Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Predictors of Future Deep Brain Stimulation Surgery in de novo Parkinson's Disease

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Abstract: Background: Deep brain stimulation (DBS) surgery is offered to a subset of Parkinson's disease (PD) patients. It is unclear if there are features at diagnosis that predict future DBS surgery.
Objective: To assess predictors of eventual DBS surgery in de novo PD patients.
Methods: Subjects from the Parkinson's Progression Marker Initiative (PPMI) database with newly diagnosed, sporadic PD ($n = 416$) were identified and stratified by their eventual DBS status (DBS+, $n = 43$; DBS-, $n = 373$). A total of 50 baseline clinical, imaging, and biospecimen features were extracted for each subject and cross-validated lasso regression was used for feature reduction. Multivariate logistic regression assessed their relationship with DBS status and a receiver operating characteristic curve evaluated model performance. Linear mixed effect models assessed disease progression over 4 years in DBS+ and DBS- patients.
Results: Age at symptom onset, Hoehn and Yahr (H&Y) stage, tremor score, and ratio of CSF Tau to amyloid-beta 1–42 (Tau: Ab) were identified as important baseline features for predicting DBS surgery. Each independently predicted DBS surgery (area under the curve = 0.83). DBS- patients had faster memory decline ($P < 0.05$), while DBS+ patients had faster decline in H&Y stage ($P < 0.001$) and motor scores ($P < 0.05$) prior to surgery.
Conclusion: The identified features may be used for early identification of patients who may be surgical candidates during the course of their disease. Disease progression in these groups reflects surgical eligibility criteria, with DBS- patients having more rapid decline in memory while DBS+ patients experienced a faster decline in motor scores prior to DBS surgery.

Parkinson's disease (PD) is a common and progressive neurodegenerative disorder that results from widespread cortical and subcortical neurodegeneration associated with dysfunction in dopamine-regulated basal ganglia circuitry.[1] Symptoms include both motor and non-motor manifestations. Most patients with PD have a robust response to dopaminergic medications, with a good effect on rigidity and bradykinesia but a more variable effect on tremor.[2] However, over time, the majority of patients develop medication related complications that compound upon the progressive nature of the disease, resulting in a significant deterioration in quality of life.[3,4] Deep brain stimulation (DBS) is an effective treatment of the motor symptoms of PD, consistently demonstrating superiority over medical management alone[5–8] in well-selected patients. About 1.6–4.5% of PD patients eventually become surgical candidates for DBS surgery based on established eligibility criteria.[9] Eligibility has been dictated by the Core Assessment Program for Surgical Interventional Therapies in Parkinson's disease (CAPSIT-PD).[10] This document states surgical intervention should be offered if (1) the patient has a diagnosis of idiopathic PD with a disease duration of at least 5 years, (2) dopamine responsiveness with a > 33% decrease in motor symptoms following a medication challenge, (3) lack of significant levodopa resistant axial symptoms, (4) presence of on–off motor fluctuations, and (5) lack of significant

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TABLE 1 *Fifty baseline clinical, imaging, and biospecimen predictors were evaluated by lasso regression for each subject*

Feature	DBS+ ($n = 43$)	DBS− ($n = 373$)	Missing (DBS+: DBS−)
Demographics			
Age (symptom onset)*	51.9 (SD 8.8)	60.5 (SD 9.8)	0:0
Sex (M:F)	27:16 (63% M)	244:129 (65% M)	0:0
Race (White:Black:Asian:Other)	40:0:1:2 (93% white)	344:6:7:16 (92% white)	
Education (years)	15.4 (SD 2.4)	15.6 (SD 3.0)	0:0
Clinical (General)			
Hoehn & Yahr stage (1:2:3)*	28:15:0 (65% stage 1)	155:216:2 (42% Stage 1)	0:0
Modified Schwab ADL	90 (IQR 10)	90 (IQR 10)	0:0
UPDRS II total score	5 (IQR 3)	5 (IQR 5)	0:1
UPDRS Total score	32.1 (SD 11.9)	32.2 (SD 13.3)	0:1
Clinical (Motor)			
Rigidity sub-score	3 (IQR 3)	3 (IQR 4)	0:0
Tremor sub-score*	5 (IQR 3)	4 (IQR 4)	0:0
Motor phenotype (TD:PIGD)	36:7 (83% tremor dominant)	260:112 (70% tremor dominant)	0:1
UPDRS III total score	20.2 (SD 7.3)	20.9 (SD 9.0)	0:0
Clinical (Cognition)			
Benton Judgment of Line Orientation	13.2 (SD 1.9)	12.7 (SD 2.2)	0:1
HVLT immediate recall	25.8 (SD 4.0)	24.2 (SD 5.1)	0:1
HVLT delayed recall	8.9 (SD 1.9)	8.3 (SD 2.6)	0:1
HVLT recognition	11.2 (SD 0.8)	11.2 (SD 1.3)	0:1
HVLT discrimination	10 (IQR 2)	10 (IQR 2)	0:1
Line-Number sequencing	10.8 (SD 2.3)	10.6 (SD 2.7)	0:1
Semantic Fluency total score	50.4 (SD 11.1)	48.6 (SD 11.8)	0:1
Symbol Digit Modality	45.0 (SD 7.1)	40.8 (SD 10.0)	0:1
MoCA	28 (IQR 3)	27 (IQR 3)	0:0
Clinical (Neuropsychiatric)			
UPDRS I total score	5 (IQR 4.5)	5 (IQR 5)	0:1
Geriatric depression scale	2 (IQR 2.5)	2 (IQR 2.0)	0:0
State Trait anxiety inventory State score	33.7 (SD 8.5)	32.8 (SD 10.3)	0:1
State Trait anxiety inventory Trait score	34.0 (SD 9.0)	32.1 (SD 9.4)	0:1
Questionnaire for Impulsive-Compulsive disorders	0 (IQR 0.5)	0 (IQR 0)	0:1
Clinical (Sleep and autonomic)			
Autonomic dysfunction (SCOPA-AUT total score)	8 (IQR 5.5)	8 (IQR 7.0)	0:8
Epworth Sleepiness Scale	6 (IQR 4)	5 (IQR 5)	0:0
REM Sleep behavior disorder questionnaire	4.2 (SD 2.3)	4.1 (SD 2.7)	0:3
Imaging			
DaTscan right caudate	2.0 (SD 0.61)	2.0 (SD 0.60)	0:4

