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Identifying Poor Responders to STN DBS in Parkinson Disease: The Role of Rapid Disease Progression in the First Year in Optimal Responders to Levodopa

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ABSTRACT

Background: The factors contributing to a poor response to subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson's disease (PD) are not yet fully understood. Accordingly, predicting the outcome might be challenging particularly in those who display an optimal response to the Levodopa challenge test.

Objective: To determine which factors may contribute to poor outcome of STN-DBS in PD.

Methods: We performed a retrospective analysis of consecutive PD patients treated with STN-DBS. Motor and non-motor variables were retrieved before surgery and at 1-year follow-up. Patients were divided into poor and good DBS responders by a cut-off value of less than 20% improvement of UPDRS-II in the OFF-medication ON-stimulation condition at 1 year.

Results: Thirty-two (26.2%) of 122 patients were categorised as poor responders. Before surgery, poor responders had significantly less impairment in activity of daily living and less severe motor severity. Response to levodopa challenge test was similar between poor and good responders. Significant worsening of axial symptoms at 1-year follow-up in the off-medication off-stimulation condition was found in poor responders. On multivariable linear regression analysis, only the relative change of activity of daily living by dopaminergic medications before surgery predicted its improvement by neurostimulation at 1-year follow-up.

Conclusions: Candidates for surgery with less impairment in activities of daily living may have less favourable outcomes after STN-DBS, despite an optimal response during the pre-operative Levodopa challenge. The worsening of axial symptoms due to disease progression might contribute to poorer outcomes, underscoring the need for better identification of these symptoms before surgery.

Francesca Morgante and Carlo Alberto Artusi equally contributed to this study.

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1 | Introduction

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is an established, safe and effective [1] treatment for advanced Parkinson's disease (PD) [2]. It is well recognised that the outcome of STN-DBS might be variable, despite respecting selection criteria which are widely accepted [3]. The magnitude of presurgical levodopa responsiveness of motor symptoms is a key criterion for expected benefit from DBS [1]. The Core Assessment Program for Surgical Interventional Therapies (CAPSIT) criteria have set a unified Parkinson's disease rating scale part III (UPDRS III) cut-off of 33% improvement after a levodopa challenge test for considering DBS in advanced PD patients, and data from trials suggest that the highest the presurgical response to levodopa of UPDRS-III, the higher the motor benefit expected by DBS [4].

However, despite the proven efficacy of DBS in improving motor and non-motor outcomes, the impact on quality of life (QoL) and activities of daily living (ADL) is less consistent and more difficult to predict. In fact, a significant yet modest correlation between motor and ADL improvement was observed in PD patients after DBS [5]. This is of major importance as such outcomes are more patient-centred and reflective of real-life function compared with clinician-rated scores of motor symptoms, such as the UPDRS-III [3]. Surprisingly, few studies have compared the predictors of good and poor outcomes in terms of QoL/ADL following STN-DBS [6–8]. These studies produced results that challenge assumptions about who might be the best candidate for DBS. For example, a recent post hoc analysis of the EARLYSTIM cohort found that better presurgical QoL measured by PDQ-39 score was associated with a smaller improvement in QoL at 24-month follow-up. In fact, those patients with presurgical PDQ-39 scores of ≤ 15 had no significant change in QoL following surgery.

These rather paradoxical findings suggest that factors outside of those included in the CAPSIT criteria may be important in determining patient-centred outcomes such as QoL and ADL following STN-DBS [3]. Here, we addressed this issue directly through assessment of the outcome of STN-DBS as measured by UPDRS II—a PD specific scale assessing ADL—in a cohort of people with PD treated with STN-DBS from a single centre. We sought to identify the preoperative and postoperative factors associated with unsatisfactory outcomes in ADL at 1 year after STN-DBS.

2 | Methods

We performed a retrospective analysis of prospectively acquired data from 203 consecutive PD patients treated with STN-DBS from September 1998 to September 2012 at the Department of Neuroscience of the University of Torino, Italy. During this time frame, people with PD at the University of Torino were routinely tested after DBS in the Off medication/Off stimulation condition. In this cohort, we identified patients with available UPDRS [9] part-II scores both at baseline (before surgery) and 1-year follow-up. As per UPDRS-II instructions, this outcome measure was scored referring to the patients' off condition (MED-OFF) and on condition (MED-ON) in the 4 weeks preceding the evaluation. In the absence of a validated minimal change threshold for defining a significant improvement in ADL functioning, we divided patients into 'poor' and 'good' DBS responders based on a cut-off value of less than 20% improvement of ADL measured by UPDRS-II score in the off condition at 12-month follow-up (while being on stimulation). In our sample, this corresponded to a maximal improvement of six points on the UPDRS-II scale. We employed the cut-off of 20% based on a seminal randomised controlled trial of STN-DBS in which the improvement of UPDRS-II by the stimulation in off condition ranged from 6.8 to 10.8 [1].

Poor and good DBS responders were compared using demographic and clinical variables at presurgical assessment (T0) and 1 year after STN-DBS (T1). Written informed consent was obtained from patients at the time of DBS screening to use their clinical data. The University of Turin ethical committee approved this retrospective study (CS/855; protocol number 475).

2.1 | Outcome Measures

Demographic and clinical variables included gender, age, age at PD onset, disease duration and duration of motor fluctuations.

According to CAPSIT [10], UPDRS-III before surgery was assessed in the practically defined OFF state (MED-OFF) and again after administering 150% of the morning Levodopa dose (MED-ON). After a 1-year follow-up, UPDRS-III was tested in the following conditions, probing different medication and stimulation (STIM) combinations: MED-OFF/STIM-OFF, MED-OFF/STIM-ON, MED-ON/STIM-OFF, MED-ON/STIM-ON. For the purposes of this study, only the scores in MED-OFF/STIM-OFF and MED-OFF/STIM-ON were entered into the analysis. We chose these conditions to assess the role of disease progression (MED-OFF/STIM-OFF) and the effect of STN DBS (MED-OFF/STIM-ON) compared to pre-DBS MED-OFF.

We also retrieved the following subscores derived by the sum of different UPDRS-III items: appendicular score (sum of items 22–26, rigidity and bradykinesia), tremor score (sum of items 20–21), axial score (sum of items 18-speech, 19-facial expression, 27-arise from chair, 28-posture, 29-gait, 30-postural stability). Hoehn and Yahr (HY) stage was assessed before and after surgery in all medication and stimulation conditions at T0 and T1.

