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Long-Term Motor and Cognitive Outcome of Deep Brain Stimulation in Patients With Parkinson Disease With a *GBA1* Pathogenic Variant

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Abstract

Background and Objectives

Deep brain stimulation (DBS) is an established treatment for Parkinson disease (PD). In patients carrying *GBA1* variants (GBA-PD), concerns persist that DBS may accelerate cognitive decline. This study investigated the potential additive effects of *GBA1* genotype and DBS on long-term motor and nonmotor outcomes.

Methods

This multicenter retrospective, controlled, Italian study included 3 groups: DBS-treated PD patients either carrying or noncarrying *GBA1* variants (DBS-nonGBA-PD and DBS-GBA-PD) and GBA-PD patients who fulfilled DBS criteria but eventually were not operated. As secondary aims, we assessed the clinical outcomes of DBS-GBA-PD stratified by *GBA1* variant classes and by different DBS targets. Cognitive, motor, and other nonmotor features were collected at baseline and after 1, 3 and, when available, 5 years. Between-group comparisons used χ^2 and Kruskal-Wallis tests with Bonferroni correction. Longitudinal changes were analyzed with linear mixed-effects models. Subgroup analyses were performed by *GBA1* variant class and DBS target.

Results

A total of 615 participants were included: 430 DBS-nonGBA-PD (age 57.4 ± 7.7 years, 32% female), 109 DBS-GBA-PD (age 53.5 ± 8.4 years, 38% female), and 76 nonDBS-GBA-PD (age 57.7 ± 8.1 years, 37% female). At baseline, groups were largely matched for clinical features. Longitudinally, both DBS groups showed marked motor improvement (dyskinesias, on-off phenomenon, and wearing-off, all p vs T0 < 0.001), a benefit which was absent in nonDBS-GBA-PD. At 5 years, dementia occurred more frequently in DBS-GBA-PD and nonDBS-GBA-PD compared with DBS-nonGBA-PD (25.5% vs 36.8% vs 10.8%, $p < 0.001$). Hallucinations and urinary problems increased in both GBA-PD groups than nonGBA-PD (p-between <0.001 and 0.02, respectively), regardless of DBS. No relevant differences emerged on stratification for variant classes or DBS targets, up to 3 years postsurgery.

Discussion

Despite its retrospective design, this study supports DBS as a valid therapeutic option for GBA-PD, providing prolonged benefits on motor symptoms and quality of life. The accelerated cognitive decline observed in GBA-PD, compared with non-mutated participants, was similarly present in both operated and non-operated groups, suggesting it is driven by the genotype rather than DBS itself.

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Supplementary Material

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Coinvestigators are listed in the Appendix at the end of the article.

Glossary

DBS = deep brain stimulation; **DLB** = dementia with Lewy bodies; **GBA-PD** = PD participants carrying GBA1 variants; **GPi** = globus pallidus pars interna; **ICD** = impulse control disorder; **LEDD** = Levodopa Equivalent Daily Dose; **MDS-UPDRS-III** = Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III; **MDRS** = Mattis Dementia Rating Scale; **MLM** = mixed linear model; **PD** = Parkinson disease; **PDQ-8 SI** = Parkinson's Disease Questionnaire-8 Summary Index; **QoL** = quality of life; **STN** = subthalamic nuclei.

Classification of Evidence

This study provides Class III evidence that DBS does not worsen cognitive function in patients with *GBA1*-associated PD.

Introduction

Heterozygous *GBA1* variants represent the most common genetic risk factor for Parkinson disease (PD), occurring in ~10% patients worldwide.[1] PD participants carrying *GBA1* variants (GBA-PD) are more likely to develop early motor complications and faster cognitive deterioration, and present a higher risk of dementia, compared with non-mutated patients (nonGBA-PD).[2,3]

Deep brain stimulation (DBS) is an established therapeutic option to improve motor symptoms in complicated phases of PD,[4,5] also in cases with proven genetic etiology.[6] Studies investigating DBS outcomes in GBA-PD have consistently shown marked motor improvements, with significant reduction of fluctuations, dyskinesias, and dosage of dopaminergic medications.[7-10] Yet, a large multicenter study reported a more rapid cognitive decline in GBA-PD participants who underwent DBS of the subthalamic nuclei (STN), compared with both operated nonGBA-PD and nonoperated GBA-PD. This suggested the occurrence of additive, detrimental effects of the *GBA1* genotype and DBS surgery on cognitive outcome,[10] and raised serious concerns about offering DBS to GBA-PD individuals.

We recently assessed the outcome of DBS in 2 large groups of GBA-PD vs nonGBA-PD participants, confirming a similar motor improvement but a more rapid cognitive deterioration of mutated individuals with GBA-PD at 5-year follow-up.[11] Analogous results were reported in a smaller cohort of Spanish patients.[12] However, in both studies, the lack of a non-DBS-GBA-PD cohort did not allow discriminating the relative effect of the genotype and the surgical procedure itself on the rate of cognitive decline.

Another unanswered issue relates to potential differences of DBS outcomes in carriers of different *GBA1* variants because, for instance, it is known that "severe" variants are associated with a worse cognitive outcome than other classes.[3,13-15] Although a stratification of DBS-GBA-PD according to variant classes was attempted, subgroups were too small for statistical comparison, and no relevant conclusions could be drawn.

Finally, a single study on 7 GBA-PD patients who underwent DBS either on the STN or on the globus pallidus pars interna (GPi) suggested that the latter target could be associated with less cognitive worsening at 1–2-year follow-up, questioning what the optimal DBS target for GBA-PD could be.[16]

This study aims to address the unsolved question about the possible additive effects of *GBA1* genotype and DBS implant on cognitive deterioration and other nonmotor features in the long term.

As secondary aims, we looked at possible differences in the clinical outcome of DBS-GBA-PD stratified for *GBA1* variant classes (severe/complex, mild, risk, and unknown), and by different DBS targets (STN or Gpi).

