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Research Report

Predicting Motor Outcome and Quality of Life After Subthalamic Deep Brain Stimulation for Parkinson's Disease: The Role of Standard Screening Measures and Wearable-Data

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Abstract.
Background: Standardized screening for subthalamic deep brain stimulation (STN DBS) in Parkinson's disease (PD) patients is crucial to determine eligibility, but its utility to predict postoperative outcomes in eligible patients is inconclusive. It is unknown whether wearable data can contribute to this aim.
Objective: To evaluate the utility of universal components incorporated in the DBS screening, complemented by a wearable sensor, to predict motor outcomes and Quality of life (QoL) one year after STN DBS surgery.
Methods: Consecutive patients were included in the OPTIMIST cohort study from two DBS centers. Standardized assessments included a preoperative Levodopa Challenge Test (LCT), and questionnaires on QoL and non-motor symptoms including cognition, psychiatric symptoms, impulsiveness, autonomic symptoms, and sleeping problems. Moreover, an ambulatory wearable sensor (Parkinson Kinetigraph (PKG)) was used. Postoperative assessments were similar and also included a Stimulation Challenge Test to determine DBS effects on motor function.
Results: Eighty-three patients were included (median (interquartile range) age 63 (56–68) years, 36% female). Med-OFF (Stim-OFF) motor severity deteriorated indicating disease progression, but patients significantly improved in terms of Med-ON (Stim-ON) motor function, motor fluctuations, QoL, and most non-motor domains. Motor outcomes were not predicted by preoperative tests, including covariates of either LCT or PKG. Postoperative QoL was predicted by better preoperative QoL, lower age, and more preoperative impulsiveness scores in multivariate models.
Conclusion: Data from the DBS screening including wearable data do not predict postoperative motor outcome at one year. Post-DBS QoL appears primarily driven by non-motor symptoms, rather than by motor improvement.

Keywords: Deep brain stimulation, subthalamic nucleus, Parkinson's disease, motor function, quality of life, screening

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INTRODUCTION

Subthalamic deep brain stimulation (STN DBS) is an effective therapy for patients with Parkinson's disease (PD) to relieve motor complications refractory to oral medication [1–3]. STN DBS has been demonstrated to be superior to best medical treatment in terms of quality of life (QoL) [1, 2], and reduces the requirement of oral dopaminergic treatment [1, 3]. However, DBS carries substantial risks, such as surgical complications including infections and brain hemorrhage, speech problems, balance and gait problems, and worsening of cognition [4, 5]. Careful screening of patients to determine eligibility for DBS, both in terms of minimizing the risks and maximizing the likelihood of benefits, is therefore of paramount importance [5–8]. Several screening algorithms for candidate selection have been previously proposed [6], mostly with high sensitivity but low specificity. To date, it remains difficult to accurately predict success after DBS, both in terms of motor improvement [9] and QoL [10]. Heterogeneity in study design, patient population, definition of 'DBS success' and follow-up duration, impair comparison across studies [11, 12]. Also, the utility of novel biomarkers such as functional magnetic resonance imaging (fMRI) [13], tractography [14], or genetic profiling [15] is reduced due to limited availability during routine DBS screening, whereas data on other potential determinants of DBS effects such as lead position only become available after surgery [16, 17].

According to current recommendations, clinical screening for DBS eligibility should include an assessment of motor, cognitive and psychiatric symptoms [4, 5, 8, 18, 19]. Once clinical eligibility is ascertained, MRI is used to determine the anatomical safety of surgical placement of leads.

A typical component of the eligibility-screening for DBS that is routinely available in most, if not all DBS centers, is the Levodopa Challenge Test (LCT), in which a patient is admitted to the hospital to assess the levodopa-responsiveness, considered to be an important indicator of motor outcomes after DBS [7, 12, 19–22]. This is done by comparing the symptoms severity motor score in the practically defined off condition (Med-OFF) and after a suprathreshold early morning Levodopa Equivalent Dose (LED - Med-ON). Limitations of this test include the patient burden associated with the Med-OFF-state [22] and the stressful hospital setting which may produce findings that do not reflect 'worst OFF' or 'best ON' as experienced by patients in their home situation [23]. Given these concerns, instruments that measure severity of motor complications in the home-situation (such as the Parkinson Kinetigraph (PKG)) may augment or replace the LCT. Several sensor-based techniques may have potential to provide results that reflect levodopa-responsiveness [20, 24–26].

It is unclear whether clinical measures used to determine DBS eligibility can also be used to predict outcomes after STN DBS, both in terms of motor functioning and in terms of QoL. The aim of this study was to evaluate the utility of different preoperative clinical scores used for determining DBS eligibility and a home-based quantitative measure of motor fluctuations in predicting motor outcomes and QoL one year after surgery.

METHODS

Consecutive patients who underwent STN DBS at the Haga/Leiden University Medical Centre (LUMC) DBS center or at the Medical Spectrum Twente (MST) between May 2017 and July 2019 were included in the OPTIMIST cohort study (OPTIMIzing patient selection for deep brain STimulation of the subthalamic nucleus) (Netherlands Trial Register NL6079). All patients fulfilled the Movement Disorders Society (MDS) PD criteria. Written informed consent was obtained from all participants. The study was approved by the medical ethics committee (METC Leiden Den Haag Delft). STROBE guidelines were adhered to during the writing of this manuscript.

Procedures and inclusion

Standardized questionnaires and routine assessments were performed as part of the DBS screening procedure [6]. with an additional 7 days continuous ambulatory assessment through the Parkinson Kinetigraph (PKG®), a wearable sensor resembling a wrist watch. The PKG is worn on the more affected arm (left arm in case of symmetric Parkinsonism), and contains an accelerometer, medication reminder and means to acknowledge and record when PD medication has actually been taken [27, 28].