In each subject, at each time point, we also assessed the following variables: UPDRS-II (OFF and ON medication) for ADL functioning, total UPDRS-IV, dyskinesia score (sum of UPDRS IV items 32-dyskinesia duration, 33-dyskinesia disability, 34-painful dyskinesia, 35-early morning dystonia), OFF score (sum of UPDRS IV items 36-predictable off, 37-unpredictable off, 38-sudden off, 39-off duration) and Schwab and England (S&E) ADL scale for measuring independence in ADL (OFF medication).

Medication data were collected at T0 and T1. Dopaminergic treatment was expressed as total levodopa daily dose (LED), levodopa equivalent daily dose (LEDD) and dopamine-agonists (D-Ag) LEDD [11]. Stimulation parameters at the time of first

programming and at T1 were reported in each group as mean frequency, pulse width and voltage. The percentage of patients treated with ventral, dorsal, monopolar and bipolar stimulation was calculated at the same time points. A formal neuropsychological assessment testing reasoning, attention, memory, executive functions and language was performed for each patient at T0 and T1. Accordingly, the number of patients who developed dementia at T1 was collected.

Finally, we classified the patients into the three recently validated phenotypes based on motor and non-motor symptoms (i.e., motor-benign, intermediate and diffuse malignant), according to the criteria proposed by Fereshtehnejad et al. [12], modified by De Pablo-Fernandez and collaborators [13].

2.2 | DBS Procedure

Bilateral stereotactic STN implantation was performed under local anaesthesia, using MRI/CT image fusion for anatomical targeting, intraoperative electrophysiological recording and micro-stimulation to evaluate clinical effects. Quadripolar leads (electrode model 3389; Medtronic, Minneapolis, MN) were implanted following the selected trajectory. The day after, under general anaesthesia, an implantable pulse generator was placed in the infraclavicular region and connected with electrodes' distal tips. Postoperative CT/MRI was performed to confirm electrode positioning and to exclude surgical complications. The procedure is described elsewhere in detail [14].

2.3 | Statistical Analysis

Demographic and clinical data were compared using *t*-test, Mann–Whitney *U*-test or chi-squared test as appropriate and according to data distribution.

We evaluated the relative change of ADL after STN-DBS applying the following formula: [(UPDRS-II MED-OFF at T0—UPDRS-II MED-OFF/STIM-ON at T1)/(UPDRS-II MED-OFF at T0) ×100]. For each variable (UPDRS-II MED-OFF, UPDRS-IV, dyskinesia score, OFF score, S&E), we conducted a repeated measure ANOVA (R-ANOVA) with 'group' (2 levels: 'poor responders', 'good responders') as a between-subject factor and time (2 levels: T0, T1) as a within-subject factor.

Total UPDRS-III scores and tremor, appendicular and axial subscores were analysed by R-ANOVA with 'group' (2 levels: 'poor responders', 'good responders') as a between-subject factor and 'condition' (3 levels: T0, T1 MD-OFF/STIM-OFF, T1 MED-OFF-STIM-ON) as a within-subject factor. Conditional on significant F-values, we conducted post hoc paired *t*-tests.

Relative change values for tremor, appendicular and axial UPDRS-III subscores, total Levodopa and total D-Ag dose were calculated as follows: [(score MED-OFF at T0—score MED-OFF/STIM-ON at T1)/score MED-OFF at T0] ×100. These values, as well as the classification of patients in motor/non-motor phenotypes, were employed in univariable and multivariable linear regression analyses to evaluate significant associations between the changes after DBS in tremor, appendicular and axial symptoms, as well as in pharmacological treatment and the relative change of UPDRS-II MED-OFF after DBS. Bonferroni's correction was applied for multiple comparisons with *p*-value set at $p < 0.025$.

For all other statistical tests, the *p*-value was set at $p < 0.05$.

Results in the text are reported as mean ± standard deviation.

3 | Results

Of 203 consecutive PD patients undergoing STN-DBS, we retrieved complete UPDRS-II data for 122 subjects. All included patients had a post-surgical verification of lead placement by CT scan, and none needed revision of lead positioning.

According to study criteria, 32 patients (26.2%) were categorised as 'poor responders' and 90 (73.8%) as 'good responders'.

3.1 | Baseline Characteristics

Table 1 shows demographic and clinical baseline features of 'poor' and 'good' responders. There were no significant differences for gender, age at PD onset, age at DBS and duration of motor fluctuations. Disease duration showed a non-significant trend to be shorter in 'poor responders' compared to 'good responders' (13.28 ± 3.91 years vs. 15.07 ± 5.01 years; $p = 0.07$).

At T0, in the MED-OFF condition, 'poor responders' had significantly less impairment in ADL function (UPDRS-II) and independence (S&E), less severe motor symptoms (UPDRS-III), less severe tremor (UPDRS-III tremor score). They also had fewer disease complications (UPDRS-IV) and less severe motor fluctuations (OFF score of UPDRS-IV).

The distribution of phenotypes before DBS in poor responders was 31% motor-benign, 55.2% intermediate and 13.8% diffuse malignant; the distribution of phenotypes in good responders was 23% motor-benign, 50.6% intermediate and 26.4% diffuse malignant.

Magnitude of improvement of UPDRS-III at the presurgical levodopa challenge test was lesser in 'poor' compared to 'good responders' (61.56% ± 12.40% vs. 67.04% ± 10.81%; $p = 0.01$), but well above the cut-off score in the CAPSIT criteria (33%). Indeed, two 'poor responders' and four 'good responders' displayed an improvement < 50% at the presurgical levodopa challenge test. Relative change of UPDRS-II MED-OFF compared to MED-ON was also smaller in 'poor responders' than in 'good responders' (57.81% ± 25.37% vs. 70.18% ± 17.64%; $p = 0.003$). All other variables were comparable between the two groups, including total LEDD and D-Ag LEDD (Table 1).

3.2 | Response to STN-DBS at 1-Year Follow-Up

Table 2 shows how STN-DBS produced significant improvement of all study variables and a decrease of dopaminergic medication in the whole PD population.

TABLE 1 | Pre-DBS demographical and clinical variables in poor and good DBS responders.