Methods

This was a multicenter, retrospective, controlled, cohort study involving 14 tertiary level Movement Disorder Centres (see eAppendix 1) in the frame of the Italian PARKNET project. This project, supported by the Italian Ministry of Health, aims to collect and harmonize clinical and genetic data of patients with PD across participating centers nationwide. Demographic, clinical motor and nonmotor variables, genetic data, and scores from a range of scales are collected in a shared case report form. Data-sharing agreements were signed by each institute.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethics approval was obtained by the respective committees, and all patients provided written informed consent.

Cohort Recruitment

From the PARKNET cohort, we first selected a validation DBS cohort (vDBS-PD) of PD participants who underwent DBS surgery according to eligibility criteria[17,18] between years 2005 and 2021. Inclusion criteria for vDBS-PD were (1) complete *GBA1* gene sequencing; (2) absence of pathogenic/likely pathogenic variants in other major PD-related genes; and (3) availability of detailed clinical data at pre-DBS and after 1, 3 and when available, 5 years after surgery.

After validation analysis, this vDBS-PD cohort was added to the DBS-PD cohort included in our previous study (DBS-PD

former cohort).[11] Based on *GBA1* genotype, participants were stratified into DBS-GBA-PD and DBS-nonGBA-PD.

Next, a group of nonoperated GBA-PD participants (nonDBS-GBA-PD), ascertained across the same timeframe, were selected. Inclusion criteria were (1) heterozygosity for a *GBA1* variant; (2) absence of pathogenic/likely pathogenic variants in other major PD-related genes; (3) an identifiable time in patients' history (defined "baseline") when they met the same eligibility criteria for surgery as the DBS cohort (eTable 1)[17,18]; and (4) detailed clinical data available at baseline and after 1, 3 and, when possible, 5 years.

Despite being eligible for DBS, these patients eventually did not undergo surgery for the following reasons: (1) they refused brain surgery and opted for modification of routine oral therapy, or for subcutaneous apomorphine therapy or intrajejunal levodopa/carbidopa; (2) lacked social/familiar support; and (3) had a general contraindication to undergo neurosurgical interventions, such as coagulopathy, coronary heart disease, pulmonary fibrosis, and intracranial vascular anomalies (details in eAppendix 1).

GBA1 variants were subclassified into 5 classes (mild, severe, complex, risk, and unknown) as reported.[19,20] A flowchart depicting the consecutive steps which led to select the 3 patients' groups is shown in Figure 1.

Clinical Assessment

Clinical data were retrospectively collected at 4 timepoints: baseline (T0) (for DBS: maximum 6 months before surgery; for nonDBS-GBA-PD: time of evaluation for surgical eligibility), after 1 (T1), 3 (T3), and when available, 5 years (T5).

The following data were collected: Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) scores in ON and OFF medication phase (stim-ON after surgery), Hoehn and Yahr stage, Mattis Dementia Rating Scale (MDRS), Levodopa Equivalent Daily Dose (LEDD), Parkinson's Disease Questionnaire-8 Summary Index (PDQ-8 SI), presence of dyskinesias, wearing-off, unpredictable "on-off" phenomenon, freezing of gait, autonomic symptoms, impulse control disorders (ICDs), dementia, depression, hallucinations, inability to walk, and recurrent falls. A detailed description of the clinical variables, along with the full list of demographic and clinical features, are presented in eAppendix 1.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 26) and RStudio (version 2024.12.0+467), with significance set at $p < 0.05$ for all tests. The newly recruited DBS-PD validation cohorts (vDBS-nonGBA-PD and vDBS-GBA-PD) were compared at each timepoint and longitudinally using the same methodology as reported in our former study,[11] to ensure replicability.

Merged DBS groups (DBS-nonGBA-PD and DBS-GBA-PD) were compared with the newly recruited group of nonDBS-GBA-PD participants.

Demographic characteristics among the 3 groups were assessed using χ^2 for dichotomous variables, and the Kruskal-Wallis test for numerical variables. For each timepoint, comparisons among groups were performed using χ^2 for categorical variables and the Kruskal-Wallis test for numerical variables.

For all analyses, multiple comparisons were performed using post hoc pairwise tests with Bonferroni correction to identify significant differences between specific groups. Longitudinal analysis was performed over 5 years using a mixed linear model (MLM), with groups as independent variable and age, sex, years of education, and disease duration as covariates. MLM was chosen because it represents a valuable tool to effectively handle correlated data points within the same participant, even in the presence of varying numbers of observations per participant, missing data, or uneven intervals between measurements.

Moreover, we repeated the longitudinal analysis after performing a propensity score matching to assess whether prior findings on the long-term cognitive outcome could be replicated in matched, albeit smaller, groups.

We also performed an exploratory analysis to investigate whether any demographic or clinical features at baseline could predict the risk of cognitive deterioration and worst quality of life (QoL) over time in the entire GBA-PD group (merging operated and nonoperated GBA-PD), and separately in the GBA-DBS group, using a backward stepwise linear or logistic regression analysis.

Finally, we assessed differences in clinical outcomes of DBS-GBA-PD stratified by *GBA1* variant classes (severe/complex, mild, risk, and unknown) and DBS targets (subthalamic nucleus or globus pallidus). Further methodologic details on statistical analysis used are reported in eAppendix 1.

Data Availability

The datasets generated during this study are available in the ZENODO repository.

