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Clinical profiles and outcomes of deep brain stimulation in G2019S *LRRK2* Parkinson disease

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Abstract

OBJECTIVE—The objective of this study was to evaluate clinical features and response to deep brain stimulation (DBS) in G2019S *LRRK2*-Parkinson disease (LRRK2-PD) and idiopathic PD (IPD).

METHODS—The authors conducted a clinic-based cohort study of PD patients recruited from the Mount Sinai Beth Israel Genetics database of PD studies. The cohort included 87 participants with LRRK2-PD (13 who underwent DBS) and 14 DBS participants with IPD enrolled between 2009 and 2017. The baseline clinical features, including motor ratings and levodopa-equivalent daily dose (LEDD), were compared among LRRK2-PD patients with and without DBS, between LRRK2-PD with DBS and IPD with DBS, and between LRRK2-PD with subthalamic nucleus (STN) and internal segment of the globus pallidus (GPi) DBS. Longitudinal motor scores (Unified Parkinson's Disease Rating Scale–part III) and medication usage were also assessed pre- and postoperatively.

RESULTS—Compared to LRRK2-PD without DBS (n = 74), the LRRK2-PD with DBS cohort (n = 13) had a significantly younger age of onset, longer disease duration, were more likely to have dyskinesia, and were less likely to experience hand tremor at disease onset. LRRK2-PD

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Author Contributions

Conception and design: Leaver, Saunders-Pullman, San Luciano. Acquisition of data: Leaver, Kopell, Miravite, Okun, Elango, Raymond, Bressman, Saunders-Pullman. Analysis and interpretation of data: Leaver, Saunders-Pullman, San Luciano. Drafting the article: Leaver, Viser. Critically revising the article: Leaver, Viser, Ortega, Okun, Bressman, Saunders-Pullman, San Luciano. Reviewed submitted version of manuscript: Leaver, Viser, Bressman, Saunders-Pullman, San Luciano. Approved the final version of the manuscript on behalf of all authors: Leaver. Statistical analysis: San Luciano. Administrative/technical/material support: Viser. Study supervision: Leaver, Bressman, Saunders-Pullman, San Luciano.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Tables 1–5. https://thejns.org/doi/suppl/10.3171/2021.7.JNS21190.

participants were also more likely to be referred for surgery because of severe dyskinesia (11/13 [85%] vs 6/14 [43%], p = 0.04) and were less likely to be referred for medically refractory tremor (0/13 [0%] vs 6/14 [43%], p = 0.02) than were IPD patients. Among LRRK2-PD patients, both STN-DBS and GPi-DBS targets were effective, although the sample size was small for both groups. There were no revisions or adverse effects reported in the GPi-DBS group, while 2 of the LRRK2-PD participants who underwent STN-DBS required revisions and a third reported depression as a stimulation-related side effect. Medication reduction favored the STN group.

CONCLUSIONS—The LRRK2-PD cohort referred for DBS had a slightly different profile, including earlier age of onset and dyskinesia. Both the STN and GPi DBS targets were effective in symptom suppression. Patients with G2019S *LRRK2* PD were well-suited for DBS therapy and had favorable motor outcomes regardless of the DBS target. LRRK2-DBS patients had longer disease durations and tended to have more dyskinesia. Dyskinesia commonly served as the trigger for DBS surgical candidacy. Medication-refractory tremor was not a common indication for surgery in the *LRRK2* cohort.

Keywords

deep brain stimulation; DBS; Parkinson's disease; *LRRK2*; GPi; STN; functional neurosurgery

Pathogenic variants of the leucine-rich repeat kinase 2 (*LRRK2*) gene have been identified as a leading genetic cause of Parkinson disease (PD).[1] The most common *LRRK2* pathogenic variant is the glycine to serine substitution at position 2019 (G2019S), which is present in approximately 1% of patients with sporadic PD and 4% of patients with familial PD.[2]

Patients with G2019S *LRRK2* parkinsonism (LRRK2-PD) develop a motor phenotype similar to those with idiopathic PD (IPD). This motor phenotype includes asymmetrical resting tremor, bradykinesia and rigidity, and a positive response to levodopa.[3] LRRK2-PD patients are also at risk for developing motor fluctuations, dystonia, and bothersome dyskinesias.[4] Group-wise clinical differences from IPD, however, have been identified. These differences include more frequent lower-extremity and gait impairment without associated cognitive impairment;[4–6] furthermore, longitudinal analyses of LRRK2-PD suggest slower motor decline.[7] Thus, many *LRRK2* characteristics including levodopa responsiveness, motor fluctuations, and better cognitive performance align well with optimal candidacy for deep brain stimulation (DBS). Other features such as greater postural instability and gait disorder[3] may augur a less positive response. How these factors influence DBS candidacy and response is not well described.