	Poor DBS responders ($N=32$)	Good DBS responders ($N=90$)	*p-value*
Gender (F/M)	16/16	35/55	0.3
Age at PD onset (y)	46.91 ± 6.47	45.91 ± 7.36	0.49
Age at surgery (y)	59.53 ± 7.36	60.89 ± 6.29	0.3
Disease duration (y)	13.28 ± 3.91	15.07 ± 5.01	0.07
MF duration (y)	5.53 ± 4.27	6.28 ± 4.17	0.38
UPDRS-I	1.78 ± 1.56	1.53 ± 1.39	0.40
UPDRS-II OFF	20.28 ± 6.40	24.32 ± 6.57	**0.003***
UPDRS-II ON	8.64 ± 5.58	7.58 ± 5.37	0.34
UPDRS-III OFF	44.09 ± 14.47	52.63 ± 14.36	**0.004***
UPDRS-III ON	17.25 ± 8.61	17.7 ± 8.62	0.8
Tremor score OFF	4.73 ± 3.45	7.15 ± 5.06	**0.01***
Tremor score ON	1.20 ± 1.51	1.07 ± 1.53	0.66
Appendicular score OFF	27.58 ± 9.96	31.93 ± 9.00	0.58
Appendicular score ON	11.16 ± 6.34	11.13 ± 6.17	0.98
Axial score OFF	11.78 ± 4.83	13.54 ± 4.38	0.06
Axial score ON	4.89 ± 2.82	5.50 ± 2.88	0.30
UPDRS-IV	6.703 ± 4.816	8.689 ± 3.308	**0.01***
OFF time score	2.52 ± 2.09	3.67 ± 1.37	**0.0005***
Dyskinesia score	3.42 ± 2.91	4.12 ± 2.454	0.18
UPDRS-II—OFF/ON (Δ)	57.81 ± 25.37	70.18 ± 17.64	**0.003***
UPDRS-III—OFF–ON (Δ)	61.56 ± 12.40	67.04 ± 10.81	**0.01***
HY—OFF	3.21 ± 1.00	3.53 ± 0.99	0.06
HY—ON	1.98 ± 0.81	2.19 ± 0.67	0.15
S&E—OFF	54.8 ± 20.0	45.5 ± 19.8	**0.02***
LEDD (mg)	1279.75 ± 392.51	1231.66 ± 460.32	0.59
D-Ag LEDD (mg)	314.37 ± 193.04	331.33 ± 271.13	0.74

Abbreviations: Δ, [(T0 − T1)/T0] × 100 (relative change); D-Ag, dopamine agonists; HY, Hoen–Yahr stage; LEDD, levodopa equivalent daily dose; MF, motor fluctuations; OFF, OFF medication; ON, ON medication; S&E, Schwab & England; UPDRS, Unified Parkinson's Disease Rating Scale.
*Significant values are bolded. All continuous variables are mean ± standard deviation.

One year after surgery, response to STN-DBS significantly differed between 'poor' and 'good responders' for many clinical variables according to R-ANOVA analysis (Figure 1, panels A-D, Table S1 for paired *t*-tests). A significant *time* x *group* interaction was found for UPDRS-II MED-OFF ($F_{(1,120)}=224.92$, $p<0.0001$) and S&E MED-OFF ($F_{(1,120)}=47.946$, $p<0.0001$). Indeed, at T1, UPDRS-II worsened in 'poor responders' as opposed to improvement in 'good responders'. Similarly, S&E improved in the 'good responders' and worsened in the 'poor responders' group. R-ANOVA disclosed a *time* x *group* interaction also for the OFF time score ($F_{(1,75)}=22.914$, $p<0.0001$), which improved significantly in 'good' but not in 'poor responders'. The two groups also differed by magnitude of improvement of dyskinesia score ($F_{(1,75)}=6.76$, $p=0.01$) and UPDRS-IV ($F_{(1,75)}=17.74$, $p<0.0001$). UPDRS-I did not differ between groups at baseline and T1.

Changes in UPDRS-III scores between groups from T0 to T1 were measured also with R-ANOVA. A condition x *group* interaction was found for total UPDRS-III ($F_{(1,120)}=15.99$, $p<0.0001$), and subscores for tremor ($F_{(1,120)}=3.048$, $p=0.0493$), appendicular symptoms ($F_{(1,120)}=9.02$, $p=0.0002$), and axial symptoms ($F_{(1,120)}=24.145$, $p<0.0001$) (Figure 2A–D, Table S2). Post hoc paired *t*-tests with Bonferroni's correction conducted in each group revealed a significant worsening of UPDRS-III total, appendicular and axial score in MED-OFF/STIM-OFF at T1 compared to MED-OFF at T0 in 'poor responders'. Yet, in the same group, those scores were improved in MED-OFF/STIM-ON compared to MED-OFF/STIM-OFF (Figure 2A–D, Table S2). 'Good responders' had significant worsening of tremor in MED-OFF/STIM-OFF compared to T0 and significant improvement of all scores associated with disease severity in MED-OFF/STIM-ON compared to T0 and MED-OFF/STIM-OFF.

TABLE 2 | Clinical variable before (T0) and after (T1) deep brain stimulation of the subthalamic nucleus in the whole sample of patients with Parkinson's disease.

	T0	T1	*p* value
UPDRS I	1.60 ± 1.44	1.94 ± 1.92	0.092
UPDRS II—MED-OFF	23.26 ± 6.74	10.24 ± 6.42[a]	**< 0.0001***
UPDRS III—MED-OFF	50.39 ± 14.82	27.32 ± 10.59[a]	**< 0.0001***
Tremor score—MED-OFF	6.52 ± 4.80	2.14 ± 2.37[a]	**< 0.0001***
Appendicular score—MED-OFF	30.80 ± 9.42	17.50 ± 6.95[a]	**< 0.0001***
Axial score—MED-OFF	13.08 ± 4.54	7.705 ± 3.93[a]	**< 0.0001***
LCT—UPDRS III (%)	65.61 ± 11.46	56.44 ± 16.13[b]	**< 0.0001***
LCT—Tremor (%)	81.75 ± 21.71	78.60 ± 22.73[b]	0.356
LCT—Appendicular (%)	64.89 ± 13.73	54.60 ± 17.60[b]	**< 0.0001***
LCT—Axial (%)	59.80 ± 13.89	49.97 ± 20.40[b]	**< 0.0001***
UPDRS IV	8.17 ± 3.84	2.06 ± 2.19	**< 0.0001***
OFF TIME score	3.36 ± 1.66	0.844 ± 1.27	**< 0.0001***
Dyskinesia score	3.94 ± 2.59	0.77 ± 1.29	**< 0.0001***
S&E (%) MED-OFF	47.8 ± 20.2	70.2 ± 22.2	**< 0.0001***
HY—MED-OFF	3.45 ± 1.0	2.66 ± 0.93[a]	**< 0.0001***

Abbreviations: HY, Hoehn–Yahr stage; LCT, percentage change of UPDRS-III total score and subscores at Levodopa challenge test; OFF MED, practically defined OFF state; S&E, Schwab and England; UPDRS, Unified Parkinson's Disease Rating Scale.
[a]STIM-ON/MED-OFF.
[b]STIM-OFF/MED-ON.
*Significant differences by paired *t*-test.