(Continues)

TABLE 1 *Continued*

Feature	DBS+ ($n = 43$)	DBS− ($n = 373$)	Missing (DBS+: DBS−)
DaTscan left caudate	2.1 (SD 0.62)	2.0 (SD 0.58)	0:4
DaTscan right putamen	0.80 (SD 0.34)	0.84 (SD 0.34)	0:4
DaTscan left putamen	0.90 (SD 0.36)	0.79 (SD 0.34)	0:4
DaTscan minimum caudate	1.9 (SD 0.55)	1.8 (SD 0.53)	0:4
DaTscan maximum caudate	2.3 (SD 0.6)	2.2 (SD 0.59)	0:4
DaTscan minimum putamen	0.65 (SD 0.22)	0.66 (SD 0.24)	0:4
DaTscan maximum putamen	1.0 (SD 0.35)	0.97 (SD 0.36)	0:4
Asymmetry Index caudate	19.7 (SD 9.0)	18.8 (SD 13.4)	0:4
Asymmetry Index putamen	45.8 (SD 21.8)	36.7 (SD 25.3)	0:4
Count density ratio right	2.8 (SD 0.95)	2.5 (SD 0.78)	0:4
Count density ratio left	2.5 (SD 0.78)	2.7 (SD 0.96)	0:4
Biospecimen			
CSF Alpha-synuclein pg/mL	1275 (SD 462)	1535 (SD 686)	0:11
CSF Alpha-beta 1–42 pg/mL	958 (SD 315)	904 (SD 422)	0:13
CSF total Tau pg/mL	145 (SD 41)	169 (SD 60)	0:10
CSF phosphorylated Tau pg/mL	12.3 (SD 3.6)	14.4 (SD 5.6)	0:10
CSF total Tau:Alpha-beta ratio*	0.157 (SD 0.03)	0.21 (SD 0.10)	0:13
CSF phosphorylated Tau:Alpha-beta ratio	0.013 (SD 0.003)	0.018 (SD 0.01)	0:13
CSF phosphorylated Tau:total Tau ratio	0.014 (SD 0.005)	0.016 (SD 0.007)	0:13
CSF total Tau:alpha synuclein ratio	0.121 (SD 0.03)	0.117 (SD 0.03)	0:11
CSF phosphorylated Tau:alpha-synuclein ratio	0.010 (SD 0.002)	0.010 (SD 0.003)	0:11

Note: Descriptive statistics reported as mean (std = standard deviation) for normally distributed variables based on Kruskal-Wallis or median (IQR = interquartile range) for non-normally distributed variables.

Abbreviation: ADL, activities of daily living; CSF, cerebrospinal fluid; DaTscan, dopamine transporter scan; HVLT, Hopkins verbal learning test; MoCA, Montreal cognitive assessment; PIGD, postural instability/gait dominant; REM, rapid eye movement; SCOPA-AUT, Scales for outcomes in Parkinson's disease- Autonomic dysfunction; TD, tremor dominant; UPDRS, unified Parkinson's disease rating scale.

*Selected by Lasso regression as an important feature for predicting DBS status.

non-motor symptoms, especially cognitive impairment. Using these guidelines, DBS has traditionally been offered for patients with advanced PD, with a disease duration averaging between 10–15 years.[5,6,11,12] More recently, some investigators have suggested offering DBS earlier in the disease course to optimize quality of life and prevent disabling medication side-effects.[13–16] In 2013, a large randomized trial demonstrated the superiority of subthalamic (STN) DBS to medical management when done with a minimum disease duration of 4 years (average disease duration of 7.5 years).[14] More recently, an open-label pilot trial offered DBS to patients prior to the manifestation of motor complications, with subjects having been on antiparkinsonian medication for an average of only 2.2 years.[16] Five-year outcomes from this latter trial demonstrated that early STN DBS resulted in lower medication usage and better tremor control as compared to best medical management alone.[17] One challenge with offering DBS this early is that the expected disease course is unclear, and surgery may be offered to those who would not have otherwise been candidates. Having biomarkers at PD diagnosis that could give insight into future surgical eligibility may help guide clinicians when discussing surgical options early in the disease course. Further, this information could be used to inform the patient about their probable disease course. The objective of the current investigation was to assess what factors at PD diagnosis may predict future surgical eligibility for DBS. A secondary objective was to characterize the early disease progression in patients who eventually had DBS surgery vs those who continued with medical management alone.