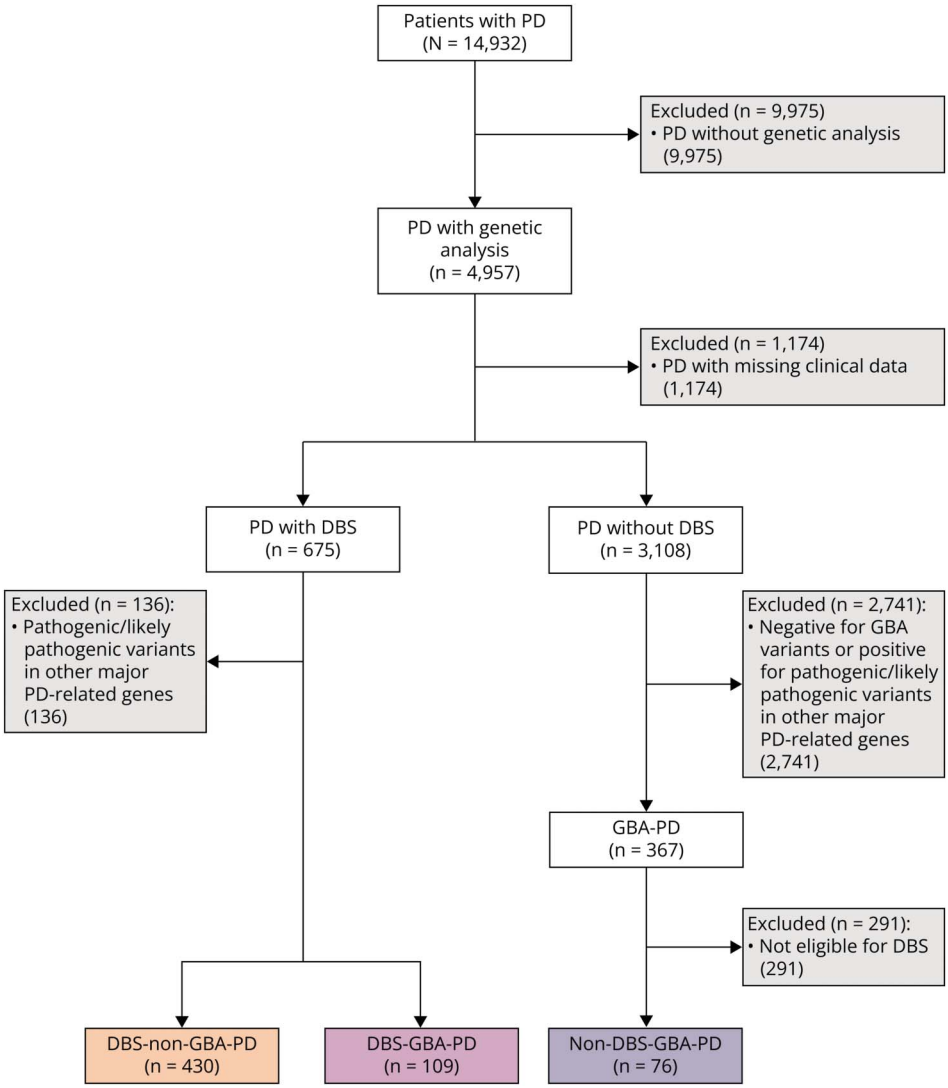
Results

Participants

A total number of 615 participants were included in this study (see Figure 1).

First, a validation DBS cohort (vDBS-PD) of 174 participants (vDBS-nonGBA-PD n = 138 and vDBS-GBA-PD n = 36) who underwent surgery according to eligibility criteria[17,18] between years 2005 and 2021 were recruited in addition to the 365 patients included in our previous study (DBS-PD former cohort).[11]

Figure 1 Study Design



The flowchart reports the starting number of ascertained PD participants and the consecutive steps which led to select the 3 patients' groups. Calculations were based on the merged data set encompassing both the validation DBS-PD cohort and the DBS-PD former cohort. DBS = deep brain stimulation; GBA-PD = PD participants carrying *GBA1* variants; PD = Parkinson disease.

To assess homogeneity between former and validation cohorts, we first compared vDBS-GBA-PD vs vDBS-nonGBA-PD groups at each timepoint and longitudinally, using the same methodology as our previous study (details in eAppendix 1).[11]

This validation analysis generated fully consistent results, allowing us to merge the 2 DBS cohorts to increase sample size and statistical power. We reached an overall numerosity of 430 DBS-nonGBA-PD and 109 DBS-GBA-PD participants who underwent DBS surgery. These participants were compared with the newly recruited group of 76 nonDBS-GBA-PD participants who fulfilled the same criteria for DBS eligibility but eventually were not operated.

The following results refer to comparisons among these 3 groups. The list of *GBA1* variants detected in the entire cohort is reported in eTable 2.

Baseline Characteristics

At baseline, DBS-GBA-PD were slightly younger and had more dyskinesias, ICD, and orthostatic hypotension symptoms than other groups. Moreover, both DBS groups had a slightly lower age at PD onset, longer disease duration, higher LEDD intake, and more prevalent freezing of gait compared with non-operated participants. All other motor and nonmotor features, cognitive scores, and QoL scores were comparable across the 3 groups (Table 1).

Long-Term Outcome

Comparison of clinical features and long-term complications across all groups at different time points is presented in Figures 2 and 3 and in Table 2.

At 1 year from baseline, both DBS groups, regardless of *GBA1* genotype, showed a marked improvement of motor features (decreased MDS-UPDRS-III-OFF) and motor fluctuations

(reduction of dyskinesias, wearing-off, and on-off phenomenon), as well as a reduction of LEDD intake and impulsive-compulsive disorders, which remained stable at the long-term follow-up. Conversely, a significant and progressive worsening in motor scores, increased LEDD intake, and dyskinesias were observed in nonDBS-GBA-PD. Complications such as recurrent falls and inability to walk were limited and comparable between DBS groups, while these were more prevalent and significantly worsened from baseline in nonDBS-GBA-PD.

When assessing cognition, MDRS scores of both GBA-PD groups, regardless of DBS, showed significant worsening from baseline, differing from the DBS-nonGBA-PD group already after 1 year. At 5-year follow-up, the proportion of patients with a diagnosis of dementia was comparable in the 2 GBA-PD groups and significantly greater than DBS-nonGBA-PD (DBS-nonGBA-PD 10.8%, DBS-GBA-PD 25.5%, and nonDBS-GBA-PD 36.8%, respectively). Similarly to cognitive decline, the prevalence of hallucinations and urinary problems also increased at 3 and 5 years in both GBA-PD groups. Depression slightly increased after 5 years in all 3 groups, with a significantly higher prevalence in nonDBS-GBA-PD compared with both operated groups.