HY stage had a similar profile with significant worsening in MED-OFF/STIM-OFF compared to T0 only in 'poor responders' and significant response to neurostimulation in MED-OFF/STIM-ON compared to T0 (condition x group interaction, $p < 0.0001$) (Figure 2E, Table S2). Dopaminergic medications were reduced at a similar extent in both groups, except for a greater change of total Levodopa dose in 'good responders' (Figure 2F). No differences were found for any of the stimulation parameters, nor for the frequency of subjects treated with ventral, dorsal, monopolar or bipolar stimulation (Table S3). Also, the two groups did not differ by number of subjects developing dementia at T1, with one patient in the 'poor responders' group (3.1%) and three patients in the 'good responders' group (3.3%) developing dementia 1 year after surgery ($p = 1$). The change in UPDRS-II scores in the MED-OFF versus MED-ON state during chronic stimulation showed a significant difference between the two groups: 'poor responders' to DBS exhibited a greater percentage improvement in activities of ADL with levodopa compared to 'good responder' (37.1% ± 25.9% vs. 13% ± 26%; $p < 0.001$).

As a confirmatory evaluation of the cut-off of 20% we used for the classification of patients in 'poor' and 'good' responders, we verified the number of patients in each group obtaining a minimal clinically important difference (MCID), considered as a score > 2 in the absolute change of UPDRS-II in advanced patients undergoing a trial on pramipexole extended release [15]. 100% of good responders obtained an improvement > 2 (group mean 14.3 ± 6); and only four patients of the poor responders group obtained an improvement > 2 (3, 3, 4 and 6 points of improvement) with the UPDRS-II score showing a worsening after DBS at a group level (−4 ± 5.9).

3.3 | Predictors of Successful STN-DBS

Univariable linear regression analysis (Table 3) revealed that the following pre-operative variables were associated with more prominent improvement of UPDRS-II by DBS: higher score of UPDRS-II in MED-OFF, UPDRS-III total score, tremor, appendicular, axial subscores in MED-OFF, UPDRS-IV. Larger total UPDRS-III change at levodopa challenge test and larger change of UPDRS-II (in on medication compared to off medication) were associated with greater improvement of UPDRS-II by DBS (Figure 3).

However, on multivariable linear regression analysis including pre-operative variables, only the magnitude of change of UPDRS-II with medications measured at T0 significantly predicted the relative change of UPDRS-II MED-OFF after DBS (Beta = 0.31, $t = 3.1$, $p = 0.002$). Interestingly, the magnitude of UPDRS-III at levodopa challenge test at T0 did not predict the UPDRS-II MED-OFF after DBS (Table 4). Using the enter method, the model explained some of the variance in the value of change in UPDRS-II MED OFF ($F_{(10,115)} = 2.9$, $p = 0.006$, $R^2 = 0.2$, $R^2_{\text{Adjusted}} = 0.14$).

A multiple linear regression analysis was also conducted to see if the changes after DBS in tremor, appendicular, axial symptoms,

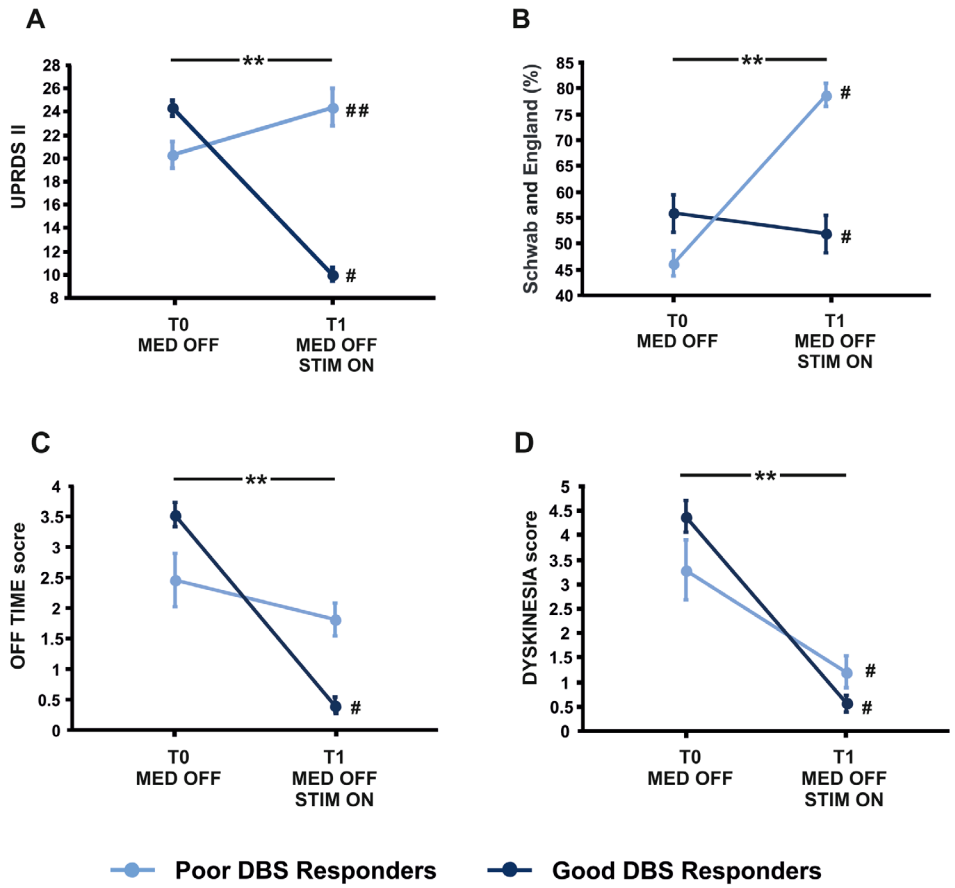

FIGURE 1 | Response to STN-DBS significantly differed between poor and good responders at 1-year follow-up. A–B show UPDRS II and Schwab and England before STN-DBS in MED OFF condition and after STN-DBS. C–D show OFF time and Dyskinesia score derived by UPDRS-IV sub-items before STN-DBS (T0) and after STN-DBS at 1-year follow-up (T1). Results are displayed as mean ± standard error. **Time × group interaction, $p < 0.0001$; #$p < 0.001$; ##$p = 0.004$.