DBS can improve motor performance in patients with IPD, specifically alleviating the cardinal symptoms of tremor, rigidity, and bradykinesia and addressing motor fluctuations and dyskinesias.[8–10] DBS is less efficacious for freezing of gait and balance disorders.[11] The most common brain targets for PD are the subthalamic nucleus (STN) and the internal segment of the globus pallidus (GPi). Both targets have been shown to be safe and effective in IPD,[12] although there is a paucity of target-specific information, especially as it relates to genotype.[13]

The objectives of the current study were to compare baseline clinical characteristics driving decisions to pursue DBS among G2019S LRRK2-PD. We also aimed to compare longitudinal motor and medication DBS outcomes between LRRK2-PD and IPD and to gather preliminary information about target-specific differences.

Methods

Participants

All participants were identified from the Genetics of PD Studies at Mount Sinai Beth Israel between July 2009 and July 2017. The main inclusion criteria included a diagnosis of IPD. Those harboring an *LRRK2* G2019S pathogenic variant were classified as LRRK2-PD. Participants enrolled in Genetics of PD Studies without known pathogenic variants, classified as IPD, were recruited if they had undergone unilateral or bilateral STN or GPI DBS. Motor and nonmotor symptom data were systematically collected from medical records. Additional information was also obtained from medical records of the subset who underwent DBS surgery. IRB approval was received, and informed written consent was obtained from all patients.

Clinical Assessments

The assessments included: demographic information, Unified Parkinson's Disease Rating Scale part I–IV (UPDRS- I–IV),[14] Hoehn and Yahr stage, levodopa-equivalent daily dose (LEDD), and cognitive status as measured by the Montreal Cognitive Assessment (MoCA). Motor assessments were performed in the ON state, as defined by the clinician and patient, as part of routine clinical visits. Because postoperative motor evaluations in the OFF state were not systematically collected, motor OFF assessments were not included. Longitudinal assessments were obtained at multiple time points before and after surgery, with postoperative assessments at least 3 months after surgery to account for any microlesion effects. For subjects undergoing DBS, the following information was additionally and systematically extracted from the medical record: indication for DBS, date of surgery, brain target and rationale for target, implanting surgeon, and any surgical complications.

DBS Surgery

DBS eligibility and brain target choice were determined clinically through a multidisciplinary team discussion. Inclusion criteria for DBS eligibility were: presence of at least 2 cardinal motor features (resting tremor, bradykinesia, or rigidity), disease duration longer than 5 years, robust response to levodopa, persistent disabling symptoms such as motor fluctuations with troublesome OFF periods or dyskinesia despite optimal medical therapy, a minimum UPDRS-III OFF medication score of 25, stable medical therapy for at least 1 month prior to baseline, and the ability to comply with follow-up visits. Exclusion criteria were intracranial abnormalities contraindicating surgery, medical contraindications to surgery, clinical evidence of an atypical parkinsonian syndrome, active alcohol or drug abuse, pregnancy, dementia or significant cognitive impairment, or uncontrolled mood disorder. Surgical implantation of DBS electrodes was performed as previously described.[15] In brief, all patients underwent stereotactic frame-based placement of bilateral DBS leads

as well as microelectrode recording for target refinement. Procedures were performed by experienced functional neurosurgeons in New York or Florida. Once the optimal track was identified for implantation, the DBS lead was inserted. Lead location was confirmed using intraoperative CT (O-arm, Medtronic) merged with preoperative MRI/CT images. Postoperative programming and selection of optimal stimulation contacts were performed using clinical criteria.[16]

Statistical Analysis

All statistical analyses were completed using Stata (version 15, StataCorp LP). Univariate analyses of demographic variables were performed using chi-square test and Student t-test or nonparametric equivalents when necessary (Table 1). Linear mixed models adjusted by gender, age at PD onset, LEDD (as a time-dependent covariate), age at first visit or at surgery, and baseline UPDRS-III, allowing for subject-specific random intercepts to be used to compare UPDRS-III trajectories between LRRK2-PD and IPD groups. No corrections were made for multiple comparisons, as the analysis presented was deemed predominately descriptive and exploratory.