During the DBS screening, a LCT was performed using a suprathreshold dosage of dispersible levodopa (120% of the early morning LED) [22]. Surgery took place approximately 1-2 months after DBS screening. Surgical procedures have been previously published

[29]. Lead-placement was confirmed using intraoperative or postoperative computed tomography (CT) scans, in both centers.

Follow-up evaluations took place 1 year after surgery (± 6 weeks) and included similar questionnaires and assessments. Preoperatively, a stimulation challenge test was performed in the morning between 8.00 and 11.00 AM according to the following timing: Med-OFF condition after an overnight withdrawal of minimum 12 hours, Med-ON condition one hour after administration of a suprathreshold dose of dispersible levodopa. Postoperatively, patients were first assessed for their Med-OFF/Stim-ON condition in a similar fashion after an overnight withdrawal. Med-OFF/Stim-OFF conditions were assessed 15 minutes later, after which patients received their suprathreshold dispersible levodopa dose. One hour later, patients were assessed in the Med-ON/Stim-ON condition [30].

Scales used

Clinical variables included disease-related motor severity (Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) III), motor fluctuations (MDS-UPDRS IV), motor- and non-motor aspects of experiences of daily living (MDRS-UPDRS I and II), LEDD [31], DBS impairment (DBS-IS, using an in-house structured translation in Dutch), severity of predominantly non-dopaminergic symptoms in Parkinson's disease (SENS-PD), QoL (Parkinson's Disease Questionnaire 39 summary index (PDQ39SI)), cognition (Montreal Cognitive Assessment (MoCA)) and Mattis Dementia Rating Scale (MDRS)), psychiatric symptoms (depression: Becks Depression Inventory (BDI), anxiety: Parkinson Anxiety Scale (PAS), apathy: Apathy Evaluation Scale (AES), and symptoms of impulsiveness / impulse control disorder (Quip-RS and Quip-RS-ICD)), autonomic symptoms (SCOPA-AUT), night time sleeping problems (SCOPA-SLEEP), excessive daytime sleepiness (EDS, SCOPA-SLEEP), and Freezing of Gait questionnaire (FOG-Q).

Motor outcomes

For prediction of motor success, age and disease duration were selected as 'baseline model' based on previous literature [11, 12, 32]. Two separate sets of preoperative predictors were identified, based on either the gold-standard LCT to reflect preoperative motor functioning in a clinically controlled setting, or alternatively metrics from the PKG to reflect ambulatory motor functioning.

Motor success was defined in several ways: continuous motor outcomes were defined as:

- 'improvement due to stimulation only': ((Med-OFF/Stim-OFF – Med-OFF/Stim-ON) / Med-OFF/Stim-OFF),
- 'improvement due to optimal therapy': ((Med-OFF/Stim-OFF – Med-ON/Stim-ON) / Med-OFF/Stim-OFF,
- 'postoperative motor functioning': (Med-ON/Stim-ON).
- Dichotomous outcomes were based on a cut-off of 45% improvement due to stimulation, selected *a priori* as being perceived as a 'large improvement' due to DBS (categorical outcome) [33]. This was calculated based on pooled estimates of pre- and postoperative MDS-UPDRS III scores [12, 34, 35]. A cut-off of 30% was selected as being perceived as an 'acceptable improvement' due to STN DBS.

To compare whether the predictive performance of the PKG is non-inferior to the more standard LCT, the contribution of LCT and PKG covariates to the baseline model (age+disease duration) were tested separately.

For the LCT model, covariates included preoperative MDS-UPDRS III Med-OFF and Med-ON, preoperative response to levodopa ((Med-OFF – Med-ON) / Med-OFF), and disease progression (defined as: (preoperative Med-OFF - follow-up Med-OFF) / preoperative Med-OFF). Subscores rigidity (items 3.3 a-e), bradykinesia (items 3.4 – 3.8), and tremor (items 3.15 – 3.18) in the preoperative Med-OFF and Med-ON conditions were included as separate predictors.

For the PKG-model, the following previously validated PKG-metrics were included: PKG Bradykinesia score (PKG-BKS) [24], percent time in bradykinesia (PKG-PTB), Dyskinesia Score (PKG-DKS) [24], percent time in dyskinesia (PKG-PTD), PKG tremor score (PKG-T) [26], PKG Fluctuation Score (PKG-FS) [25], PKG response to early morning LED (PKG-LCT) [20], PKG response across dose, and PKG readiness for advanced therapies (PKG DAT readiness; an indicator-metrics of being 'suitable on motor grounds') [36].

QoL outcomes

For the prediction of postoperative QoL, absolute PDQ39 (PDQ39 SI) scores were used, both in terms of absolute scores and 'improvement due to stimulation' ((preoperative PDQ39 – follow-up PDQ39)/preoperative PDQ39). Based on the Minimal Clinically Important Difference (MCID) of the PDQ39 [37], patients with an improvement ≥ 5 points were classified as successfully improved, whereas patients with stable or deteriorated QoL scores were considered the negative class. Preoperative demographic and clinical characteristics were added as covariates to determine their association.

Statistical analyses

Sample size calculation was performed based on a previously identified correlation coefficient of 0.58 [38], using a two-sided 95% confidence interval (95%CI) width of 0.300 (0.43–0.73, PASS sample size software) resulting in an estimated sample size of 74 which would allow detection of a small-to-medium effect size (i.e., 0.11) to detect a significant increase of explained variance with an α of 0.05 and a β of 0.20. We assumed a drop-out rate of 10%, resulting in a sample-size of 83 required for inclusion.

Comparisons between demographic and clinical variables between baseline and follow-up were made with paired *T*-tests, Wilcoxon signed rank tests and Pearson χ^2 tests, where appropriate. *P*-values were reported using Monte Carlo estimation in case of Wilcoxon signed ranks tests, and Fisher's exact test in case of dichotomous χ^2 tests.