Levodopa and D-Ag treatment, predicted the magnitude of change in UPDRS-II MED-OFF after DBS. Using the enter method, it was found that the change of tremor, axial symptoms and the decrease of Levodopa treatment explained some of the variance in the value of change in UPDRS II ($F_{(3,115)} = 17.0$, $p < 0.0001$, $R^2 = 0.31$, $R^2_{\text{Adjusted}} = 0.29$). The analysis showed that the change in tremor severity did not significantly predict the value of UPDRS-II change after DBS (Beta = 0.15, $t = 1.85$, ns). However, the change in axial symptoms (Beta = 0.45, $t = 5.6$, $p < 0.0001$) and Levodopa dose (Beta = 0.25, $t = 3.1$, $p = 0.002$) significantly predicted the relative change of UPDRS-II at 1-year follow-up after STN-DBS (Table S4).

4 | Discussion

This study was conducted to explore pre- and post-operative variables associated with poor outcomes of activities of daily living at 1 year after STN-DBS in a cohort of PD patients. Based on our cut-off score for ADL improvement, 26% of patients undergoing STN-DBS had a poor response. We specifically chose ADL as a marker of treatment response as it is a patient-centred measure likely to reflect function in daily life. This methodological choice was supported by previous studies showing a relative dissociation between motor improvement and change in ADL and QoL following DBS [10–16]. This group, here defined as 'poor responders', had specific baseline and follow-up clinical features.

Before surgery, poor responders to DBS had significantly less impairment in activity of daily living and less severe motor severity. In the same group, significant worsening of axial symptoms at 1-year follow-up in the MED-OFF/STIM-OFF condition was found. On multivariable linear regression analysis, the relative change of ADL between off and on medication condition (by UPDRS II) before surgery predicted its improvement by neurostimulation at 1-year follow-up. Finally, the improvement of ADL at 1-year after surgery was associated with the magnitude of improvement of axial symptoms.

Since 1999, CAPSIT has guided selection of suitable candidates for STN-DBS. A central criterion, and universally part of presurgical assessment, is the change in motor symptoms with a levodopa challenge. While in our cohort the magnitude of improvement in motor symptoms at presurgical levodopa challenge was on average smaller in 'poor responders' than in 'good responders', the mean reduction of UPDRS-III at the levodopa challenge test was at least 50% in both groups. This demonstrates an average excellent presurgical response to levodopa even in those who had a poor outcome in terms of ADL after 1 year. Only two 'poor responders' and four 'good responders' had a presurgical reduction of UPDRS III of less than 50%, and