Methods

The Parkinson's Progression Markers Initiative (PPMI) is a multicenter longitudinal observational study of a deeply phenotyped cohort of patients with PD. The PPMI study methodology has

been described in detail elsewhere.[18–20] The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines after approval of the local ethics committees of the participating site. As PPMI is an international multisite study, each site received ethical approval and written consent from all participating subjects from study investigators. Briefly, PPMI enrolled subjects with de novo PD within 2 years of diagnosis. Participants were untreated at baseline, not expected to require therapy for at least 6 months, and had confirmed dopamine transporter deficit on single-photon-emission CT scan. The PPMI database was accessed on Aug 20, 2022. All statistical analyses were performed in MATLAB (2022a, Mathworks, Natick, MA, USA). We utilized the sporadic PD cohort, which consists of newly diagnosed sporadic PD patients enrolled prior to medication initiation ($n = 423$). Six subjects were removed from this cohort due to a subsequent diagnosis change, and one was removed due to receiving non-DBS surgery (L-dopa pump). This resulted in a final sample of 416 subjects. Subjects undergoing DBS during the course of their follow-up were identified (DBS+, $n = 43$; DBS-, $n = 373$). A total of 50 baseline clinical, imaging, and biospecimen variables for each subject were extracted (Table 1). Details regarding the collection of these variables have previously been reported.[18,0] Complete case analysis was performed for the feature reduction and logistic regression, resulting in a total of 386 subjects with complete data across the 50 variables (DBS+, $n = 43$; DBS-, $n = 343$). Phosphorylated-tau that was recorded as "below the detectable limit (<8pg/L)" was substituted as 7 pg/L in order to retain the subjects' data in this analysis. Similarly, for t-tau "below the detectable limit (<80pg/L)" we substituted the value 70 pg/L. When applicable, we utilized the "off" state motor scores.

Normality of each variable was assessed with a Kruskal-Wallis test. Descriptive statistics, including mean and standard deviation (for normally distributed variables), median and inter-quartile range (for non-normally distributed variables) and proportions (for categorical variables) were assessed. For the purpose of feature selection and subsequent analysis, variables were standardized to a mean of 0 and a standard deviation of 1. Data-driven feature reduction using least absolute shrinkage and selection operator (Lasso) regularization was performed.[21] Lasso is a regularization technique that includes a penalty term (λ) that constrains the size of the estimated coefficients. As the penalty term increases, Lasso sets more coefficients to zero thereby reducing the feature space. This was implemented in MATLAB with the function *lassoglm*, with the response variable specified as DBS

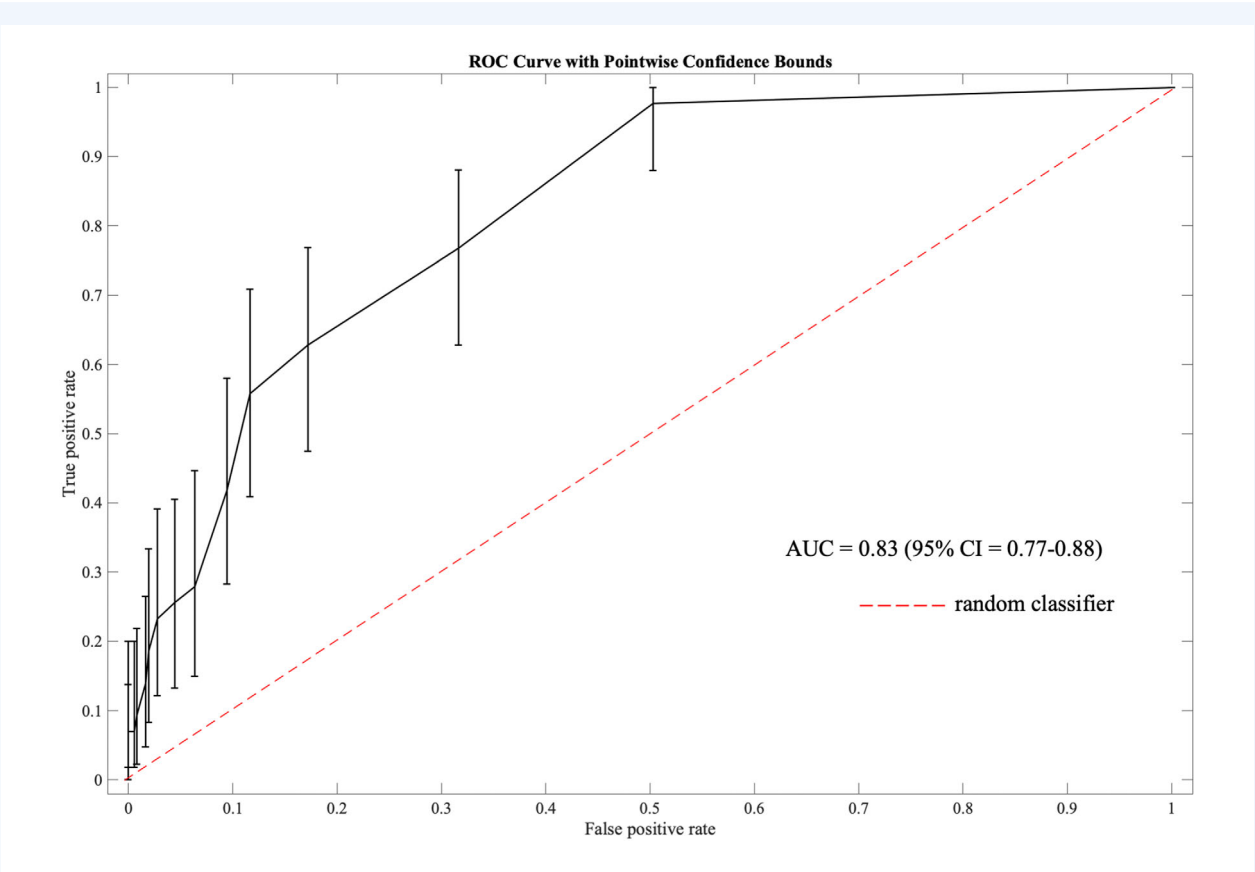

FIG. 1. Receiver operating curve with point-wise 95% confidence interval evaluating logistic regression performance for predicting deep brain stimulation surgery. Predictors included the four variables identified by cross-validated Lasso regression. AUC, area under the curve.

outcome. We constructed a regularized binomial regression using 100 λ values and ten-fold cross validation. To select the most parsimonious model, we identified the non-zero model coefficients at the λ value with the minimum deviance plus one standard deviation point.[22] These identified features were subsequently used as predictors of DBS status in a multivariate logistic regression. We constructed a receiver operating characteristic (ROC) curve to specify the performance of the model. Area under the ROC curve was calculated and a 95% confidence interval (CI) was computed with bootstrapping (1000 random samples using resampling with replacement).