For the motor outcomes 'improvement due to stimulation', 'improvement due to optimal therapy', and 'postoperative motor functioning', linear regression analyses were performed. A first block with a forced entry covariance matrix included the predictors age and disease duration; a second block was added to test the individual contribution of either PKG or LCT variables using a forced entry covariance matrix. A regression model using backward variable selection was used on all covariates simultaneously, with separate analyses for a 'PKG-model' and a 'LCT-model' (both models included age and disease duration as additional variables).

For the outcomes '> 45% improvement due to stimulation' and '> 30% improvement due to stimulation', logistic regression analyses were performed. Similar block constructions were used as for the linear regression analyses.

For QoL outcomes, linear regression analyses were used for the outcomes 'follow-up PDQ39 SI' and 'QoL improvement after DBS'. Forced entry covariance matrices were used for each individual demographic or clinical variable. Observing the 10-cases-per-variable rule-of-thumb, the 8 variables with the highest individual R^2 were selected for a backward variable selection model for both continuous outcomes. Logistic regression analyses were performed for the dichotomous QoL outcomes; the 4 outcomes with the highest individual area-under-the-curve (AUC) (assuming a relatively similar class-division) were used for a multivariate model using backward variable selection.

All analyses were performed using IBM Statistical Package for the Social Sciences 25 Software (SPSS). Data may be shared upon request.

RESULTS

Eighty-three patients (LUMC: $n = 73$, MST: $n = 10$) were included in this study (median (interquartile range (IQR)) age 63 (56–68) years, 36% female, median (IQR) disease duration 9.6 (6.7–12.6) years) (see Table 1). Eight patients refused the follow-up visit and received no assessment of motor function, one patient had the DBS leads explanted due to infection and subsequently refused to stop his medication for the follow-up challenge test and only contributed MDS-UPDRS III Med-ON (Stim-OFF) scores, as well as other non-motor tests. Ten patients received Vercise Cartesia (Boston Scientific) directional electrodes; all other patients received Medtronic 3389 leads.

Change after STN DBS

Preoperative characteristics and evolution of symptoms after STN DBS is shown in Table 1. Compared to preoperative Med-OFF (mean (SD) 43.4 (11.2)) Med-OFF/Stim-OFF (50.3 (13.0)) showed a significant worsening of motor function at 1 year follow-up. Nonetheless, motor function in the Med-ON/Stim-ON condition was similar to preoperative Med-ON scores. The mean (SD)% improvement due to optimal therapy (Med-ON/Stim-ON vs. preoperative Med-ON) was significantly higher than the preoperative improvement with medication (66 (14)% vs. 56 (14)%).

At 1 year follow-up motor fluctuations and LEDD were significantly reduced, as well as FOG-Q scores. Depressive symptoms and anxiety (using abso-

Table 1
Baseline characteristics and evolution of symptoms

		Baseline	Follow-up	p*
N		83	75 (tests)	
80 (questionnaires)				
% female sex (n)		36 (30)		
Age at baseline [a]		63 (56–68)		
Disease duration [a]		9.6 (6.7–12.6)		
GIC [a]			6 (improved) (5–7)	
GSS [a]			6 (satisfied) (5–7)	
% opt for DBS again (n)			80 (61)	
MDS-UPDRS III (Med-OFF) [b]	Med-OFF Stim-OFF	43.4 (11.2)	50.3 (13.0)	<0.001
	Med-OFF Stim-ON		27.6 (9.8)	< 0.001
MDS-UPDRS III (Med-ON) [b]		19.1 (8.3)		< 0.001
	Med-ON Stim-ON		17.4 (9.4)	0.066
% improvement MDS-UPDRS III through therapy ((OFF – ON) / (OFF)) [b]	% improvement through stimulation (Med-OFF/Stim-ON)	56 (14)	44 (15)	< 0.001
	% improvement through optimal therapy (Med-ON/Stim-ON)		66 (14)	< 0.001
MDS-UPDRS I [b]		14.9 (5.9)	13.1 (5.6)	0.001
MDS-UPDRS II [b]		14.6 (6.5)	12.7	0.006
MDS-UPDRS IV [a]		9 (7–11)	3 (0 – 6)	< 0.001
LED [b]		1148 (473)	492 (294)	< 0.001
Levodopa challenge test dose [a]		271 (180–366)	120 (62–180)	< 0.001
SENS-PD total [a]		11 (8–15)	11 (7–15)	0.828
MoCA [b]		26.1 (2.2)	26.0 (2.5)	0.294
MDRS [a]		139 (137–142)	139 (137–142)	0.459
FOG-Q [a]		7 (3–12)	4 (1 – 8.5)	< 0.001
BDI [b]		12.0 (6.8)	10.3 (6.9)	0.025
	% minimal complaints (n) [c]	62 (51)	73 (58)	0.001
	% mild depression (n) [c]	22 (18)	16 (13)	
	% moderate depression (n) [c]	15 (12)	10 (8)	
	% severe depression (n) [c]	1 (1)	1 (1)	
PAS [a]		10 (6–17)	8 (3 – 15)	0.012
	% low PAS (n) [c]	61 (51)	70 (55)	< 0.001
	% high PAS (n) [c]	39 (32)	30 (24)	
Apathy Scale [b]		10.7 (3.0)	11.9 (3.7)	0.116
	% no or mild apathy (n) [c]	83 (69)	78 (53)	0.275
	% severe apathy (n) [c]	17 (14)	22 (15)	
Quip-RS-ICD [a]		3 (0–8.3)	1 (0 – 6)	0.040
Quip-RS total [a]		8 (0–17)	3.5 (0 – 12)	0.002
SCOPA-AUT [b]		16.7 (7.2)	14.6 (7.5)	0.002
SCOPA-Sleep [b]		6.0 (3.2)	3.8 (3.3)	< 0.001
	% no night-time sleeping problems (n) [c]	55 (46)	80 (64)	0.161
	% night-time sleeping problems (n) [c]	45 (37)	20 (16)	
SCOPA-EDS [b]		4.0 (3.1)	3.7 (3.3)	0.386
	% no EDS (n) [c]	61 (51)	70 (56)	0.006
	% EDS (n) [c]	39 (32)	30 (24)	
PDQ-39 [b]		46.1 (20.8)	36.2 (23.1)	< 0.001
EQ5D [a]		11 (9 – 12)	8 (7 – 10)	< 0.001
DBS IS [b]		17.7 (9.6)	19.0 (13.1)	0.412