Longitudinal evaluation showed that QoL significantly improved after surgery in both operated groups. Such improvement was sustained over time in DBS-nonGBA-PD, while it returned to baseline levels after 3 years, and then, it remained stable in DBS-GBA-PD. Conversely, QoL

Table 1 Demographic Characteristic and Clinical Features at Baseline

	DBS-nonGBA-PD (n = 430) (a)	DBS-GBA-PD (n = 109) (b)	nonDBS-GBA-PD (n = 76) (c)	*p* Value	Post hoc
Age at baseline (y)	57.4 ± 7.7	53.5 ± 8.4	57.7 ± 8.1	<0.001	b < a, c
Age at PD onset (y)	46.4 ± 8.2	44.2 ± 8.3	50.3 ± 7.5	<0.001	c > a, b
Age at DBS (y)	57.7 ± 7.6	53.5 ± 8.4	—	<0.001	b < a
Sex (F/M)	137/293	42/67	28/48	0.14	—
Disease duration at baseline (y)	10.9 ± 4.4	9.1 ± 3.7	7.5 ± 3.0	<0.001	b < a; c < a, b
Education (y)	11.8 ± 3.7	11.4 ± 3.8	12.5 ± 3.8	0.60	—
DBS target: STN vs GPi (% STN)	92.10	89.40	—	0.40	—
Family history for PD (% yes)	85/404 (21)	42/107 (39.3)	35/75 (46.7)	<0.001	a < b, c
Hoehn and Yahr	2.2 ± 0.6	2.3 ± 0.6	2.1 ± 0.5	0.12	
LEDD (mg)	1,053.6 ± 415.8	1,095.5 ± 400.2	790.8 ± 297.2	<0.001	c < a, b
MDS-UPDRS-III (OFF med)	41.6 ± 14.4	43.1 ± 16.3	36.2 ± 13.4	0.06	—
MDS-UPDRS-III (ON med)	18.3 ± 9.8	18.1 ± 9.5	17.1 ± 8.5	0.61	—
MDRS	138.5 ± 5.4	138.5 ± 5.2	138.5 ± 5.7	0.77	—
PDQ-8 (Summary Index)	33.9 ± 41.4	27.5 ± 33.1	27.2 ± 15.3	0.25	—
Dyskinesias (% yes)	340/430 (79.1)	96/109 (88.1)	55/76 (72.4)	0.02	b > c
On-off phenomenon (% yes)	253/429 (59)	75/109 (68.8)	50/76 (65.8)	0.12	—
Wearing-off (% yes)	393/430 (91.4)	104/109 (95.4)	73/76 (96.1)	0.17	—
Freezing of gait (% yes)	209/429 (48.7)	51/108 (47.2)	23/76 (30.3)	0.01	c < a, b
Orthostatic hypotension symptoms (% yes)	34/410 (8.3)	17/107 (15.7)	10/76 (13.2)	0.04	a < b
ICD (% yes)	116/429 (27)	19/109 (17.4)	13/76 (17.1)	0.06	—
REM behavior disorders (% yes)	168/407 (41.3)	45/109 (41.3)	42/76 (55.3)	0.07	—
MCI (% yes)	38/426 (8.9)	9/108 (11.6)	10/74 (13.5)	0.42	—

Abbreviations: DBS = deep brain stimulation; GBA-PD = PD participants carrying *GBA1* variants; GPi = globus pallidus pars interna; ICD = impulsive-compulsive disorder; MCI = mild cognitive impairment; MDRS = Mattis Dementia Rating Scale; OFF med = OFF medication; ON med = ON medication; PD = Parkinson disease; PDQ-8 = Parkinson's Disease Questionnaire-8; STN = subthalamic nuclei.
Chi-squared and Kruskal-Wallis nonparametric tests were performed to compare demographics and clinical features at baseline between groups. Multiple comparisons with Bonferroni correction were applied to highlight significant differences between specific groups for both tests, with a significance level of 0.05. Numerical variables are presented as mean ± SD, while categorical variables are reported as absolute numbers and the percentage of "yes" responses.