TABLE 2 *Linear mixed effect models assessing difference in rate of symptom progression prior to DBS surgery (time × outcome interaction) over 4 years*

Dependent variable	Main effect time	Time × outcome (DBS+/DBS-)
General		
Hoehn and Yahr	$t = 8.5$, $P < 0.0001$***	$t = 4.3$, $P < 0.0001$***
Modified Schwab ADL	$t = -13.1$, $P < 0.0001$***	$t = -0.86$, $P = 0.39$
UPDRS II total score	$t = 15.3$, $P < 0.0001$***	$t = 2.1$, $P = 0.036$*
UPDRS Total score	$t = 18.5$, $P < 0.0001$***	$t = 2.5$, $P = 0.012$*
LEDD	$t = 29.8$, $P < 0.0001$***	$t = 0.88$, $P = 0.38$
Motor		
Rigidity sub-score	$t = 11.5$, $P < 0.0001$***	$t = 0.91$, $P = 0.36$
Tremor sub-score*	$t = 8.9$, $P < 0.0001$***	$t = 2.4$, $P = 0.014$*
UPDRS III total score	$t = 17.3$, $P < 0.0001$***	$t = 2.1$, $P = 0.035$*
Cognitive		
Benton Judgment of Line Orientation	$t = 0.42$, $P = .67$	$t = 0.55$, $P = .58$
HVLT immediate recall	$t = -0.52$, $P = 0.09$	$t = 2.2$, $P = 0.03$*
HVLT delayed recall	$t = -2.5$, $P = 0.011$*	$t = 3.6$, $P = 0.0003$***
HVLT recognition	$t = -1.4$, $P = .15$	$t = 1.7$, $P = 0.08$
HVLT discrimination	$t = 2.2$, $P = 0.03$*	$t = 2.9$, $P = 0.003$**
Line-Number sequencing	$t = -3.7$, $P = 0.0002$***	$t = 2.8$, $P = 0.006$**
Semantic Fluency total score	$t = -20.0$, $P = 0.044$*	$t = 1.5$, $P = 0.14$
Symbol Digit Modality	$t = 8.9$, $P < 0.0001$***	$t = 0.75$, $P = 0.45$
MoCA	$t = -3.3$, $P = 0.0010$***	$t = 2.4$, $P = 0.015$*
Neuropsychiatric		
UPDRS I total score	$t = 12.4$, $P < 0.0001$***	$t = 0.71$, $P = 0.48$
Geriatric depression scale	$t = 1.2$, $P = 0.21$	$t = -0.19$, $P = 0.85$
State Trait anxiety inventory State score	$t = -1.8$, $P = 0.07$	$t = 0.11$, $P = 0.91$
State Trait anxiety inventory Trait score	$t = .27$, $P = 0.79$	$t = -0.18$, $P = 0.86$
Questionnaire for Impulsive-Compulsive disorders	$t = 2.2$, $P = 0.026$*	$t = -0.25$, $P = 0.80$
Sleep/autonomic		
Autonomic dysfunction (SCOPA-AUT total score)	$t = 8.9$, $P < 0.0001$***	$t = 0.75$, $P = 0.45$
Epworth Sleepiness Scale	$t = 6.5$, $P < 0.0001$***	$t = 1.4$, $P = 0.17$
REM Sleep behavior disorder questionnaire	$t = 3.7$, $P = 0.0002$***	$t = 0.56$, $P = 0.58$

Note: Model included age and levodopa equivalent daily dosage as nuisance covariates.
Abbreviation: ADL, activities of daily living; HVLT, Hopkins verbal learning test; LEDD, levodopa equivalent daily dose; MoCA, Montreal cognitive assessment; REM, rapid eye movement; SCOPA-AUT, Scales for outcomes in Parkinson's disease- Autonomic dysfunction; UPDRS, unified Parkinson's disease rating scale.
***$P < 0.05$ Bonferroni corrected for 24 variables;
**$P < 0.01$;
*$P < 0.05$ uncorrected.

To characterize the progression of PD in DBS+ and DBS- cohorts prior to DBS surgery, we assessed the change in motor and non-motor symptoms over the first 4 years that patients were enrolled in PPMI. A total of 4 years was chosen because no patient received DBS prior to this time point. To compare motor and non-motor symptom progression, we utilized repeated measure linear mixed effect models with a random effect of subject while controlling for age at diagnosis and levodopa equivalent daily dose (LEDD). We assessed the time by outcome (DBS− vs. DBS+) interaction term. We report significant differences in the rate of symptom progression at an uncorrected *P*-value of <0.05. We also note the categories where a difference was observed at a more stringent threshold of $P < 0.05$ with a Bonferroni correction for 24 tests.

Results

DBS surgery occurred at an average time of 101.4 (±30.0, range 44.4–154.8) months from diagnosis in the PPMI cohort. The average age at the time of DBS was 62.5 years. There were 11 globus pallidus internal (GPi) and 22 STN cases. The remaining 10 DBS patients did not have a target documented. Descriptive statistics of all 50 features extracted from the PPMI database are displayed in Table 1. Ten-fold cross-validated lasso regression reduced the feature space from 50 to 4 (Figure S1, S2). Age at symptom onset, Hoehn and Yahr stage, tremor score, and the ratio of CSF Tau to amyloid-beta 1–42 (Tau:Ab) were identified as important baseline features for predicting subsequent DBS surgery. A multivariate logistic regression ($X^2 = 58.4$, $P < 0.001$) demonstrated younger age ($\beta = -0.78$, $P < 0.001$; OR = 0.46, 95% CI 0.32–0.66), lower Hoehn and Yahr stage ($\beta = -0.42$, $P = 0.026$; OR = 0.66, 95% CI = 0.46–0.95), higher tremor score ($\beta = 0.62$, $P < 0.001$; OR = 1.9, 95% CI = 1.3–2.7), and lower CSF Tau:Ab ($\beta = -1.7$, $P = 0.003$; OR = 0.21, 95% CI = 0.08–0.59) independently predicted DBS surgery (area under the ROC curve = 0.83, 95% CI = 0.77–0.88) (Fig. 1).