[a]Median (interquartile range), Wilcoxon signed rank tests; [b]Mean (standard deviation), paired *T*-tests; [c]Pearson χ^2 tests. *Monte Carlo estimation in case of Wilcoxon signed rank tests; Fisher's exact test in case of Pearson χ^2 tests. A False Discovery Rate (FDR) corrected cut-off for significance to account for multiple testing, based on an α of 0.050, would be 0.033. BDI, Becks Depression Inventory; DBS, Deep Brain Stimulation; DBS IS, DBS Impairment Scale; EQ5D, EuroQol 5 dimensions; GIC, Global Impression of Change; GSS, Global Satisfaction with Surgery; FOG-Q, Freezing of Gait Questionnaire; LED, Levodopa Equivalent Dose; MoCA, Montreal Cognitive Assessment; MDRS, Mattis Dementia Rating Scale; MDS-UPDRS, Movement Disorders Society – Unified Parkinson's Disease Rating Scale; PAS, Parkinson's disease Anxiety Scale; PDQ 39, Parkinson's Disease Questionnaire; Quip-RS (ICD), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (Impulsive-Compulsive Disorder symptoms); SCOPA (AUT / EDS), SCales for Outcomes in PArkinson's disease (Autonomic symptoms / Excessive Daytime Sleepiness); SENS-PD, SEverity of predominantly Nondopaminergic Symptoms in PD.

lute and cut-off scores) and impulsive-compulsive symptoms were also significantly lower at 1 year follow-up. Autonomic symptoms and night-time sleeping problems were significantly relieved after STN DBS; both generic and disease-specific QoL was improved after STN DBS. Apathy, cognition and EDS were not significantly different at follow-up. Patients were on average 'satisfied' with STN DBS, and reported an improvement after DBS, both estimated using seven-point Likert scales (median response value 6 in in both instances). Eighty percent of patients would opt for STN DBS again. Thirty-four patients had > 45% improvement in MDS-UPDRS III due to combined stimulation and oral therapy; 64 patients had > 30% improvement.

Prediction of motor success

For the outcome '% improvement due to stimulation only', the only significant univariate predictor was age (i.e., higher age was predictive of less improvement). Age was also retained as the only predictor in multivariate prediction models, both for the LCT-model and the PKG-model (see Table 2).

In the univariate '% improvement due to optimal therapy' outcome model, higher age similarly predicted less improvement; in addition, higher severity of PKG bradykinesia predicted less improvement, and more PKG % time spent in dyskinesia predicted more improvement.

In the multivariate PKG model ($R^2 = 0.307$), the following variables were retained: age, PKG-DKS (higher severity of dyskinesias predicted more improvement), and PKG DAT readiness (greater readiness predicted less improvement). For the multivariate LCT model, only age was retained (regression coefficient (B)=–0.007, 95%CI –0.011, –0.003; $R^2 = 0.154$) (see Table 3).

For the outcome 'postoperative motor function (ON)', lower severity of motor symptoms was predicted by lower age, and lower scores for PKG-BKS, less % time spent in bradykinesia, and higher PKG-T, lower scores for the preoperative MDS-UPDRS III Med-ON, Med-OFF, subscore tremor Med-ON, subscore tremor Med-OFF, and LCT response to levodopa (greater levodopa responsiveness predicted postoperative lower motor severity) (see Table 2).

In the multivariate PKG model ($R^2 = 0.478$), age was retained, as well as PKG-BKS, PKG-DKS, and PKG-T. In the multivariate LCT model ($R^2 = 0.470$), age was retained ($B = 0.448$, 95%CI 0.257, 0.640), as well as LCT MDS-UPDRS III Med-OFF, and disease progression (more disease progression predicted greater motor severity (see Table 3).

For the dichotomous outcome 'motor success based on 45% improvement due to stimulation', no covariate was a significant univariate predictor. In the multivariate PKG model, age was retained in the multivariate prediction models (higher age was predictive of a lower odds of having successful STN DBS surgery (AUC 0.659, 95%CI 0.534, 0.784). In the multivariate LCT model (AUC 0.695, 95%CI 0.575, 0.816), age was retained (OR = 0.926, 95%CI 0.865, 0.992), as well as MDS-UPDRS III OFF, and response to levodopa. A prediction model based on 'motor success based on 30% improvement due to stimulation' was unsuccessful due to severe class imbalance (64 vs. 9 patients; all patients were classified as having successful surgery by the model) (see Table 3).

Prediction of QoL success

Univariate prediction coefficients of PDQ39 scores at follow-up and PDQ39 improvement are shown in Table 4.

Better QoL at follow-up was significantly associated with univariate preoperative predictors lower age, lower PDQ39 scores at baseline, and better cognition at baseline (MoCA). A multivariate prediction model ($R^2 = 0.431$), using backward variable selection, showed that better QoL was associated with lower age, higher impulsive-compulsive symptoms, less symptoms of depression, and better QoL (see Table 5).

QoL improvement was significantly associated with univariate preoperative predictors male sex, more motor fluctuations, more non-dopaminergic symptoms, higher scores on the DBS-IS, worse QoL scores, more depressive symptoms, more symptoms of anxiety, more autonomic symptoms, and more freezing-symptoms. A multivariate prediction model ($R^2 = 0.274$), using backward variable selection, showed that more QoL improvement was associated with more symptoms of anxiety, and higher scores on the DBS-IS.