Table 2 Clinical Motor and Nonmotor Parameters of the 3 Groups at T1, T3, and T5

	DBS-nonGBA-PD (a)			DBS-GBA-PD (b)			nonDBS-GBA-PD (c)				
1-y (T1)	**n = 389**			**n = 110**			**n = 75**				
3-y (T3)	**n = 285**			**n = 81**			**n = 62**				
5-y (T5)	**n = 226**			**n = 51**			**n = 20**				
Longitudinal		***p* vs T0**	***p* vs T1**		***p* vs T0**	***p* vs T1**		***p* vs T0**	***p* vs T1**	***p*-between (post hoc)**	
MDS-UPDRS-III (OFF med)											
1-y (T1)	28.4 ± 10.4	<0.001	—	31.3 ± 13.3	<0.001	—	37.6 ± 12.9	0.07	—	0.001	a < c
3-y (T3)	30.9 ± 12	<0.001	0.004	32.1 ± 10.4	<0.001	0.04	44.3 ± 16.4	<0.001	<0.001	<0.001	c > a, b
5-y (T5)	32.2 ± 11.2	<0.001	<0.001	36.2 ± 14.5	0.02	0.01	47.6 ± 19.0	<0.001	<0.001	0.04	a < c
MDS-UPDRS-III (ON med)											
1-y (T1)	16.6 ± 8.7	<0.001	—	18.0 ± 9.3	0.44	—	20.0 ± 10.4	0.02	—	0.02	a < c
3-y (T3)	19.8 ± 9.9	0.002	<0.001	20.5 ± 9.5	<0.001	0.001	24.3 ± 11.0	<0.001	0.01	0.01	a < c
5-y (T5)	22.3 ± 10.5	<0.001	<0.001	23.2 ± 10.6	0.001	<0.001	27.7 ± 13.3	<0.001	<0.001	0.20	—
LEDD (mg)											
1-y (T1)	685.5 ± 351.8	<0.001	—	685.8 ± 327.5	<0.001	—	878.7 ± 326.6	0.14	—	<0.001	c > a, b
3-y (T3)	733.7 ± 389.9	<0.001	0.01	733.3 ± 347.5	<0.001	0.13	989.7 ± 346.2	0.001	0.05	<0.001	c > a, b
5-y (T5)	813.2 ± 413.9	<0.001	<0.001	740.2 ± 335.7	<0.001	0.10	984.0 ± 309.5	0.04	0.26	0.03	b < c
Hoehn & Yahr											
1-y (T1)	2.1 ± 0.5	0.004	—	2.2 ± 0.5	0.04	—	2.1 ± 0.5	0.43	—	0.27	—
3-y (T3)	2.3 ± 0.8	0.01	<0.001	2.4 ± 0.5	0.07	<0.001	2.4 ± 0.7	0.002	0.02	0.08	—
5-y (T5)	2.5 ± 0.6	<0.001	<0.001	2.7 ± 0.6	<0.001	<0.001	2.6 ± 0.9	0.001	0.003	0.38	—
MDRS											
1-y (T1)	138.2 ± 6.7	0.01	—	136.3 ± 6.5	0.04	—	136.6 ± 7.8	0.24	—	0.01	a > b, c
3-y (T3)	135.3 ± 8.1	<0.001	<0.001	131.5 ± 7.9	<0.001	<0.001	130.0 ± 15.6	<0.001	0.001	0.002	a > b, c
5-y (T5)	132.0 ± 10.1	<0.001	<0.001	123.1 ± 15.5	<0.001	<0.001	123.9 ± 16.7	<0.001	<0.001	0.007	a > b, c
	DBS-nonGBA-PD (a)			**DBS-GBA-PD (b)**			**nonDBS-GBA-PD (c)**				
		***p* vs T0**	***p* vs T1**		***p* vs T0**	***p* vs T1**		***p* vs T0**	***p* vs T1**	***p*-between (post hoc)**	
PDQ-8 (Summary Index)											
1-y (T1)	24.9 ± 17.7	<0.001	—	20.4 ± 14.9	0.04	—	31.5 ± 22.9	0.28	—	0.11	—
3-y (T3)	27.2 ± 17.9	0.007	0.21	27.7 ± 14.7	0.95	0.07	36.7 ± 15.5	0.05	0.37	0.02	c > a, b
5-y (T5)	31.8 ± 19.2	0.27	0.005	34.7 ± 21.9	0.31	0.003	43.7 ± 29.5	0.03	0.19	0.48	—
Dyskinesias (% yes)											
1-y (T1)	168/391 (43.0)	<0.001	—	58/110 (52.7)	<0.001	—	55/75 (73.3)	0.23	—	<0.001	c > a, b
3-y (T3)	154/285 (54.0)	<0.001	0.001	49/81 (60.5)	<0.001	0.13	49/62 (79.0)	0.1	0.63	0.001	c > a
5-y (T5)	132/227 (58.1)	<0.001	<0.001	31/51 (60.8)	<0.001	0.15	19/20 (95.0)	0.04	0.12	0.005	c > a, b
On-off phenomenon (% yes)											
1-y (T1)	54/391 (13.8)	<0.001	—	23/108 (21.3)	<0.001	—	41/75 (54.7)	0.3	—	<0.001	c > a, b

Continued

Table 2 Clinical Motor and Nonmotor Parameters of the 3 Groups at T1, T3, and T5 *(continued)*

	DBS-nonGBA-PD (a)			DBS-GBA-PD (b)			nonDBS-GBA-PD (c)				
		p vs T0	*p* vs T1		*p* vs T0	*p* vs T1		*p* vs T0	*p* vs T1	*p*-between (post hoc)	
3-y (T3)	49/285 (17.2)	<0.001	0.45	28/81 (34.6)	<0.001	0.001	41/62 (66.1)	0.53	0.11	<0.001	c > a, b; b > a
5-y (T5)	47/227 (20.7)	<0.001	0.04	24/51 (47.1)	0.001	<0.001	13/19 (68.4)	0.95	0.52	<0.001	c > a; b > a
Wearing-off (% yes)											
1-y (T1)	189/390 (48.5)	<0.001	—	53/109 (48.6)	<0.001	—	60/75 (80.0)	0.26	—	<0.001	c > a, b
3-y (T3)	173/285 (60.7)	<0.001	<0.001	53/81 (65.4)	<0.001	0.003	56/62 (90.3)	0.61	0.12	<0.001	c > a, b
5-y (T5)	155/227 (68.3)	<0.001	<0.001	35/51 (68.6)	<0.001	0.007	17/19 (89.5)	0.07	0.32	0.14	—
Freezing of gait (% yes)											
1-y (T1)	123/387 (31.8)	<0.001	—	45/109 (34.2)	0.25	—	27/75 (36.0)	0.18	—	0.19	—
3-y (T3)	144/285 (50.5)	0.75	<0.001	42/81 (51.9)	0.26	0.03	32/62 (51.6)	<0.001	0.009	0.93	—
5-y (T5)	139/223 (62.3)	<0.001	<0.001	34/51 (66.7)	0.02	0.002	13/19 (68.4)	<0.001	0.003	0.85	—
Orthostatic hypotension (% yes)											
1-y (T1)	33/367 (9.0)	0.25	—	18/107 (16.8)	0.67	—	11/75 (14.7)	0.66	—	0.04	—
3-y (T3)	28/280 (10.0)	0.14	0.66	20/81 (24.7)	0.06	0.13	13/62 (21.0)	0.32	0.57	0.001	a < b
5-y (T5)	29/201 (14.4)	0.04	0.01	14/51 (27.5)	0.07	0.14	6/19 (31.6)	0.04	0.09	0.03	a < b
	DBS-nonGBA-PD (a)			**DBS-GBA-PD (b)**			**nonDBS-GBA-PD (c)**				
		p vs T0	*p* vs T1		*p* vs T0	*p* vs T1		*p* vs T0	*p* vs T1	*p*-between (post hoc)	
ICD (% yes)											
1-y (T1)	38/388 (9.8)	<0.001	—	8/108 (7.4)	<0.001	—	15/75 (20.0)	0.47	—	0.02	c > a, b
3-y (T3)	28/285 (9.8)	<0.001	0.98	11/81 (13.6)	0.02	0.38	13/62 (21.0)	0.49	0.99	0.04	a < c
5-y (T5)	29/218 (13.3)	<0.001	0.33	6/51 (11.8)	0.01	0.85	6/19 (31.6)	0.2	0.44	0.03	—
Dementia (% yes)											
1-y (T1)	6/388 (1.5)	—	—	4/109 (3.7)	—	—	4/74 (5.4)	—	—	0.09	—
3-y (T3)	19/284 (6.7)	—	0.001	10/80 (12.5)	—	0.02	12/61 (19.7)	—	0.04	0.005	a < c
5-y (T5)	24/224 (10.7)	—	<0.001	12/47 (25.5)	—	<0.001	7/19 (36.8)	—	<0.001	<0.001	a < b, c
Depression (% yes)											
1-y (T1)	115/386 (29.8)	—	—	39/109 (35.8)	—	—	33/75 (44.0)	—	—	0.04	—
3-y (T3)	106/284 (37.3)	—	0.01	32/81 (39.5)	—	0.50	30/62 (48.4)	—	0.87	0.33	—
5-y (T5)	91/218 (41.7)	—	<0.001	22/50 (44.0)	—	0.04	13/18 (72.2)	—	<0.001	0.04	c > a
Hallucinations (% yes)											
1-y (T1)	12/374 (3.2)	—	—	7/109 (6.4)	—	—	3/75 (4.0)	—	—	0.28	—
3-y (T3)	11/285 (3.9)	—	0.66	13/80 (16.3)	—	0.02	14/62 (22.6)	—	0.002	<0.001	a < b, c