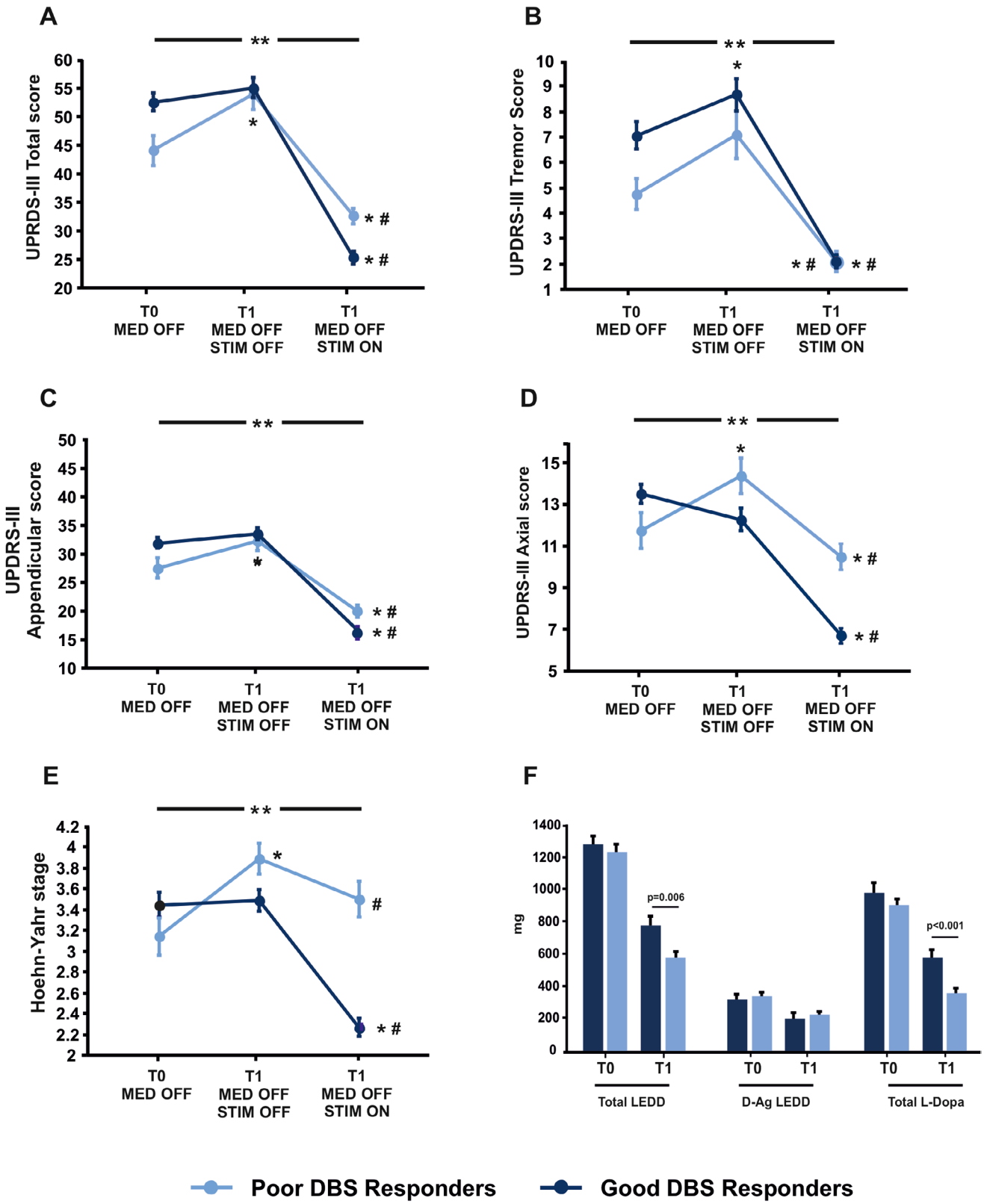

FIGURE 2 | UPDRS III total score (A) and subscores for tremor (B), appendicular (C) symptoms, axial (D) symptoms and Hoehn–Yahr (HY) (E) stage before STN-DBS (T0) in MED OFF and after STN-DBS (T1) in MED-OFF/STIM-OFF and MED-OFF/STIM-ON. F shows total dopaminergic daily dose (LEDD), dopamine agonists (D-Ag) LEDD and total levodopa dose at T0 and T1. Results are displayed as mean ± standard error. ** condition x group interaction by R-ANOVA, $p < 0.0001$ (panels A,D,E), $p = 0.0493$ (panel B), $p = 0.0002$ (panel C). *Significant by Bonferroni's correction ($p < 0.0116$) compared to T0 MED-OFF. #Significant by Bonferroni's correction ($p < 0.0116$) compared to T1 MED-OFF/STIM-OFF.

TABLE 3 | Univariable linear regression analysis with change in UPDRS II as dependent variable.

		95.0% CI for B		
	B	**LB**	**UB**	***p***
Gender	−0.05	−20.4	10.7	0.5
Age at surgery	0.03	−0.9	1.3	0.7
Disease duration	0.13	−0.4	2.7	0.1
UPDRS-I	−0.06	−7.2	3.5	0.5
UPDRS-II OFF	**0.27**	**0.6**	**2.8**	**0.003**
UPDRS-II ON	−0.11	−2.2	0.5	0.2
UPDRS-III OFF	**0.2**	**0.1**	**1.2**	**0.007**
UPDRS-III ON	0.02	−0.7	1.0	0.7
Tremor score OFF	**0.1**	**−0.0**	**3.1**	**0.05**
Tremor score ON	−0.1	−7.5	2.0	0.2
Appendicular score OFF	**0.1**	**0.1**	**1.7**	**0.02**
Appendicular score ON	0.03	−1.0	1.4	0.7
Axial score OFF	**0.18**	**0.0**	**3.4**	**0.04**
Axial score ON	0.06	−1.7	3.6	0.4
UPDRS-IV	**0.2**	**0.8**	**4.7**	**0.005**
OFF time score	**0.3**	**3.3**	**12.1**	**0.001**
Dyskinesia score	**0.1**	**0.0**	**5.8**	**0.048**
HY OFF	0.11	−3.0	12.1	0.2
HY ON	0.05	−7.8	13.8	0.5
PD phenotype	0.81	−589	1508	0.387
LEDD	−0.02	−0.0	0.0	0.7
UPDRS-II—OFF/ON (%)	**0.32**	**0.3**	**1.0**	**<0.0001**
UPDRS-III—LDR (%)	**0.19**	**0.0**	**1.3**	**0.03**
Tremor score—LDR (%)	**0.18**	**0.0**	**0.7**	**0.049**
Appendicular score—LDR (%)	0.03	−1.0	1.4	0.7
Axial score—LDR (%)	0.10	−0.2	0.8	0.2

Note: Significant values are bolded. All indipedent variables refer to pre-operative (T0) values.
Abbreviations: CI, confidence interval; HY, Hoehn–Yahr stage; LB, lower bound; LDR, Levodopa response; PD, Parkinson's disease; UB, upper bound; UPDRS, Unified Parkinson's Disease Rating Scale.

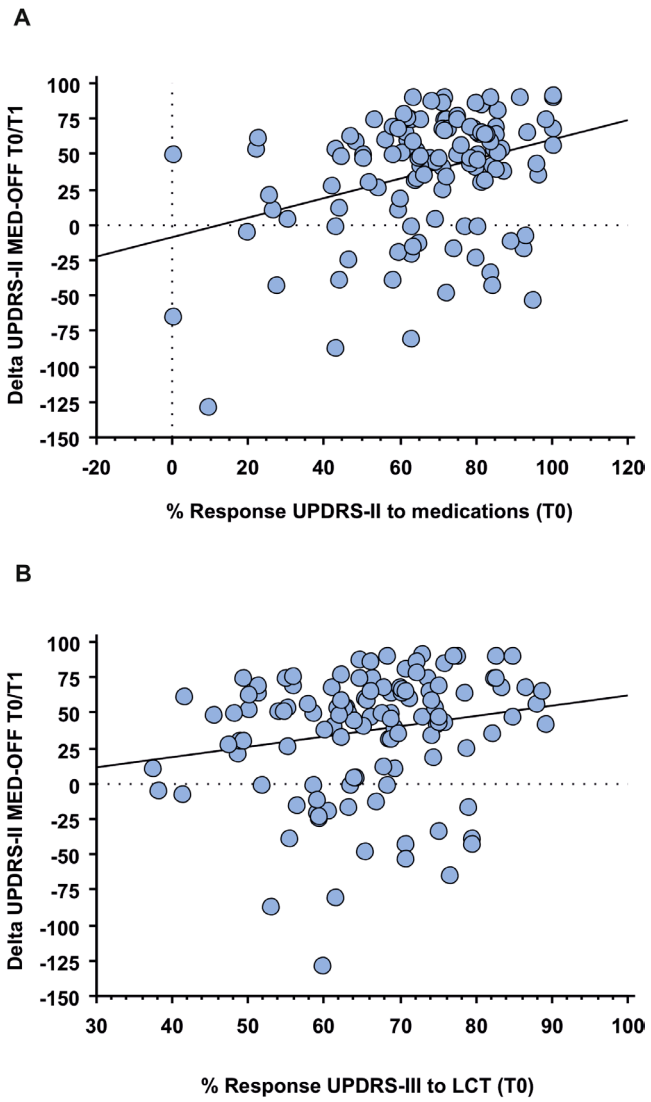

FIGURE 3 | Univariable linear regression analysis disclosed a significant correlation between magnitude of UPDRS-II change with medications at T0 and value of change of UPDRS-II MED-OFF after DBS (panel A). A similar correlation was found between magnitude of change of UPDRS-III total score after levodopa challenge test (LCT) and value of change of UPDRS-II MED-OFF after DBS (panel B).