If a cut-off to predict improvement based on the MCID is used (AUC 0.729, 95%CI 0.613, 0.845), better QoL is predicted by preoperative univariate variables lower age, lower QoL scores, more impulsive-compulsive symptoms, and more autonomic symptoms. A multivariate prediction model, using backward variable selection, showed that clinically important QoL improvement was significantly

Table 2
Predictors of postoperative motor outcomes (univariate)

	Relative improvement due to stimulation [a]		Relative improvement due to optimal therapy [b]		Postoperative motor function [c]		Success based on 45% cut-off	
Univariate covariates	B	95%CI	B	95%CI	B	95%CI	OR	95%CI OR
Age	–0.006	–0.010, –0.002	–0.007	–0.011, –0.003	0.467	0.200, 0.734	0.946	0.888, 1.009
Disease duration (y)	0.003	–0.005, 0.010	–0.002	–0.009, 0.006	–0.003	–0.490, 0.483	0.949	0.845, 1.066
PKG-BKS	<0.001	–0.006, 0.006	–0.008	–0.013, –0.003	0.382	0.007, 0.756	1.000	0.920, 1.086
PKG % time in bradykinesia	<0.001	–0.002, 0.002	–0.001	–0.003,<0.001	0.132	0.037, 0.227	0.999	0.975, 1.023
PKG-DKS	–0.002	–0.010, 0.005	0.003	–0.004, 0.010	0.170	–0.307, 0.646	0.936	0.834, 1.052
PKG % time in dyskinesia	<0.001	–0.002, 0.002	0.002	<0.001, 0.004	–0.030	–0.172, 0.112	0.988	0.956, 1.021
PKG tremor	0.001	–0.007, 0.008	–0.004	–0.011, 0.003	0.668	0.318, 1.018	0.955	0.895, 1.106
PKG-FS	–0.003	–0.014, 0.008	0.003	–0.007, 0.014	–0.127	–0.821, 0.568	0.959	0.814, 1.130
PKG-LCT	0.015	–0.021, 0.051	0.010	–0.024, 0.044	0.424	–1.888, 2.737	1.146	0.706, 1.862
PKG-response across dose	–0.003	–0.036, 0.043	–0.010	–0.047, 0.028	–0.200	–2.956, 2.565	1.113	0.638, 1.942
PKG-DAT readiness	<0.001	–0.001, 0.001	<0.001	–0.001,<0.001	0.051	–0.008, 0.109	1.000	0.986, 1.013
LCT MDS-UPDRS III response to levodopa (relative)	0.011	–0.232, 0.254	0.163	–0.066, 0.392	–14.485	–28.636, –0.335	10.204	0.287, 362.835
LCT MDS-UPDRS III Med-ON	<0.001	–0.004, 0.004	–0.003	–0.007, 0.001	0.387	0.150, 0.624	0.959	0.903, 1.020
LCT MDS-UPDRS III Med-ON – subscore rigidity	<0.001	–0.011, 0.012	–0.004	–0.015, 0.007	0.530	–0.191, 1.250	0.926	0.779, 1.101
LCT MDS-UPDRS III Med-ON – subscore bradykinesia	–0.002	–0.010, 0.006	–0.005	–0.012, 0.003	0.390	–0.081, 0.862	0.915	0.814, 1.029
LCT MDS-UPDRS III Med-ON – subscore tremor	<0.001	–0.012, 0.011	–0.009	–0.019, 0.002	1.047	0.412, 1.683	0.987	0.835, 1.165
LCT MDS-UPDRS III Med-OFF	–0.001	–0.004, 0.002	–0.002	–0.005, 0.001	0.278	0.101, 0.455	0.973	0.932, 1.016
LCT MDS-UPDRS III Med-OFF – subscore rigidity	–0.001	–0.013, 0.011	–0.001	–0.013, 0.010	0.668	–0.068, 1.404	0.855	0.710, 1.030
LCT MDS-UPDRS III Med-OFF – subscore bradykinesia	–0.003	–0.008, 0.003	–0.003	–0.008, 0.003	0.175	–0.170, 0.521	0.955	0.880, 1.036
LCT MDS-UPDRS III Med-OFF – subscore bradykinesia	–0.001	–0.007, 0.005	–0.005	–0.010, 0.001	0.246	0.050, 0.802	0.979	0.898, 1.068
LCT disease progression (MDS-UPDRS III Med-OFF-Stim-OFF / baseline Med-OFF)	0.065	–0.019, 0.149	0.007	–0.074, 0.089	3.625	–1.717, 8.967	1.254	0.370, 4.249

PKG and LCT variables were added to a baseline model (linear regression with forced entry covariance matrix) which included age and disease duration. [a](Med-OFF-Stim-OFF – Med-OFF-Stim-ON) / Med-OFF-Stim-OFF. [b](Med-OFF-Stim-OFF – Med-ON-Stim-ON) / Med-OFF-Stim-OFF. [c] Med-ON-Stim-ON. [d]45% improvement through Stim-ON (Med-OFF) relative to Stim-OFF-Med-OFF. 95%CI, 95% Confidence Interval; B, regression coefficient; LCT, Levodopa Challenge Test; MDS-UPDRS, Movement Disorders Society – Unified Parkinson's Disease Rating Scale; OR, odds ratio; PKG, Parkinson Kinetigraph; PKG-BKS, Bradykinesia Score; PKG-DAT: an indicator-metrics of being 'suitable on motor grounds' for DBS; PKG-DKS, Dyskinesia Score; PKG-FS: Fluctuation Score; PKG-LCT, PKG response to early morning LED.