Continued

Table 2 Clinical Motor and Nonmotor Parameters of the 3 Groups at T1, T3, and T5 *(continued)*

	DBS-nonGBA-PD (a)			DBS-GBA-PD (b)			nonDBS-GBA-PD (c)				
		p vs T0	*p* vs T1		*p* vs T0	*p* vs T1		*p* vs T0	*p* vs T1	*p*-between	(post hoc)
5-y (T5)	15/210 (7.1)	—	0.007	14/51 (27.5)	—	<0.001	5/19 (26.3)	—	0.004	<0.001	a < b, c
Inability to walk (% yes)											
1-y (T1)	5/387 (1.3)	—	—	2/107 (1.8)	—	—	2/75 (2.7)	—	—	0.65	—
3-y (T3)	10/285 (3.5)	—	0.05	2/81 (2.5)	—	0.57	4/62 (6.5)	—	0.08	0.43	—
5-y (T5)	7/215 (3.3)	—	0.02	4/51 (7.8)	—	0.01	3/19 (15.8)	—	0.002	0.03	—
Recurrent falls (% yes)											
1-y (T1)	37/377 (9.8)	—	—	13/109 (11.9)	—	—	10/75 (13.3)	—	—	0.54	—
3-y (T3)	60/285 (21.1)	—	<0.001	16/81 (19.8)	—	0.03	18/62 (29.0)	—	0.02	0.33	—
5-y (T5)	70/218 (32.1)	—	<0.001	17/51 (33.3)	—	<0.001	9/19 (47.4)	—	0.004	0.34	—
Urinary incontinence (%yes)											
1-y (T1)	35/371 (9.4)	—	—	14/108 (13.0)	—	—	17/75 (22.7)	—	—	0.001	a < c
3-y (T3)	41/283 (14.5)	—	0.005	17/81 (21.0)	—	0.35	20/62 (32.3)	—	0.15	0.004	a < c
5-y (T5)	35/202 (17.3)	—	<0.001	16/51 (31.4)	—	0.001	7/19 (36.8)	—	0.03	0.02	a < c

Abbreviations: DBS = deep brain stimulation; GBA-PD = PD participants carrying *GBA1* variants; ICD = impulsive-compulsive disorders; LEDD = Levodopa Equivalent Daily Dose; MDRS = Mattis Dementia Rating Scale; MDS-UPDRS-III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III; OFF med = OFF medication; ON med = ON medication; PD = Parkinson disease; PDQ-8 = Parkinson's Disease Questionnaire-8.
Between-group comparisons at T1, T3, and T5 were performed using the Kruskal-Wallis test for numerical variables, and the χ^2 test for categorical variables. Multiple comparisons with Bonferroni correction were applied to highlight significant differences between specific groups for both tests. Longitudinal within-group comparison was performed with linear mixed-effects model with groups as independent variable and age, sex, years of education, and disease duration as covariates. A significance level of 0.05 was applied for both tests. Numerical variables are presented as mean ± SD, while categorical variables are reported as absolute numbers and the percentage of "yes" responses.

significantly worsened from baseline to the 5-year follow-up in the nonDBS-GBA-PD group.

A subgroup analysis after propensity score matching of the 3 groups (DBS-nonGBA-PD, DBS-GBA-PD, and nonDBS-GBA-PD; n = 76 participants in each group) matched for disease duration (mean 7.5 years) confirmed the cognitive findings obtained in the entire cohorts. In particular, MDRS scores of both GBA-PD groups, regardless of DBS, showed significant worsening from baseline, differing from the DBS-nonGBA-PD group already after 3 years. At 5-year follow-up, the proportion of patients with a diagnosis of dementia was comparable in the 2 GBA-PD groups and significantly greater than DBS-nonGBA-PD (DBS-nonGBA-PD 8.1%, DBS-GBA-PD 25.8%, and nonDBS-GBA-PD 38.9%, respectively) (eTables 3 and 4, eFigures 1 and 2).

Finally, in an exploratory analysis, we investigated whether any demographic or baseline clinical features could predict the risk of cognitive deterioration and worse quality of life over time, in both GBA-PD groups and in the DBS-GBA-PD group only. An older age at PD onset seemed to be associated with dementia and lower MDRS scores, both when considering the 2 GBA-PD groups together or DBS-GBA-PD only. Of interest, when considering the entire GBA-PD cohort, we observed that male sex, a greater prevalence of the "on-off" phenomenon, a higher age at onset, and a nonDBS state were baseline predictors of worse QoL at follow-up. Conversely, this was only predicted by a higher prevalence of ICD at baseline when considering the GBA-DBS group alone (eTable 5).