Results

Between July 2009 and July 2017, 94 participants with PD were identified who carried at least one copy of the G2019S pathogenic variant, 4 of whom were excluded for also harboring a *GBA* pathogenic variant. Demographic and clinical information was available for 87 LRRK2-PD participants, including 13 who had undergone DBS surgery (LRRK2-DBS). Of this subset, 4 LRRK2-PD participants had undergone GPi-DBS (3 bilateral and 1 unilateral) while 9 had undergone STN-DBS (8 bilateral and 1 unilateral). Of the 14 IPD-DBS patients identified with known genetic status, 2 had undergone GPi-DBS (1 bilateral and 1 unilateral) and 12 had undergone STN-DBS (11 bilateral and 1 unilateral; Supplementary Table 5).

Comparisons Among LRRK2-PD: DBS Versus No DBS

Univariate comparisons between 74 LRRK2-PD participants who had not undergone DBS (LRRK2-nonDBS) during the observation period and the 13 LRRK2-PD patients who had been treated with DBS are listed in Table 1. No significant differences were found in gender, baseline UPDRS-III score, Hoehn and Yahr stage, or baseline cognitive status (as measured by MoCA and UPDRS-I question 1). However, LRRK2-DBS participants had a younger age of onset (mean 49.2 ± 11.3 vs 61.6 ± 10.8 years, $p < 0.001$) and longer duration of disease at baseline (12.4 ± 6.3 vs 9.8 ± 10.3 years, $p = 0.04$). They were also less likely to have presented with hand tremor at onset (38.5% vs 77.6%, $p = 0.01$) and were more likely to have developed dyskinesia prior to DBS surgery (100% vs 40.3%, $p < 0.001$).

Longitudinal information was available for 32 LRRK2-nonDBS and 9 LRRK2-DBS individuals. LRRK2-nonDBS participants were seen an average of 6.2 times (range 1–15 times), whereas LRRK2-DBS participants were seen an average of 8.3 times (range 1–13 times), of which 3.8 visits (range 1–5 visits) took place prior to DBS surgery. An exploratory analysis was conducted on progression of symptoms. Prior to DBS, the LRRK2-DBS group

progressed 0.02 UPDRS-III points per month, which was 0.10 points per month less rapidly than the LRRK2-nonDBS group (Fig. 1, Supplementary Table 1). This difference, however, was not found to be statistically significant and the sample size was small (odds ratio [OR] 0.10, 95% confidence interval [CI] −0.2 to 0.2, p = 0.93).

Comparisons Among Participants Undergoing DBS: LRRK2-PD Versus IPD

Baseline information was available for 9 LRRK2-DBS and 14 IPD-DBS participants (Table 2, Supplementary Table 1). LRRK2-DBS individuals had a significantly longer duration of disease at diagnosis than IPD-DBS patients (1.7 ± 1.2 vs 0.7 ± 0.7 years, p = 0.03), but the groups were otherwise comparable with similar gender distribution, age at diagnosis and disease onset, site of onset, duration of disease at surgery, UPDRS-III scores at baseline, and age at surgery. Additionally, there were no statistically significant differences between LEDD and median UPDRS-III scores (Table 2) at the time of surgery.

The majority of individuals in both groups underwent bilateral DBS placement (11/13 in the LRRK2-DBS group and 12/14 in the IPD-DBS group), and the frequency of surgical complications and adverse effects were similar: 3/13 revisions for LRRK2-DBS patients versus 2/14 for IPD-DBS, 3/13 adverse effects for the LRRK2-DBS group versus 5/14 for IPD-DBS. However, LRRK2-DBS participants were significantly more likely to be referred for surgery because of severe dyskinesia (11/13 [85%] vs 6/14 [43%], p = 0.04) and were significantly less likely to be referred for medically refractory tremor (0/13 [0%] vs 6/14 [43%], p = 0.02) relative to IPD-DBS participants (Supplementary Table 5).

An exploratory longitudinal analysis of progression was performed. LRRK2-DBS and IPD-DBS participants had similar rates of motor worsening prior to surgery (Fig. 2 left, Supplementary Table 1), with IPD-DBS participants progressing an average of 0.10 UPDRS-III points per month less rapidly than LRRK2-DBS participants (95% CI −0.16 to 0.36, p = 0.47). Following surgery (Fig. 2 right, Supplementary Table 1), IPD-DBS participants worsened at a rate of 0.07 points per month more rapidly than did LRRK2-DBS participants (95% CI −0.16 to 0.02, p = 0.14). However, these differences in trajectories did not reach statistical significance.