Table 3
Predictors of postoperative motor outcomes (multivariate)

	Relative improvement due to stimulation [a]		Relative improvement due to optimal therapy [b]		Postoperative motor function [c]		Success based on 45% cut-off [d]	
Multivariate covariates	B	95%CI	B	95%CI	B	95%CI	OR	95%CI OR
Age	–0.006	–0.010, –0.002	–0.009	–0.013, –0.004	0.317	0.039, 0.596	0.922	0.856, 0.994
PKG-BKS					0.908	0.207, 1.609		
PKG-DKS			0.024	–0.051, 0.003	1.415	0.485, 2.345		
PKG tremor					0.760	0.311, 1.209		
PKG-DAT readiness			–0.001	–0.002,<0.001				
LDCT MDS-UPDRS III response to levodopa (relative)							> 100	0.572,> 10000
LDCT MDS-UPDRS III Med-OFF					0.510	0.339, 0.681	0.836	0.699, 1.001
LDCT disease progression (MDS-UPDRS III Med-OFF-Stim-OFF / baseline Med-OFF)					12.615	7.356, 17.874		

PKG and LDCT variables were added to a baseline model (linear regression with forced entry covariance matrix) which included age and disease duration. [a](Med-OFF-Stim-OFF – Med-OFF-Stim-ON) / Med-OFF-Stim-OFF. [b](Med-OFF-Stim-OFF – Med-ON-Stim-ON) / Med-OFF-Stim-OFF. [c]Med-ON-Stim-ON. [d]45% improvement through Stim-ON (Med-OFF) relative to Stim-OFF-Med-OFF. Blank spaces indicate that the pertaining variable was not retained. 95%CI, 95% Confidence Interval; B, regression coefficient; LCT, Levodopa Challenge Test; MDS-UPDRS, Movement Disorders Society – Unified Parkinson's Disease Rating Scale; OR, odds ratio; PKG, Parkinson Kinetigraph; PKG-BKS, Bradykinesia Score; PKG-DAT: an indicator-metrics of being 'suitable on motor grounds' for DBS; PKG-DKS, Dyskinesia Score; PKG-FS: Fluctuation Score; PKG-LCT, PKG response to early morning LED.

predicted by lower QoL scores, and higher Quip-RS-ICD scores.

DISCUSSION

The aim of this study was to evaluate the utility of the different DBS screening measures to predict outcomes 1 year after STN DBS.

Several screening factors predicted lower severity of motor symptoms after STN DBS in multivariate analyses, including better preoperative motor function in the Med-OFF condition, slower disease progression in terms of motor function (although arguably measured at a different time-point than during the DBS screening and therefore a suboptimal reflection of the actual progression), lower age, as well as several PKG-metrics related to bradykinesia, tremor, and dyskinesias. A better response to optimal therapy (i.e., preoperative dopaminergic medication) was associated with a lower age during screening, and several PKG-metrics related to dyskinesias and readiness for advanced therapies; a better response to STN DBS was only related to age. Strikingly, higher age was predictive of less motor improvement after STN DBS regardless of the definition of motor success, albeit with a relatively small effect. In all instances, the amount of variance explained by multivariate models was relatively modest (range R^2 for motor function during Med-ON-Stim-ON 0.470 – 0.478, response to therapy R^2 0.154 – 0.307, response to DBS R^2 0.086).

Despite being widely considered to be an important predictor of STN DBS motor outcomes and as an integral part of many guidelines on DBS eligibility criteria, our results do not clearly support the use of a LCT specifically in order to predict STN DBS motor effects one year after surgery. A meta-analysis demonstrated a linear correlation of preoperative levodopa-response and postoperative motor outcomes, although follow-up duration was not taken into account and a high degree of variability among studies is apparent [12, 39]. Preoperative levodopa-responsiveness predicted motor outcomes of DBS after three months in two studies [38, 40] but not at medium-to-long-term (i.e., 3–8 years) [41, 42]. A previous systematic review also suggests that follow-up duration plays a role in the predictive potential of levodopa-responsiveness, with significant short-term predictive success (i.e., 6 months) which becomes lessened after 12 months follow-up [43]. This observation may be due to modification of the disease characteristics in time, with increase in medication- and stimulation-resistant symptoms in the longer follow-up. Previous literature has demonstrated that patients who do not fulfil the commonly used benchmark of 30% improvement during LCT may still be appropriate candidates for STN DBS [44]. Similarly, a fMRI study reported that oral

Table 4
Predictors of postoperative QoL outcomes (univariate)

	PDQ39 SI (follow-up)		PDQ39 SI improvement (continuous)[a]		PDQ39 SI improvement (dichotomous)[b]	
Univariate covariates	B	95%CI	B	95%CI	OR	95%CI
Age	0.056	–0.586, 0.697	0.009	0.004, 0.015	0.934	0.877, 0.994
Disease duration (y)	< –0.001	–0.023, 0.023	0.005	–0.939, 0.950	0.963	0.887, 1.046
Sex	0.119	–0.140, 0.377	–9.910	–20.308, –0.488	1.604	0.640, 4.021
MDS-UPDRS III (Med-OFF)	0.004	–0.008, 0.015	0.329	–0.130, 0.788	0.993	0.953, 1.033
MDS-UPDRS III (Med-ON)	0.002	–0.014, 0.017	0.236	–0.389, 0.860	1.000	0.947, 1.056
% improvement MDS-UPDRS III through therapy ((OFF – ON) / (OFF))	0.326	–0.535, 1.187	0.489	–34.899, 35.878	1.001	0.046, 21.576
MDS-UPDRS IV	0.020	–0.010, 0.050	1.249	0.048, 2.451	1.018	0.914, 1.135
LED	< 0.001	< 0.001,< 0.001	0.002	–0.009, 0.013	0.999	0.998, 1.000
SENS-PD	0.011	–0.016, 0.039	1.615	0.546, 2.685	1.053	0.952, 1.164
DBS IS	0.009	–0.004, 0.023	1.076	0.579, 1.572	1.037	0.986, 1.090
PDQ-39	0.009	0.004, 0.015	0.505	0.287, 0.724	1.039	1.012, 1.066
MoCA	–0.073	–0.129, –0.018	1.149	–1.211, 3.509	0.833	0.669, 1.039
BDI	0.015	–0.003, 0.034	1.586	0.882, 2.289	1.073	0.996, 1.156
PAS	0.013	–0.004, 0.030	1.415	0.779, 2.052	1.064	0.996, 1.137
Apathy Scale	0.020	–0.022, 0.061	0.080	–1.631, 1.791	1.071	0.919, 1.248
Quip-RS-ICD	0.017	–0.004, 0.038	0.321	–0.518, 1.159	1.119	1.014, 1.235
Quip-RS total	0.008	–0.003, 0.020	0.322	–0.138, 0.783	1.049	0.995, 1.106
SCOPA-AUT	0.015	–0.002, 0.032	0.845	0.155, 1.534	1.071	1.001, 1.145
SCOPA-Sleep	0.024	–0.015, 0.063	1.146	–0.453, 2.745	1.129	0.974, 1.310
SCOPA-EDS	0.009	–0.032, 0.049	1.489	–0.146, 3.124	1.043	0.901, 1.207
FOG-Q	0.012	–0.014, 0.037	1.494	– 0.495, 2.494	1.011	0.922, 1.108