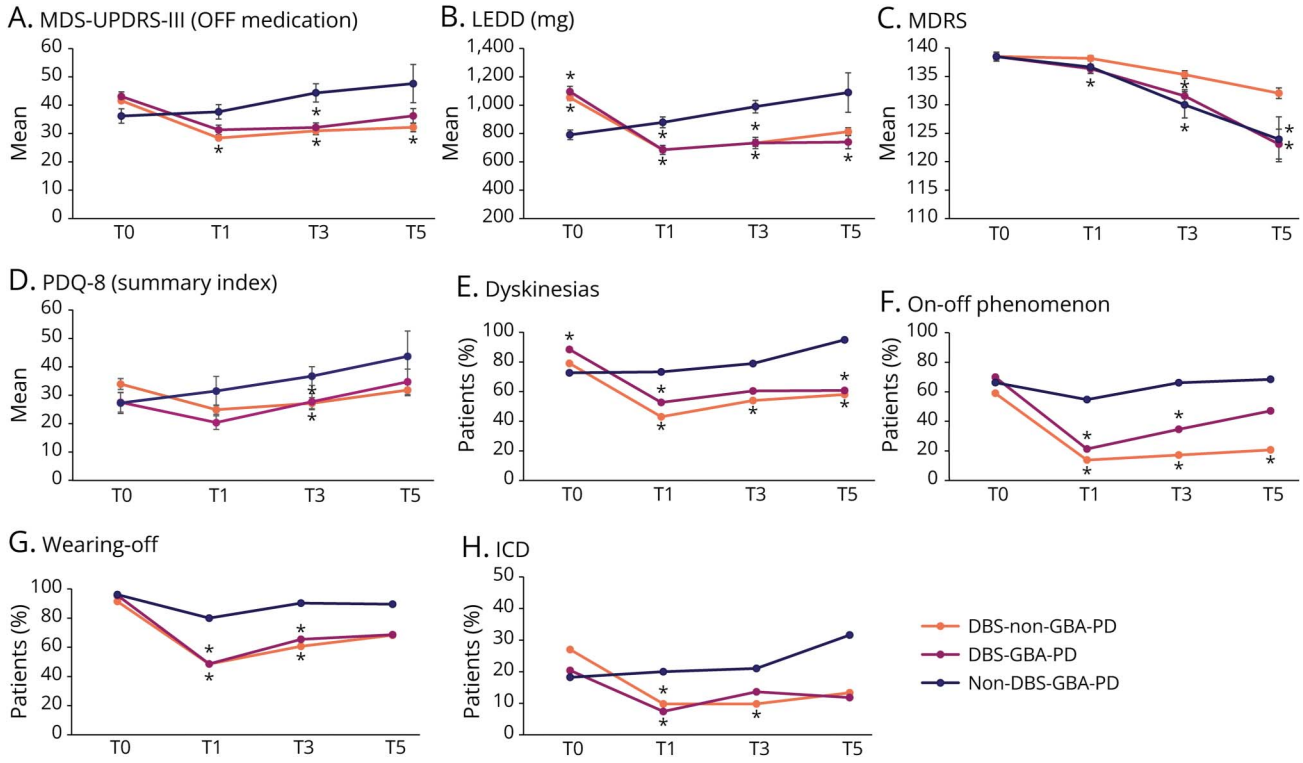
Comparison Across *GBA1* Variant Classes

Among 109 DBS-GBA-PD participants, mild variants were detected in 23 (21.1%) participants, risk variants in 26 (22.9%), severe/complex variants in 47 (43.1%), and unknown variants in 13 (11.9%). Of the 76 nonDBS-GBA-PD participants, 14 (18.4%) had mild variants, 23 (30.3%) risk, 30 (39.5%) severe/complex, and 9 (11.8%) unknown (eTable 2). *GBA1* variant distribution across classes was comparable between DBS and nonDBS groups (eFigure 3).

Demographic data at baseline are given in eTable 6, while comparison of the longitudinal data stratified by *GBA1* variant classes up to 3-year follow-up, is presented in Figure 4 and eTable 7.

No major differences emerged across variant subgroups for demographic characteristics, motor and nonmotor features at baseline, with the exception of orthostatic hypotension symptoms, which were considerably less common in nonDBS-GBA-PD carrying risk and unknown variants

Figure 2 Evolution of Clinical Motor and Nonmotor Parameters of the 3 Groups Over Time



Line plots show the mean ± SE for (A) MDS-UPDRS-OFF med, (B) MDRS, (C) LEDD, and (D) PDQ-8-SI, as well as the percentage of patients with (E) dyskinesias, (F) on-off phenomenon, (G) wearing-off, and (H) ICD, at baseline (T0), T1, T3, and T5. Multiple comparisons were performed using post hoc pairwise tests with Bonferroni correction. Statistically significant p values ($p < 0.05$) are marked with (*). ICD = impulse control disorder; LEDD = Levodopa Equivalent Daily Dose; MDRS = Mattis Dementia Rating Scale; MDS-UPDRS-III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III; OFF med = OFF medication; PDQ-8-SI = Parkinson's Disease Questionnaire-8 Summary Index.

compared with other subgroups. T1 and T3 evaluations also revealed a similar outcome across variant classes except for orthostatic symptoms, which were less prevalent in nonDBS-GBA-PD carrying risk variants compared with those carrying mild and severe variants. Overall, all DBS-GBA-PD variant subgroups had a comparable, prolonged benefit after surgery, with significantly reduced motor symptoms, complications, and a lower LEDD. Conversely, a global motor worsening was observed in all nonDBS-GBA-PD variant subgroups.

The deterioration in MDRS scores was similar in all DBS-GBA-PD and nonDBS-GBA-PD subgroups, with a trend toward a more marked worsening in the nonDBS-GBA-PD subgroup carrying severe variants. At 3 years, no differences were observed in the prevalence of dementia across *GBA1* classes in both operated and non-operated groups.

Outcome Comparison Between DBS Targets

In the DBS-GBA-PD group, the target was bilateral STN in 89.4% and GPi in 10.6%. The clinical outcome up to 3 years is presented in Figure 5 and eTable 8.