Medication use was compared before and after surgery between LRRK2 and IPD cohorts (Supplementary Table 2). Both the LRRK2-DBS and IPD-DBS groups had significant reductions in medication dose with a median LEDD reduction of 378 units (interquartile range [IQR] 774 units) among LRRK2-DBS participants and of 487.5 units (IQR 655 units) among IPD-DBS participants (p = 0.02 for each).

Brain Target Choice Within the LRRK2-DBS Group

Four LRRK2-DBS participants underwent GPi-DBS while 9 underwent STN-DBS (Supplementary Table 5). Across both groups, the majority received bilateral electrode placement (3/4 [75%] for GPi-DBS and 8/9 [88%] for STN-DBS). There were no revisions or adverse effects reported in the GPi-DBS group, but 2 of the LRRK2-DBS participants who underwent STN-DBS required revisions and a third reported depression as a stimulation-related side effect. Indications for DBS were similar across groups, with the most common being motor fluctuations (3/4 [75%] in the GPi-DBS group and 7/9

[78%] in the STN-DBS group) and severe dyskinesia (3/4 [75%] in the GPi-DBS group and 8/9 [89%] in the STN-DBS group). Medication reduction was the primary rationale for target choice for all 9 of the STN-DBS patients, whereas the targets for each of the 4 GPi-DBS patients were chosen for different indications, including concern for cognition and significant dystonia.

Longitudinally, among the LRRK2-DBS cohort, those who underwent GPi-DBS had similar motor outcomes compared to those who underwent STN-DBS (Fig. 3). The LEDD was analyzed according to brain target. Overall, when combining groups, patients with STN-DBS had greater medication reduction (median 542 units, IQR 760 units, $p = 0.004$) than did those with GPi-DBS (median 238 units, IQR 524 units, $p = 0.10$). This effect was also present within the LRRK2-PD group, with significant LEDD reduction shown only among those with STN-DBS ($p = 0.04$; Supplementary Tables 3 and 4).

Discussion

The current study characterized a cohort of patients with G2019S *LRRK2* parkinsonism, with and without DBS, and collected preliminary outcome data on STN and GPi brain targets.

The cohort of 94 LRRK2-PD patients was relatively large and 13 were referred for DBS. Those referred for DBS had a distinct profile with a younger age of onset and longer duration of disease at the time of surgery (12.38 vs 9.75 years). The disease duration was longer than that observed in multiple randomized controlled DBS cohorts.[17] This finding is consistent with prior studies showing slower *LRRK2* progression[7] and thus potentially presents a somewhat different, wider, optimum “window” for surgical intervention.[17–23]

The LRRK2-PD patients referred for surgery were less likely to present with hand tremor at disease onset (38% vs 78%). However, all LRRK2-DBS patients developed dyskinesia prior to DBS compared to only 40% of LRRK2-PD patients not referred for surgery. The causes for the excess of dyskinesia may be multifactorial and possible contributors include longer duration of disease and levodopa exposure. Regardless, the observation that the most common indication for surgical referral in LRRK2-PD patients was severe dyskinesia (85%) is an important one for the clinician. Another notable observation in this group is that medically refractory tremor did not occur in the LRRK2-DBS group and this information may be useful to the implanting team. Tremor is a commonly reported symptom in LRRK2-PD,[2] but in our series it did not translate to a reason for proceeding to DBS surgery.

Although the sample size was small, our exploratory analysis of longitudinal progression in patients with LRRK2-PD who underwent DBS showed that these patients had a slightly slower rate of motor progression postoperatively compared to IPD-DBS patients. This improvement was observed for more than 2 years following surgery. Our findings should be interpreted with caution, but add to the growing body of literature favoring improved motor outcomes in G2019S *LRRK2* PD compared to IPD.[24,25]

Our results demonstrate the safety and potential effectiveness of both STN and GPi-DBS in LRRK2-PD and are consistent with the two largest published studies on *LRRK2* STN-DBS,

which included 15 and 13 patients (all of whom had the G2019S pathogenic variant). Both of these previously published studies demonstrated improved motor outcomes for LRRK2-PD patients as compared to patients without pathogenic variants.[25,26] In contrast, smaller studies have found either improvement or no difference in motor outcomes when comparing STN-DBS in LRRK2-PD to IPD.[24,27,28]