To characterize and compare symptom progression in these two groups, we utilized linear mixed effect models, with a random effect of subject and controlling for age at diagnosis and LEDD. We assessed the time by outcome interaction for 24 clinical variables (Table 2). DBS+ patients demonstrated slower progression in memory scores (HVLT delayed recall: $\beta = 0.32$, 95% CI 0.15–0.50, $t = 3.6$, $P < 0.05$ Bonferroni corrected; HVLT immediate recall: $\beta = 0.36$, 95% CI 0.03–0.69, $t = 2.2$, $P = 0.03$ uncorrected; HVLT discrimination: $\beta = 0.30$, 95% CI 0.10–0.49, $t = 2.9$, $P = 0.003$ uncorrected), slower progression in working memory (Letter-number sequencing: $\beta = 0.23$, 95% CI 0.07–0.39, $t = 2.8$, $P = 0.006$ uncorrected), and slower progression in overall cognitive decline (MoCA: $\beta = 0.23$, 95% CI 0.05–0.42, $t = 2.4$, $P = 0.015$ uncorrected). Along with this slower progression in cognitive decline, DBS+ patients had faster progression in disease stage (Hoehn and Yahr stage: $\beta = 0.09$, 95% CI 0.05–0.13, $t = 4.3$, $P < 0.05$ Bonferroni corrected) and motor scores (UPDRS II: $\beta = 0.32$, 95% CI 0.02–0.62, $t = 2.1$, $P = 0.036$ uncorrected; UPDRS III: $\beta = 0.79$, 95% CI 0.05–1.5, $t = 2.1$, $P = 0.035$ uncorrected; UPDRS total score: $\beta = 1.3$, 95% CI 0.29–2.4, $t = 2.5$, $P = 0.012$ uncorrected; and tremor sub-score: $\beta = 0.33$, 95% CI 0.06–0.59, $t = 2.4$, $P = 0.015$ uncorrected) as compared to DBS- patients. With respect to the main effect of time, 18 of 24 symptoms, distributed across motor and non-motor domains, showed significant progression irrespective of the group over 4 years (Table 2). The time course of motor, cognitive, and neuropsychiatric symptoms are displayed in Figs 2, 3, and Figure S3, respectively.

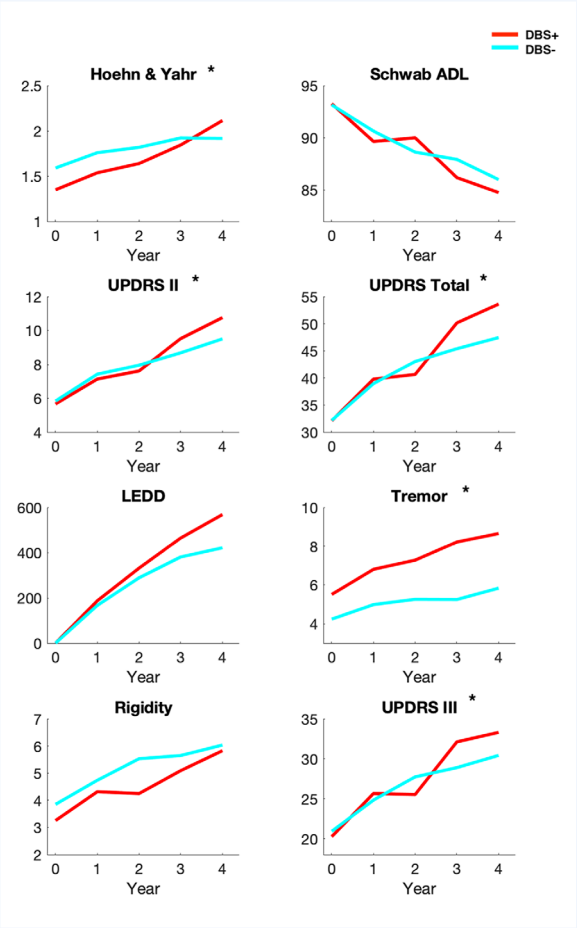

FIG. 2. Time course of motor and general clinical scores over 4 years, stratified by eventual deep brain stimulation surgery status. ADL, activity of daily living; DBS, deep brain stimulation; LEDD, levodopa equivalent daily dosage; UPDRS, unified Parkinson's disease rating scale.

Data Sharing

Data used in the preparation of this article were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/access-data-specimens/download-data).