[a](Baseline PDQ39 SI – follow-up PDQ39 SI) / baseline PDQ39 SI, higher scores indicate greater improvement. [b]Based on PDQ39 SI MCID. 95%CI, 95% Confidence Interval; B, regression coefficient; BDI, Becks Depression Inventory; DBS, deep brain stimulation; DBS IS, DBS Impairment Scale; EQ5D, EuroQol 5 dimensions; GIC, Global Impression of Change; GSS, Global Satisfaction with Surgery; FOG-Q, Freezing of Gait Questionnaire; LED, Levodopa Equivalent Dose; MCID, Minimal Clinically Important Difference; MoCA, Montreal Cognitive Assessment; MDS-UPDRS, Movement Disorders Society – Unified Parkinson's Disease Rating Scale; OR, odds ratio; PAS, Parkinson's disease Anxiety Scale; PDQ 39, Parkinson's Disease Questionnaire; SI, Summary Index; Quip-RS (ICD), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (Impulsive-Compulsive Disorder symptoms); SCOPA (AUT / EDS), SCales for Outcomes in PArkinson's disease (Autonomic symptoms / Excessive Daytime Sleepiness); SENS-PD, SEverity of predominantly Nondopaminergic Symptoms in PD.

Table 5
Predictors of postoperative QoL outcomes (multivariate)

	PDQ39 SI (follow-up)		PDQ39 SI improvement (continuous)[a]		PDQ39 SI improvement (dichotomous)[b]	
Multivariate covariates	B	95%CI	B	95%CI	OR	95%CI
Age	0.461	–0.085, 1.008				
DBS IS			0.702	0.154, 1.251		
PDQ-39	0.447	0.111, 0.783			1.032	1.003, 1.062
BDI	1.615	0.577, 2.654				
PAS			1.036	0.304, 1.767		
Quip-RS-ICD					1.096	0.988, 1.216
Quip-RS total	–0.686	–1.423, 0.050				

[a](Baseline PDQ39 SI – follow-up PDQ39 SI) / baseline PDQ39 SI, higher scores indicate greater improvement. [b]Based on PDQ39 SI MCID. Blank spaces indicate that the pertaining variable was not retained. 95%CI, 95% Confidence Interval; B, regression coefficient; BDI, Becks Depression Inventory; DBS IS, DBS Impairment Scale; MCID, Minimal Clinically Important Difference; PDQ 39, Parkinson's Disease Questionnaire; PAS, Parkinson's disease Anxiety Scale; Quip-RS (ICD), Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease–Rating Scale (Impulsive-Compulsive Disorder symptoms).

dopaminergic therapy has differential effect on brain motor activity compared to DBS, suggesting an alternative mechanism of action [45].

Another reason for this finding is that our study encompassed a slightly different population than the older cohorts included in the meta-analyses. Simi-

larly to what is reported in other more recent studies, our population included on average older patients and patients at an earlier disease stage, with lower and less heterogeneous values of motor severity at baseline. In these patients, larger changes may be expected after one year due to disease progression, as demonstrated by the deterioration in off motor scores in our population. It is possible that for these reasons the size of levodopa responsiveness is less predictive of STN DBS results as compared to a more heterogeneous population, while the influence of age may become stronger. We hypothesize that a higher variability in levodopa responsiveness would increase its predictive utility. When comparing our results with those of older studies it is of importance to notice that we used the MDS-UPDRS to score motor and non-motor symptoms, while earlier studies mainly used the old UPDRS. While these scales are considered to be consistent with each other, the use of a different instrument might explain the different results to some extent.

The PKG provides several metrics that can contribute to patient management in PD and has been described in the literature to benefit both home-based assessments and medication management [46–48]. PKG has already been previously suggested as a tool to support patient selection for advanced therapies [20, 36, 49]. The outcome measures obtained from the PKG measurements are not directly comparable to the traditional (motor) scores and may be complementary [48, 50, 51]. Despite its obvious benefits in term of home-based monitoring and potential during outpatient management, there is insufficient basis that the PKG may supplant the traditional motor assessment during the DBS eligibility screening in terms of predicting motor effects.