This is the first study to report on GPi-DBS outcomes in G2019S *LRRK2* PD. The rationale for the GPi target choice in our cohort was concern for preserving cognition, mood, or the presence of significant dystonia. A few recent studies have suggested a slight worsening of cognition after STN-DBS,[21,29] or a better effect on mood using GPi-DBS.[30] More recent studies using different outcomes have shown conflicting results.[31,32] GPi-DBS is, however, recognized for its strong antidyskinetic effects.[33] Given that the majority of the LRRK2-DBS patients in this study were referred for DBS for severe dyskinesia, GPi-DBS may represent a reasonable and attractive brain target for LRRK2-PD with dyskinesia. Longitudinally, our GPi-DBS data demonstrated similar motor improvements to STN-DBS in UPDRS-III ON scores from 6 months to 2 years after surgery. The significant reduction in LEDD favored the STN-DBS group and this closely matched the results in other published cohorts.[30,32] The number of surgical revisions and postoperative adverse effects was low in both cohorts and consistent with rates in IPD-DBS.[21]

This study has several limitations. The number of surgical subjects was small, which precluded confident interpretations of statistical analysis, especially regarding the brain target subgroups. Most, but not all, of the DBS procedures were performed by a single surgeon at a single site. The variability in site and surgeon may have also affected the DBS outcomes. Additionally, longitudinal data for motor outcomes were only available for ON UPDRS-III scores. A potential limitation of our study is the recruitment of all individuals from participants in genetics studies. Even among those not carrying known pathogenic variants, approximately half had a family history of PD, thus this comparison group may have not been as typical of a group with less likely genetic burden. However, if that was the case, it would have biased the results of our study toward the null hypothesis, and the found differences might have been more apparent had we compared them with a less genetic cohort.

Future larger longitudinal studies are warranted and should expand to examine cognitive and nonmotor outcomes, and quality of life. Lastly, our study was limited to one pathogenic *LRRK2* genetic variant and investigating pathogenic and risk variants beyond G2019S will be needed but could be challenging, given even smaller numbers of available subjects.

Conclusions

Patients with G2019S *LRRK2* parkinsonism are well-suited for DBS therapy and have favorable motor outcomes in both DBS targets. Among LRRK2-PD patients, those undergoing DBS have longer disease durations and tend to have more dyskinesia, and dyskinesia is commonly the trigger for DBS surgery. Medication-refractory tremor was not a common indication for surgery in our *LRRK2* cohort.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

CI	confidence interval
DBS	deep brain stimulation
GPi	internal segment of the globus pallidus
IPD	idiopathic PD
IQR	interquartile range
LEDD	levodopa-equivalent daily dose
MoCA	Montreal Cognitive Assessment
OR	odds ratio
PD	Parkinson disease
STN	subthalamic nucleus
UPDRS	Unified Parkinson's Disease Rating Scale

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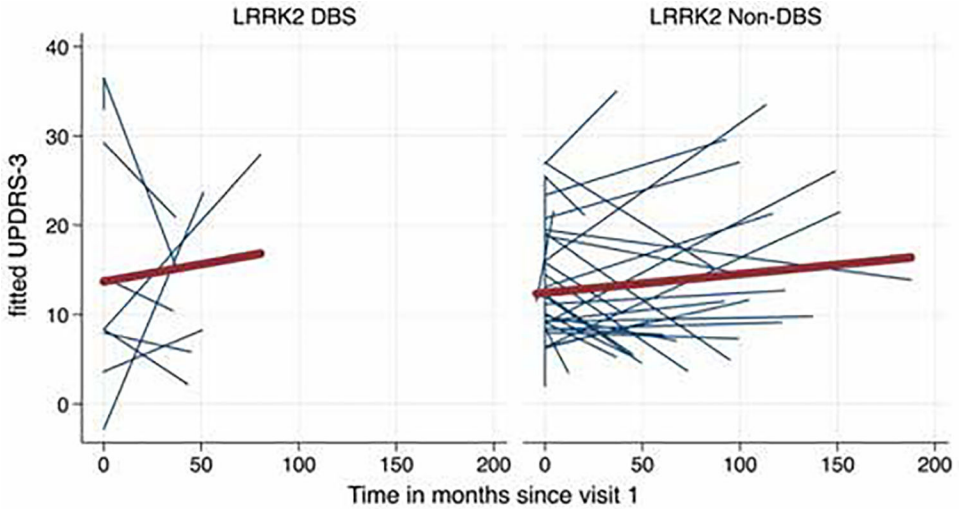

FIG. 1.