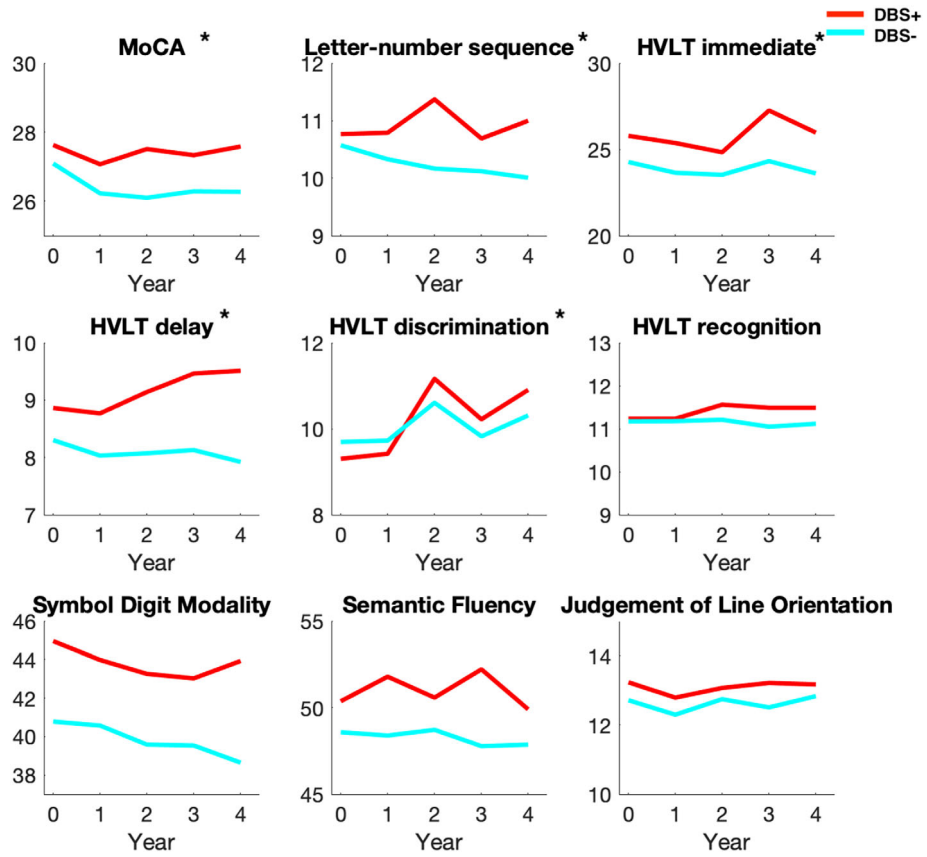

FIG. 3. Time course of cognitive scores over 4 years, stratified by eventual deep brain stimulation surgery status. HVLT, Hopkins verbal learning test; MoCA, Montreal cognitive assessment.

Discussion

DBS surgery is an effective treatment for the motor symptoms of PD.[5–7,11,23–26] Traditionally, this surgery is offered to eligible patients 10–15 years following their diagnosis, when they are in an advanced disease stage. Offering DBS earlier in the disease course has been suggested as a way of maintaining the quality of life and preventing disabling medication induced side-effects.[13–15] Predicting who may be a good surgical candidate at the time of diagnosis can help guide conversations about early surgery and may be used to help clinicians identify optimal patients. However, the relationship between DBS surgery and individual clinical and biospecimen features at diagnosis has never been investigated. In this study, we identified baseline features present at diagnosis that may help predict future surgical eligibility. This study was enabled by a deeply phenotyped cohort of PD patients who were enrolled early in their disease course and followed for many years. We identified 43 subjects in the sporadic PD cohort who underwent DBS surgery at an average time of 8.5 years. Overall, this constitutes 10% of the original PPMI cohort, which is a higher proportion than would be expected based on epidemiological studies.[27] The fact that such a large proportion undergo surgery compared to the general PD population suggests a potential bias in the PPMI cohort. These patients are highly educated (average 15.5 years of education) and are followed frequently at academic centers by neurologists knowledgeable about current treatment options. As such, it is likely their awareness of DBS is higher, and they may have more access to surgical options. Indeed, having more frequent access to a neurologist[28] has been associated with an increased chance of DBS surgery. Possibly related to this, sex did not play a significant role in eventual DBS surgery (DBS+ 37% female, DBS− 35% female). This is contrary to observations of DBS in the general population,[29] and again suggests that patients enrolled in the PPMI database are a selected group of patients. Previous investigations have assessed other epidemiological factors related to DBS surgery. For example, DBS surgery has been related to living in neighborhoods with high socioeconomic status[30] or predominantly Caucasian neighborhoods.[28] Most participants in the PPMI cohort (92%) are white and this may partially explain the greater than expected proportion of DBS+ patients. In this cohort, we did not observe differences in ethnicity, but the lack of ethnic diversity in this group limits our ability to detect such differences. We did find that the average age at surgery was

slightly younger than most of the large DBS trials, suggesting an evolving trend towards earlier surgical treatment at large academic centers.

In this cohort, younger age at diagnosis was the most important feature predicting eventual DBS surgery. This is unsurprising given that elderly patients are typically excluded from surgery due to increased comorbidities and surgical risks.[31] Further, early onset disease has been associated with an increased risk for levodopa induced dyskinesias,[3,32] which is a major surgical selection criterion. Less severe initial disease stage and increased tremor scores at diagnosis were also important predictors, reflecting surgical decision-making biases towards treating tremor dominant patients. Levodopa resistant axial symptoms, including postural instability and freezing of gait, typically do not respond to DBS. In the most novel finding of this investigation, the ratio of CSF Tau:Ab was also identified as a predictor of DBS surgery. CSF Tau:Ab has previously been shown to be a marker of amyloid burden[33] and higher Tau:Ab levels can predict subsequent cognitive decline in non-PD[34] and PD patients.[35] Consistent with this, we found that DBS- patients experienced a faster decline in cognitive function early in their disease course as compared to patients who were later offered DBS surgery. The role of CSF Tau:Ab in predicting surgical eligibility, and more importantly, in predicting surgical outcomes is an exciting avenue for future research. Conversely, DBS+ patients experienced a more rapid decline in motor function, exemplified by an increase in the rate of change of H&Y disease stage, UPDRS II, III, and total score, and an increased rate of change of the tremor sub-score. Overall, these results reflect the surgical eligibility criteria, with DBS being offered to patients with tremor who have disabling symptoms and preserved cognitive abilities. By characterizing the early disease course of patients enrolled in the PPMI who eventually receive DBS, we confirm that the surgical indications in this cohort are reflective of general clinical practice.

