervous system and ascends bilaterally, leading to a more symmetric involvement of the substantia nigra, resulting in more symmetric motor signs.[60]

Table 5 Spearman correlations between change scores of PDQ-8 Summary Index and motor changes scores

	PDQ-8 Summary Index					
	Overall cohort		Symmetric		Asymmetric	
Characteristic	r_s	P value	r_s	P value	r_s	P value
SCOPA-M						
Activities of daily living	**0.27*****	<0.001	–0.10	0.545	**0.38*****	<0.001
Tremor (%)	**0.19****	0.006	0.16	0.290	**0.20***	0.015
Bradykinesia (%)	**0.18***	0.011	0.17	0.260	**0.18***	0.029
Axial symptoms (%)	**0.22****	0.002	0.15	0.314	**0.24****	0.003
Dysphagia and dysarthria (%)	**0.20****	0.005	–0.15	0.329	**0.30*****	<0.001
Dyskinesia (%)	–0.01	0.862	–0.11	0.463	0.02	0.797
Fluctuations (%)	0.06	0.379	0.14	0.346	0.04	0.665
UPDRS-III	**0.26*****	<0.001	0.23	0.118	**0.26****	0.001

Correlation coefficients for significant results are highlighted in bold.
*p<0.050.
**p<0.010.
***p<0.001.
PDQ-8, Parkinson's Disease Questionnaire-8; SCOPA-M, Scales for Outcomes in Parkinson's Disease-Motor scale; UPDRS, Unified Parkinson's Disease Rating Scale.

In contrast, in brain-first PD, it is postulated that the pathology appears unilaterally in the central nervous system and initially affects the ipsilateral structures more, resulting in more asymmetric motor signs.[56] A clinically relevant research question could be whether DBS is clinically efficacious in patients with body-first PD despite more extensive spread of pathological alterations, for example, in the autonomic and somatic peripheral nervous system. To our knowledge, no study has directly examined DBS outcomes in relation to the body-first versus brain-first classification. Future studies incorporating imaging correlates or molecular biomarkers may help determine whether these brain-first and body-first subtypes differentially respond to DBS. Moving forward, future studies should implement a multidimensional approach that integrates clinical and lateralised neuropsychological assessments with biomarker assessments and advanced statistical analyses in prospective, multicentre designs to clarify how motor symmetry/asymmetry relates not only to motor severity but also to the profile, severity and progression of non-motor symptoms, thereby enabling more personalised management.

Irrespective of symmetry status, STN-DBS should be embedded in structured, goal-directed rehabilitation (task-specific occupational and physical therapy) and focus on balance and strength, cueing and dual-task training with iterative programming and medication optimisation. In ADL non-responders, we advocate multidisciplinary intensive rehabilitation blocks.[61–63]

Limitations

Some limitations must be considered when interpreting our results. The primary research question of this study did not address DBS outcome differences resulting from laterality (left vs right hemibody PD) but from symmetry (symmetric vs asymmetric PD). Hence, our study's method of determining symmetry was based on the asymmetry index, which is a well-established method.[42 43] A limitation regarding this classification method in our study is that we used baseline motor scores in the medication on state (MedON). An assessment in the medication off state (MedOFF) would have been preferable to reduce potential confounding factors. Standardised MedOFF motor assessments were available from a subsample of 115 patients and indicated no difference from MedON assessments of symmetry. Furthermore, although the cohort size was one of the largest in studies of its kind (n=254), the symmetric group was relatively small (n=54), limiting statistical power and subgroup analyses with more advanced statistical methods. However, effect size classifications of within-group changes at 6-month follow-up were larger in the asymmetric group for a range of clinical outcomes, including ADL, tremor, motor examination and motor fluctuations, which indicates that the favourable effects of STN-DBS in the asymmetric PD group resulted from the observed greater clinical efficacy and not from a larger group size than in the symmetric groups. In this context, the only baseline difference was a less severe tremor subscore in the symmetric group, whereas demographic and main clinical parameters did not differ between the symmetric and asymmetric groups. Therefore, broad demographic and clinical baseline differences are not likely to account for the observed outcome difference in ADL outcomes. ADL and quality of life improvements were still moderately associated, irrespective of tremor improvement, when controlled for in partial correlations, which indicates their relatively small role for postoperative ADL and quality of life outcomes.

Furthermore, additional analyses in a subcohort of patients with well-balanced tremor scores after propensity score matching confirmed the main result of a lack of postoperative ADL improvement in the symmetric group, instead of considerable ADL benefits in the asymmetric group. However, propensity score matching is limited to clinically assessed parameters and does not account for potentially relevant factors not investigated in this study, for example, impulse control disorders, apathy and other neuropsychiatric and behavioural disturbances, cognitive deficits and autonomic symptoms, which could influence functional outcomes after DBS but are not included in the matching analyses. To address this limitation, comparisons between the matched groups were conducted conservatively using independent samples tests. In this context, a strength of our study is the multicentre design, which increases generalisability and external validity of our results. Between-centre analyses showed no difference in postoperative scheduling. Nevertheless, centre-specific differences in surgical technique and perioperative management may have influenced the outcomes. To reduce potential heterogeneity across clinical settings, we followed published DBS programming and postoperative medication change algorithms of our centres and MDS guidelines.[64 65] To assess the potential impact of differences in follow-up protocols, for example, resulting from the use of different assessment scales at the Toronto centre, we repeated the analyses after excluding this centre and reported both the full cohort and sensitivity analyses. Another limitation of our study is the short-term follow-up period of six months. Future multicentre studies with larger group sizes in the symmetric PD group and more than 12-month follow-up assessments are needed to confirm our findings, as the efficacy of DBS may vary beyond this period, especially in patients with more rapidly progressing symmetric symptoms.

CONCLUSIONS

We provide class IIb evidence of a lack of ADL improvement in patients with symmetric PD as opposed to moderate ADL benefits observed in patients with asymmetric PD following STN-DBS treatment. Patients with symmetric PD can be identified with a simple and straightforward method, a ratio right by left hemibody score equalling 1. This requires no additional time, effort or specialised neuroimaging or laboratory resources. The information that patients with symmetric PD have a 23.8% higher absolute risk for a postoperative 'ADL non-response' may improve the stratification of ADL outcomes and, thereby, refine the selection of patients for STN-DBS treatment. We advocate that in patients with symmetric PD, postoperative care should prioritise evidence-based complementary rehabilitation, specifically structured physiotherapy, exercise and functional-task training, and, where feasible, inpatient multidisciplinary intensive rehabilitation, which have been associated with improvements in ADL in systematic reviews.[61–63]

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