Spaghetti plot of fitted (predicted) motor trajectories (UPDRS-III) of LRRK2-PD subjects. *Blue lines* represent individual subjects and the *red line* is average trend of all subjects. **Left:** Preoperative motor trajectories of LRRK2-DBS subjects. **Right:** Preoperative motor trajectories of LRRK2 non-DBS subjects.

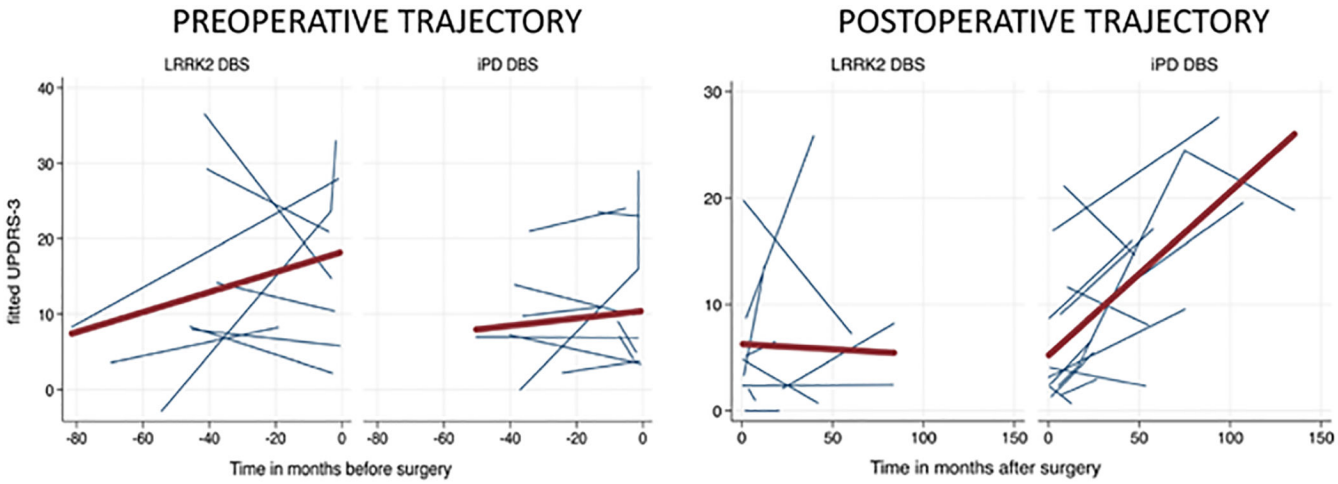

FIG. 2.

Spaghetti plot of fitted (predicted) motor trajectories (UPDRS-III) of LRRK2 and IPD subjects undergoing DBS. *Blue lines* represent individual subjects and the *red line* is average trend of all subjects. **Left:** Preoperative motor trajectories by *LRRK2* status. **Right:** Postoperative motor trajectories by *LRRK2* status.