Limitations

There are several limitations of this investigation that should be considered. Firstly, the UPDRS IV score (reflecting motor complications) was not documented at the early subject visits in the PPMI cohort, likely because patients were mostly untreated. We are therefore unable to quantitate early motor complications in this cohort. However, we can reasonably assume that patients who received DBS had significant motor complications, and this is reflected in their faster H&Y stage increase, as well as the faster rate of increase in the UPDRS II and III off scores. A second limitation is that we are unable to determine what proportion of patients were offered DBS surgery but declined, or those who were eligible but were not offered due to unrealistic expectations. One study found that only 28% of DBS eligible patients consented to referral to a specialized DBS center,[36] while another found that 4% of eligible patients were not provided surgical options because of unrealistic expectations.[37] This information is not documented in the PPMI database. We are also unable to determine how many patients were excluded from surgery due to medical comorbidities or psychiatric comorbidities. Lastly, while we record whether or not patients underwent DBS surgery, we do not document the response of patients to surgery. Response to DBS depends not only on the proper selection of patients but also on surgical technique and post-operative stimulation programming. Our results must be interpreted as factors that predict surgical eligibility rather than those that predict surgical outcomes. We note that at this time there is insufficient evidence to consider surgical options earlier than in patients similar to those in the EarlyStim trial.[14] However, biomarkers may still guide clinicians when discussing surgical options and their utility may increase if evidence emerges to support surgical options earlier in the disease course. At this time they should not be used to select patients for surgery prior to the development of established clinical indications.

Conclusion

Younger age at symptom onset, lower disease stage, higher tremor score, and lower baseline CSF Tau:Ab are predictors of eventual DBS surgery and can be used for early identification of patients who may be surgical candidates during the course of their disease. Patients who receive DBS surgery have sustained cognitive function with a more rapid decline in motor symptoms compared to patients who do not receive DBS surgery. This is likely related to surgical selection criteria, which excludes elderly patients and those with cognitive decline, while biased towards treating patients with tremor who have significant impairment. These results may be used to guide discussions about disease progression and DBS surgery with newly diagnosed patients.

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Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution. (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique. (3) Manuscript: A. Writing of the first draft, B. Figures, C. Review and Critique. (4) Study Supervision.

S.L.: 1A, 1B, 1C, 2A, 2B, 3A, 3B
A.V.: 2C, 3C
C.C.: 2C, 3C
L.K.: 2C, 3C
S.K.: 2C, 3C, 4
A.L.: 2C, 3C, 4.

Disclosures

Ethical Compliance Statement: As PPMI is an international multisite study, each individual site received ethical approval and written consent from all participating subjects from study investigators. The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines after approval of the local ethics committees of the participating sites. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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References