all were above the cut-off of 33%, which is set as a threshold in the CAPSIT criteria for surgery selection [10]. In addition, using multivariable linear regression analysis, the magnitude of levodopa response of UPDRS-III presurgery did not predict the outcome of ADL at 1 year. This finding is in keeping with the results of a multicentre study demonstrating that the magnitude of response to pre-operative levodopa challenge is unable to predict the individual patient's response with precision [4]. At the time of DBS selection, variables representative of disease severity and ADL function and independence when OFF medication (by UPDRS-II and III) were all less severe in the 'poor responders' group as were their complications of therapy assessed by UPDRS-IV. No other differences were identified between groups in criteria for eligibility for STN-DBS by CAPSIT criteria.

There have been indications from other studies that CAPSIT criteria may not link well to improvements in ADL and QoL in all patients [3]. As mentioned above, in the EARLYSTIM cohort, better presurgical QoL correlated with a smaller improvement in QoL at 24 months post-surgery, and those with presurgical PDQ-39 scores of ≤15 had no significant change in QoL following surgery. In the EARLYSTIM cohort, improvement of QoL after 2 years was independent of age, disease duration, duration of motor complications and severity of motor signs and motor complications at baseline. In a separate cohort of 85 patients, the

TABLE 4 | Multivariable regression analysis with change in UPDRS II as dependent variable.

		95.0% CI for B		
	B	**LB**	**UB**	***p***
UPDRS-II OFF	1.30	−0.3	2.9	0.1
UPDRS-III OFF	4.94	−25	34.9	0.7
UPDRS-IV OFF	−1.6	−10.6	7.5	0.7
Axial score OFF	−1.57	−4.6	1.5	0.3
Appendicular score OFF	−4.53	−34.5	25.5	0.7
Tremor score OFF	−3.65	−33.6	26.4	0.8
OFF time score	5.40	−6.3	17.1	0.4
Dyskinesia score	3.36	−6.7	13.4	0.5
UPDRS-II – OFF/ON (%)	**0.57**	**0.2**	**1.0**	**0.008**
UPDRS-III—OFF/ON (%)	0.38	−0.4	1.2	0.4
Tremor score—LDR (%)	−0.51	−0.4	0.3	0.8

Note: Significant values are bolded. All indipedent variables refer to pre-operative (T0) values.
Abbreviations: CI, confidence interval; HY, Hoehn–Yahr stage; LB, lower bound; LDR, Levodopa response; UB, upper bound; UPDRS, Unified Parkinson's Disease Rating Scale.

magnitude of motor symptoms improvement with a presurgical levodopa challenge was only borderline associated ($p = 0.053$) with improvement of quality of life after DBS [16].

Interestingly, we found that the magnitude of pre-operative UPDRS-II change in ON compared to OFF was a predictor of DBS outcome, a finding not assessed or reported in any previous study. Noteworthy, the new version of UPDRS-II by the Movement Disorders Society does not encompass separate OFF and ON ratings for standard assessment, except for individual programmes or protocols [17]. We suggest that pre-operative response to medication of UPDRS-II should be also considered in the DBS selection process. Yet, we have to acknowledge that the model explained some of the variance in the value of change in UPDRS-II before DBS and prediction of ADL outcome after STN DBS might depend on many other factors not investigated in this study, such as burden of non-motor symptoms and their response to levodopa.

Our data demonstrate that 'good' and 'poor responders' appear to have a different trajectory of disease progression, consistent with the hypothesis that the unsatisfactory outcome after STN-DBS might relate to a different pattern of disease progression rather than just a different response to DBS. The severity of motor symptoms measured by UPDRS-III MED-OFF/STIM-OFF, which reflects the disease state itself, significantly worsened only in 'poor responders'. In particular, axial signs (speech, gait and balance) were responsible for this finding. After DBS, motor fluctuations were less improved in 'poor responders' and the reduction in levodopa equivalent dose was less than in 'good responders'. These findings might suggest a worse disease progression. Conversely, neurostimulation led to a significant improvement of motor symptoms in both groups, as underlined by a significant decrease of UPDRS-III and its subscores in the MED-OFF/STIM-ON condition compared to MED-OFF/STIM-OFF. This argues against the poor response being due to inaccurate lead placement or other technical issues related to the DBS itself. As further evidence of the efficacy of STN-DBS in both groups, dyskinesia and disease complications, as measured by UPDRS-IV, showed similar improvements. However, in poor DBS responders, axial symptoms significantly worsened in the MED-OFF/STIM-OFF state, likely due to faster disease progression during the first year of STN-DBS compared to good responders. While DBS improved axial symptoms in poor responders, the improvement was less pronounced.

Overall, these findings suggest that, in subjects with pre-operative good levodopa response and correct lead position, disease progression may be a more important factor in poor ADL outcomes after STN-DBS than the efficacy of stimulation itself. Indeed, speech, gait and balance disorders have a major impact on ADL, determining reduced mobility, falls, possible injuries and loss of independence [18]. Moreover, worsening of axial signs represents a significant milestone of PD progression [19, 20], in particular over the course of STN-DBS treatment [21, 22]. Axial disability may be improved by either dopaminergic medication or neurostimulation at short follow-up, but this effect significantly decreases over long-term follow-up (up to 10 years) [21, 23] and also strongly predicts mortality [23]. Noteworthy, we observed a significant difference in the UPDRS-II improvement between the two groups during DBS chronic stimulation, with the 'poor responders' group having a higher percentage improvement of ADL in ON compared to 'good.' This finding suggests that despite faster disease progression, the suboptimal improvement of ADL provided by DBS in these patients can be at least partially recovered by dopaminergic therapy, which is still effective on ADL.