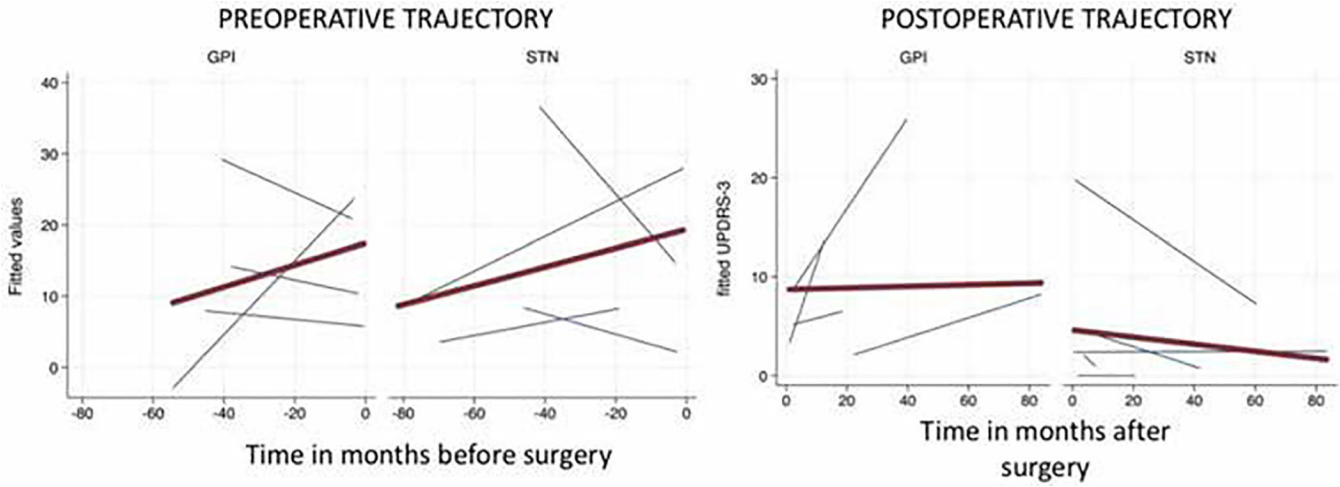

FIG. 3.

Spaghetti plot of fitted (predicted) motor trajectories (UPDRS-III) of LRRK2-PD subjects undergoing DBS. *Blue lines* represent individual subjects and the *red line* is average trend of all subjects. **Left:** Preoperative motor trajectories by brain target. **Right:** Postoperative motor trajectories by brain target.

TABLE 1.

Demographic and baseline clinical characteristics of G2019 *LRRK2* carriers, according to DBS status

Clinical Characteristic	LRRK2 non-DBS (n = 74)	LRRK2 DBS (n = 13)	p Value
Male	34/74 (45.95)	9/13 (69.23)	0.14
Age at PD motor symptom onset, yrs	61.63 ± 10.76	49.15 ± 11.31	<0.001
Age at PD diagnosis, yrs	63.21 ± 10.86	50.62 ± 10.91	<0.001
Age at last non-DBS visit, yrs	72.03 ± 10.36	63.08 ± 13.41	0.04
Duration of disease, yrs	9.75 ± 10.31	12.38 ± 6.27	0.04
UPDRS-III score	18.61 ± 13.18	18.30 ± 10.75	0.88
Hoehn & Yahr score	2.38 ± 1.03	2.25 ± 0.42	0.67
Site of onset in leg	35/67 (52.24)	9/13 (69.23)	0.36
Tremor as presenting feature	52/67 (77.61)	5/13 (38.46)	0.01
MoCA score	25.31 ± 3.63 (n = 52)	24.43 ± 3.26 (n = 7)	>0.99
UPDRS-I, question 1, intellectual impairment, score ≥1	32/56 (57.14)	5/11 (45.45)	0.52
Dyskinesia ever present prior to DBS	27/67 (40.3)	13/13 (100)	<0.001
Sustained levodopa response >5 yrs	30/67 (44.78)	11/13 (84.62)	0.01

Data given as mean ± SD or number (%), unless otherwise indicated.

TABLE 2.

Demographic and baseline clinical characteristics of patients undergoing DBS, according to *LRRK2* status

Clinical Characteristic	IPD DBS (n = 14)	LRRK2 DBS (n = 9)	p Value
Male	13/14 (92.86)	7/9 (77.78)	0.53
Age at PD motor symptom onset, yrs	52.33 ± 9.01	50.11 ± 13.56	0.72
Age at PD diagnosis, yrs	53.00 ± 9.12	51.11 ± 12.83	0.72
Site of onset			
Arm	7/14 (50.00)	3/9 (33.3)	0.39
Leg	4/14 (28.57)	3/9 (33.3)	>0.99
Gait	1/14 (7.14)	3/9 (33.3)	0.27
Duration of disease at diagnosis, yrs	0.67 ± 0.72	1.67 ± 1.22	0.03
Disease duration at levodopa institution, yrs	2.69 ± 1.93	6.25 ± 6.80	0.14
Age at surgery, yrs	64.1 ± 6.33	63.11 ± 15.09	0.97
Duration of disease (diagnosis) at surgery, yrs	10.59 ± 6.68	11.11 ± 5.13	0.52
Duration of disease (symptoms) at surgery, yrs	10.53 ± 6.27	12.78 ± 4.38	0.22
Median LEDD at surgery (IQR)	938 (498.5)	1228 (491)	0.09
Median UPDRS-III score at surgery (IQR)	9 (11)	16 (21)	0.13

Data given as mean ± SD or number (%), unless otherwise indicated.