1. Kalia LV, Lang AE. Parkinson's disease. *Lancet* 2015;386(9996):896–912. https://doi.org/10.1016/S0140-6736(14)61393-3.
2. Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: a review. *JAMA* 2014;311(16):1670–1683. https://doi.org/10.1001/jama.2014.3654.
3. Jankovic J. Motor fluctuations and dyskinesias in Parkinson's disease: clinical manifestations. *Mov Disord* 2005;20(Suppl. 11):S16. https://doi.org/10.1002/mds.20458.
4. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. *JAMA* 2020;323(6):548–560. https://doi.org/10.1001/jama.2019.22360.
5. Williams A, Gill S, Varma T, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial. *Lancet Neurol* 2010;9(6):581–591. https://doi.org/10.1016/S1474-4422(10)70093-4.
6. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355(9):896–908. https://doi.org/10.1056/nejmoa060281.
7. Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial. *JAMA* 2009;301(1):63–73. https://doi.org/10.1001/jama.2008.929.
8. Hariz M, Blomstedt P. Deep brain stimulation for Parkinson's disease. *J Intern Med* 2022;292:764–778. https://doi.org/10.1111/joim.13541.
9. Morgante L, Morgante F, Moro E, et al. How many parkinsonian patients are suitable candidates for deep brain stimulation of subthalamic nucleus? Results of a questionnaire. *Park Relat Disord* 2007;13(8):528–531. https://doi.org/10.1016/j.parkreldis.2006.12.013.
10. Defer GL, Widner H, Marié RM, Rémy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999;14(4):572–584. https://doi.org/10.1002/1531-8257(199907)14:4<572::AID-MDS1005>3.0.CO;2-C.
11. Okun MS, Gallo BV, Mandybur G, et al. Subthalamic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial. *Lancet Neurol* 2012;11(2):140–149. https://doi.org/10.1016/S1474-4422(11)70308-8.
12. Desouza RM, Moro E, Lang AE, Schapira AHV. Timing of deep brain stimulation in Parkinson disease: a need for reappraisal? *Ann Neurol* 2013;73(5):565–575. https://doi.org/10.1002/ana.23890.
13. Beukers RJ, Weisfelt M, De Bie RMA. Neurosurgery at an earlier stage of Parkinson disease. *Neurology* 2007;69(8):811–812. https://doi.org/10.1212/01.wnl.0000281349.66009.35.
14. Rau J, Knudsen K, Volkmann J, et al. Neurostimulation for Parkinson's disease with early motor complications. *N Engl J Med* 2013;368(21):2037–2038. https://doi.org/10.1056/nejmc1303485.
15. Suarez-Cedeno G, Suescun J, Schiess MC. Earlier intervention with deep brain stimulation for Parkinson's disease. *Parkinsons Dis* 2017;2017:1–9. https://doi.org/10.1155/2017/9358153.
16. Charles D, Konrad PE, Neimat JS, et al. Subthalamic nucleus deep brain stimulation in early stage Parkinson's disease. *Park Relat Disord* 2014;20(7):731–737. https://doi.org/10.1016/j.parkreldis.2014.03.019.
17. Hacker ML, Turchan M, Heusinkveld LE, et al. Deep brain stimulation in early-stage Parkinson disease: five-year outcomes. *Neurology* 2020;95(4):E393–E401. https://doi.org/10.1212/WNL.0000000000009946.
18. Marek K, Chowdhury S, Siderowf A, et al. The Parkinson's progression markers initiative (PPMI) – establishing a PD biomarker cohort. *Ann Clin Transl Neurol* 2018;5(12):1460–1477. https://doi.org/10.1002/acn3.644.
19. Simuni T, Siderowf A, Lasch S, et al. Longitudinal change of clinical and biological measures in early Parkinson's disease: Parkinson's progression markers initiative cohort. *Mov Disord* 2018;33(5):771–782. https://doi.org/10.1002/mds.27361.
20. Marek K, Jennings D, Lasch S, et al. The Parkinson progression marker initiative (PPMI). *Prog Neurobiol* 2011;95(4):629–635. https://doi.org/10.1016/j.pneurobio.2011.09.005.
21. Tibshirani R. Regression shrinkage and selection via the lasso. *J R Stat Soc Ser B* 1996;58(1):267–288. https://doi.org/10.1111/j.2517-6161.1996.tb02080.x.
22. Hastie T, Tibshirani R, Friedman J. *The Elements of Statistical Learning: Data Mining, Inference, and Prediction*. 2nd ed. Berlin and Heidelberg: Springer; 2009.
23. Castrioto A, Lozano AM, Poon Y-Y, Lang AE, Fallis M, Moro E. Ten-year outcome of subthalamic stimulation in Parkinson disease: a blinded evaluation. *Arch Neurol* 2011;68(12):1550–1556. https://doi.org/10.1001/archneurol.2011.182.
24. Bronstein JM, Tagliati M, Alterman RL, et al. Deep brain stimulation for Parkinson disease an expert consensus and review of key issues. *Arch Neurol* 2011;68(2):165–171. https://doi.org/10.1001/archneurol.2010.260.
25. Thomsen BLC, Jensen SR, Clausen A, Karlsborg M, Jespersen B, Løkkegaard A. Deep brain stimulation in Parkinson's disease: still effective after more than 8 years. *Mov Disord Clin Pract* 2020;7(7):788–796. https://doi.org/10.1002/mdc3.13040.
26. 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.
27. Kestenbaum M, Ford B, Louis ED. Estimating the proportion of essential tremor and Parkinson's disease patients undergoing deep brain stimulation surgery: five-year data from Columbia University Medical Center (2009–2014). *Mov Disord Clin Pract* 2015;2(4):384–387. https://doi.org/10.1002/mdc3.12185.
28. Crispo JAG, Lam M, Le B, et al. Disparities in deep brain stimulation use for Parkinson's disease in Ontario, Canada. *Can J Neurol Sci* 2020;47(5):642–655. https://doi.org/10.1017/cjn.2020.79.
29. Jost ST, Strobel L, Rizos A, Loehrer PA, Ashkan K, Evans J. Gender gap in deep brain stimulation for Parkinson's disease. *npj Park Dis* 2022;8(1):1–10. https://doi.org/10.1038/s41531-022-00305-y.
30. Willis AW, Schootman M, Kung N, Wang X-Y, Perlmutter JS, Racette BA. Disparities in deep brain stimulation surgery among insured elders with Parkinson disease. *Neurology* 2014;82(2):163–171. https://doi.org/10.1212/WNL.0000000000000017.
31. Munhoz RP, Picillo M, Fox SH, Bruno V, Panisset M, Honey CR, Fasano A. Eligibility criteria for deep brain stimulation in Parkinson's disease, tremor, and dystonia. *Can J Neurol Sci* 2016;43(4):462–471. https://doi.org/10.1017/cjn.2016.35.
32. Wickremaratchi MM, Ben-Shlomo Y, Morris HR. The effect of onset age on the clinical features of Parkinson's disease. *Eur J Neurol* 2009;16(4):450–456. https://doi.org/10.1111/j.1468-1331.2008.02514.x.
33. Tapiola T, Alafuzoff I, Herukka SK, Parkkinen L, Hartikainen P, Soininen H, Pirttilä T. Cerebrospinal fluid β-amyloid 42 and tau proteins as biomarkers of Alzheimer-type pathologic changes in the brain. *Arch Neurol* 2009;66(3):382–389. https://doi.org/10.1001/archneurol.2008.596.

34. Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/β-amyloid42 ratio as a prediction of cognitive decline in nondemented older adults. *Arch Neurol* 2007; 64(3):343–349. https://doi.org/10.1001/archneur.64.3.noc60123.

35. Liu C, Cholerton B, Shi M, et al. CSF tau and tau/Aβ42 predict cognitive decline in Parkinson's disease. *Park Relat Disord* 2015;21(3):271–276. https://doi.org/10.1016/j.parkreldis.2014.12.027.

36. Wächter T, Mínguez-Castellanos A, Valldeoriola F, Herzog J, Stoevelaar H. A tool to improve pre-selection for deep brain stimulation in patients with Parkinson's disease. *J Neurol* 2011;258(4):641–646. https://doi.org/10.1007/s00415-010-5814-y.

37. Geraedts VJ, Kuijf ML, van Hilten JJ, Marinus J, Oosterloo M, Contarino MF. Selecting candidates for deep brain stimulation in Parkinson's disease: the role of patients' expectations. *Park Relat Disord* 2019;66:207–211. https://doi.org/10.1016/j.parkreldis.2019.07.011.

Supporting Information

Supporting information may be found in the online version of this article.

Figure S1. Cross-validated deviance of Lasso fit using 50 baseline predictors with DBS outcome (DBS+/DBS-) as outcome variable.

Figure S2. Trace plot of coefficients fit by Lasso.

Figure S3. Time course of neuropsychiatric, autonomic and sleep-related clinical scores over four years, stratified by eventual deep brain stimulation surgery status.