Younger age at onset, good levodopa response, absence of levodopa-resistant symptoms, cumulative daily OFF time and its improvement after surgery, as well as accurate lead positioning are proven predictors of STN-DBS efficacy when using UPDRS-III as primary endpoint [24–28]. A recent study on a large cohort of PD patients showed that baseline scores of frontal lobe dysfunction, off-medication MDS-UPDRS III scores, levodopa responsiveness and tremor-dominant phenotype were independent preoperative predictors of greater short-term motor improvement after surgery [29].

The apparently paradoxical finding of better presurgical motor scores and ADL predicting worse ADL outcomes at 1-year follow-up raises an interesting question: why are patients who appear to be less impaired in their activities of daily living being assessed for DBS? One hypothesis, which needs validation, is that there are other symptoms, not captured by current presurgical assessments, which lead to an unsatisfactory response to medical treatment and therefore patient requests for device-aided treatment. One strong contender for this unmeasured treatment burden is represented by non-motor symptoms. 'Poor responders' might have higher burden of non-motor symptoms that lead them to be dissatisfied with medical treatment. This links to a new data-driven classification of PD subtypes, dividing patients into three phenotypes: mild-motor, diffuse-malignant and intermediate [12]. This classification has been supported by

neuropathological data [13] and these groups of patients differ in their disease course and survival according to the burden of motor and non-motor symptoms occurring during the first years of the disease. We previously showed that PD patients with a mild-motor phenotype have significantly better preserved ADL independence both in the short- and long-term follow-up than the malignant phenotype in spite of a similar efficacy on motor symptoms, fluctuations and ambulatory capacity [30]. However, in the present study we did not observe a difference in the distribution of these phenotypes between 'good' and 'poor responders', which is liklely influenced by the way PD subtypes were defined in this classification (using retrospective data and without formal tools for non-motor symptoms assessment).

Some limitations should be taken into account in the interpretation of our results, primarily the retrospective study design. We employed an arbitrary cut-off of UPDRS-II change to define poor and good DBS responders. The cut-off of 20% was based on the results of a large randomised controlled trial of STN-DBS [1]. We also did not employ specific outcome scales for measuring non-motor symptoms, as well as the severity of gait, balance and speech disturbances. Indeed, by UPDRS-III subscores, axial symptoms evaluated at the time of surgery were only marginally but not significantly less severe in the 'poor responders' group ($p = 0.06$). This may reflect the poor sensitivity of current clinical instruments in detecting subtle signs of gait, speech and balance disorder at the time of DBS selection. Instrumented assessment by wearable sensors may be a useful adjunct to clinical evaluation in this regard [31]. Another aspect worth mentioning is the potential influence of genetics on DBS outcomes. In our study, which is based on a historical cohort of patients, we were unable to control for genetic factors. Indeed, there is growing evidence suggesting that genotypes might impact on response to DBS, such as being carriers of variants of the glucocerebrosidase (*GBA1*) gene [32]. However, this concept has been recently challenged by a large multicentre study showing a benefit of DBS on motor symptoms in PD associated with GBA variants, thus supporting the role of DBS surgery as a valid therapeutic strategy in these subjects [33].

Limitations notwithstanding, our exploratory study suggests that the dissociation between ADL and motor severity outcome after STN-DBS in PD might be due to disease progression and, in particular, deterioration of axial signs. This points to the need for attention towards a better evaluation of PD patients at the time of selection for surgical therapies. We suggest that poor DBS responders might have a different phenotype where the disability leading to DBS referral is not fully captured by standard presurgical assessments. Further studies are warranted to confirm these findings, clarify the role of presurgical UPDRS-II as a DBS outcome predictor, identify more precise clusters of PD features that relate to the outcome of PD surgical therapies and develop accurate screening instruments to detect those individuals whose disease might deteriorate significantly after DBS [3].

Author Contributions

Francesca Morgante: conceptualization, methodology, writing – original draft, writing – review and editing, formal analysis, supervision, data curation. **Carlo Alberto Artusi:** conceptualization, writing – original draft, methodology, writing – review and editing, formal analysis, supervision, data curation. **Lucia Ricciardi:** methodology, formal analysis, writing – review and editing. **Marianna Sarchioto:** writing – review and editing, investigation. **Elisa Montanaro:** investigation, writing – review and editing. **Mark J. Edwards:** writing – review and editing, supervision. **Leonardo Lopiano:** writing – review and editing, supervision, data curation, conceptualization. **Maurizio Zibetti:** writing – review and editing, conceptualization, data curation, supervision.

Ethics Statement

Institutional ethics approval was obtained and approved by the ethical Committee of University of Turin (CS/855; protocol number 475). The study was conducted in accordance with the Declaration of Helsinki. Each participant provided written informed consent before study participation. 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.

Conflicts of Interest

Francesca Morgante: Research support from NIHR, Innovate UK. Speaking honoraria from Abbvie, Medtronic, Boston Scientific, Bial, Merz; Travel grants from the International Parkinson's disease and Movement Disorder Society; Advisory board fees from Merz and Boston Scientific; Consultancies fees from Boston Scientific, Merz and Bial; Research support from Boston Scientific, Merz; Royalties for the book 'Disorders of Movement' from Springer; member of the editorial board of Movement Disorders, Movement Disorders Clinical Practice, European Journal of Neurology, European Journal of Neurology. Lucia Ricciardi: Research support from the UK's Medical Research Council (MRC), Clinical Academic Research Partnerships. Mark J. Edwards: Honoraria from Merz Pharma and Boehringer Ingelheim. Royalties from the Oxford University Press. Leonardo Lopiano: Speaking honoraria from UCB Pharma, AbbVie, DOC, Zambon and Bial. Maurizio Zibetti: Speaking honoraria from Medtronic, UCB Pharma, AbbVie and Merz Pharma. The other authors do not have any disclosures to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Paired *t*-test comparing poor and good DBS responders at T0 (before surgery) and T1 (1-year follow-up). **Table S2:** Main effects and interactions as significant paired comparisons in good and poor DBS responders as for total UPDRS-III, tremor, appendicular and axial score and Hoehn–Yahr (HY) stage. **Table S3:** DBS stimulation parameters in good and poor DBS responders. **Table S4:** Univariable and multivariable linear regression analyses with change in UPDRS II as dependent variable.