There were several preoperative factors that significantly predicted QoL at follow-up during univariate analyses, although not all variables were retained during multivariate analyses. Lower age, higher preoperative impulsive-compulsive symptoms, less symptoms of depression at baseline, and better preoperative QoL, predicted QoL one year after surgery. Findings on age and preoperative QoL were in accordance with previous literature [10], whereas lower scores for depression symptoms as predictor of better QoL at follow-up has not been reported previously (i.e., previous studies reported a non-significant association) [52, 53], although depression is known to impact QoL of patients with PD in general. Impulsive-compulsive symptoms as predictor of QoL has not been studied previously. We hypothesize that the improvement of impulsive-compulsive symptoms after STN DBS observed in our cohort and in the literature [54], possibly due to a reduction of dopaminergic medication, may positively impact QoL and may be an important consideration during the DBS screening and patient education. In terms of QoL improvement, only two variables were retained in a multivariate prediction model: the DBS-IS, which is a relatively new scale measuring symptoms related to DBS effects/side-effects specifically and has not been studied previously in relation to QoL, and symptoms of anxiety which were positively associated with QoL improvement (i.e., more preoperative anxiety predicted greater QoL improvement). The latter result has not been previously found as two previous studies reported no significant association between preoperative anxiety and QoL [52, 55]. We speculate that patients with a high severity of anxiety-symptoms also have the greatest potential for improvement, which may result in greater improvement in QoL in case of DBS-induced relief. Moreover, anxiety induced by the anticipation of surgery may be relieved post-surgery which in turn may have an effect on QoL. In accordance with previous literature [10], preoperative motor severity (both Med-ON, Med-OFF, and levodopa-responsiveness) were not significantly associated with QoL or QoL improvement. These results further support the notion that patient wellbeing and satisfaction with STN DBS may be highly subjective or primarily driven by non-motor symptoms than by symptoms for which STN DBS was primarily indicated (i.e., motor symptoms) [30], and may warrant further attention during the post-operative phase.

One study reported that worse QoL at baseline predicted better QoL after two years follow-up, irrespective of age or disease duration [53]. Despite this seeming discrepancy, this study was part of the EARLYSTIM trial which included younger patients with shorter disease duration and may reflect a different study population altogether.

Even if our results suggest that LCT cannot reliably predict postoperative outcomes 1 year after STN DBS, the role of this test in the selection process and its utility for patient-selection cannot be inferred from our results due to inherent selection bias (i.e., only accepted patients were included in this trial). Moreover, the LCT may serve an additional purpose beyond estimating levodopa-responsiveness, in terms of defining qualitative ON-OFF differences for domains such as speech and balance impairment, or to better characterize symptoms such as dysto-

nia which are in some cases difficult to ascribe to the ON or OFF condition exclusively on anamnestic ground. These domains are often considered to be at risk after STN DBS, whereas a levodopa-induced improvement would indicate a beneficial effect of STN DBS as well. Accurate assessment of the dopaminergic response of these domains may therefore improve domain-specific predictions, separate from levodopa-responsiveness of the main motor domains. Furthermore, centers that are not using general anesthesia for DBS surgery may find the OFF condition useful to prepare patients for coping during surgery. In this context, the LCT provides still additional information with respect to a wearable device and may often be preferable than the subjective recall of an individual patient. The LCT is costly, time-consuming, and burdensome for patients, so ideally ambulatory assessments would take over the role of the LCT; unfortunately, the at-home use of a wearable sensor (PKG) as investigated here does not provide much more predictive information than the LCT in predicting postoperative motor effects.

Although the screening for DBS is primed towards patient-selection, its utility in predicting outcomes after STN DBS in selected patients appears somewhat limited. Although some indications can be inferred from preoperative factors, stable prediction of postoperative outcomes for both motor and non-motor symptoms appears difficult and probably requires additional instruments to complement current screening procedures [56].

Strengths of this study include the prospective multicenter longitudinal design with consecutive inclusion of patients and the standardized and comprehensive test battery at baseline and follow-up. Limitations include the loss-to-follow-up of some patients and inherent missing data. Reasons for not participating in the follow-up included difficulties in reaching the center and not wanting to have the stimulation turned off [30]; furthermore, an effect of the COVID-19 pandemic on follow-up participation cannot be discarded. Although loss-to-follow-up was anticipated during the power calculation and was within its anticipated limit (required sample size 75 with an expected 10% drop-out rate), the drop-out rate may result in a potential misestimation of our results. Furthermore, both directional and non-directional leads were implanted, and we did not correct the results for the actual position of the leads with respect to the target. Future research should identify whether there are differential results for either type of electrode; our cohort currently carries insufficient statistical power to address this question. In terms of prediction modelling, no external validation or coefficient-shrinkage to improve validity was performed due to limited accuracies in the initial models. Finally, as the data from the DBS eligibility screening was used for both determination of DBS eligibility and analysis, an inherent selection bias cannot be discarded.

Our results are primed towards screening for STN DBS and may not necessarily hold true for other targets such as pallidal (GPi) DBS. Previous results from the NSTAPS trial have demonstrated different postoperative results in terms of Med-OFF motor function, LED reduction, and motor fluctuations between the two targets [57, 58]. Future research should not only validate our findings in STN DBS patients, but also expand our findings to other DBS targets.

The utility of standard data collected during the DBS-screening process has limited potential in predicting postoperative outcomes, both in terms of motor function and QoL. A LCT does not appear warranted to predict postoperative motor outcomes and the use of variables derived from wearables seems not to add substantially to the picture. If future studies validate these findings, it may be considered to omit the LCT from the DBS screening in individual instances. However, the LCT remains of value during the screening procedure for other reasons as discussed above, including to ascertain the nature of reported features during the OFF or ON-phase in the management of patient expectations.

It is plausible that the development of prediction models in PD patients eligible for STN DBS requires future research studying additional measurement instruments. On the other hand, the improvement after STN DBS procedures may be individually determined by several specific symptoms and factors rather than global changes in comprehensive scores: weighing of the importance of postoperative outcomes to define 'success of STN DBS' should be warranted on an individual basis, especially when considering QoL.

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CONFLICT OF INTEREST

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DATA AVAILABILITY

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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