A longitudinal comparison of the estimated rate of change of motor and nonmotor parameters disclosed no relevant differences between the 2 subgroups. Compared with baseline, we evidenced a significantly greater improvement of motor function in the DBS-GBA-PD_STN than in the GPi counterpart. Furthermore, DBS-GBA-PD_GPi exhibited a substantial worsening from baseline in the PDQ-8 SI scores, while these improved at 1 year and then remained stable in the STN subgroup.

Of note, cognitive decline and other nonmotor features evolved similarly in both subgroups regardless of the target, except for a slightly increased prevalence of hallucinations in DBS-GBA-PD_STN at the 3-year follow-up.

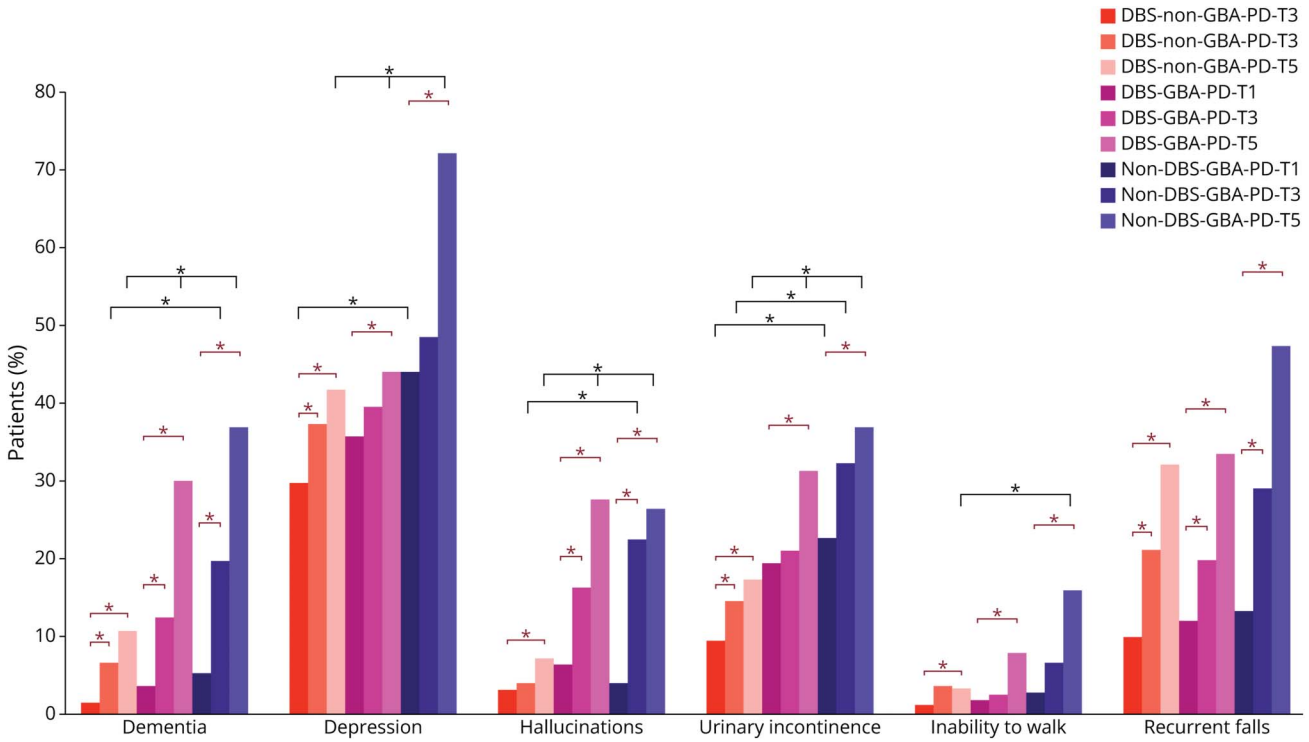
Classification of Evidence

This study provides Class III evidence that DBS does not worsen cognitive function in patients with *GBA1*-associated PD.

Discussion

DBS is an effective treatment for advanced PD, able to improve motor symptoms and reduce the need for medications.[21,22] The postsurgical evolution is known to be influenced by technical aspects and clinical presentation, yet the patient's genetic background is recently emerging as a relevant variable.[6,23-25] In this light, understanding the effect of genetic risk factors on DBS

Figure 3 Occurrence of Long-Term Complications in the 3 Groups Over Time



Bar plots show the percentage of patients with (A) dementia, (B) depression, (C) hallucinations, (D) inability to walk, (E) recurrent falls, and (F) urinary incontinence at T1, T3, and T5. Black (*) indicates statistically significant differences between groups at different time points based on Bonferroni-corrected post hoc pairwise comparisons; red (*) indicates significant intragroup differences over time ($p < 0.05$). DBS = deep brain stimulation; GBA-PD = PD participants carrying *GBA1* variants; PD = Parkinson disease.

response is crucial to optimize the selection of candidates and predict the clinical outcome. This is particularly relevant for *GBA1*, with a carrier frequency of ~10% among PD.[2] Previous studies in GBA-PD patients demonstrated that DBS is beneficial on motor symptoms and fluctuations,[7-10] but raised concerns on its possible detrimental effects on cognitive and other neuropsychiatric symptoms.[7,9,10,26] So far, this issue remains unresolved.

To address this key question, we expanded our former DBS cohort by including new referring centers across Italy. Before merging the newly recruited with the former cohort,[11] a validation study was conducted to ensure that the 2 cohorts were fully comparable in the frequency of *GBA1* variant classes, baseline clinical features, and postsurgical outcomes. This was an essential step because an unbalanced distribution of *GBA1* variants or different clinical features at baseline could have biased subsequent analyses in the extended cohort. It is more important that we included a third group of GBA-PD participants who matched the same DBS eligibility criteria as the operated cohort, but eventually did not undergo surgery. The frequency of variant classes was homogeneous in the operated and nonoperated groups, with severe/complex variants being the commonest ones, in line with previous Italian studies.[11,19]

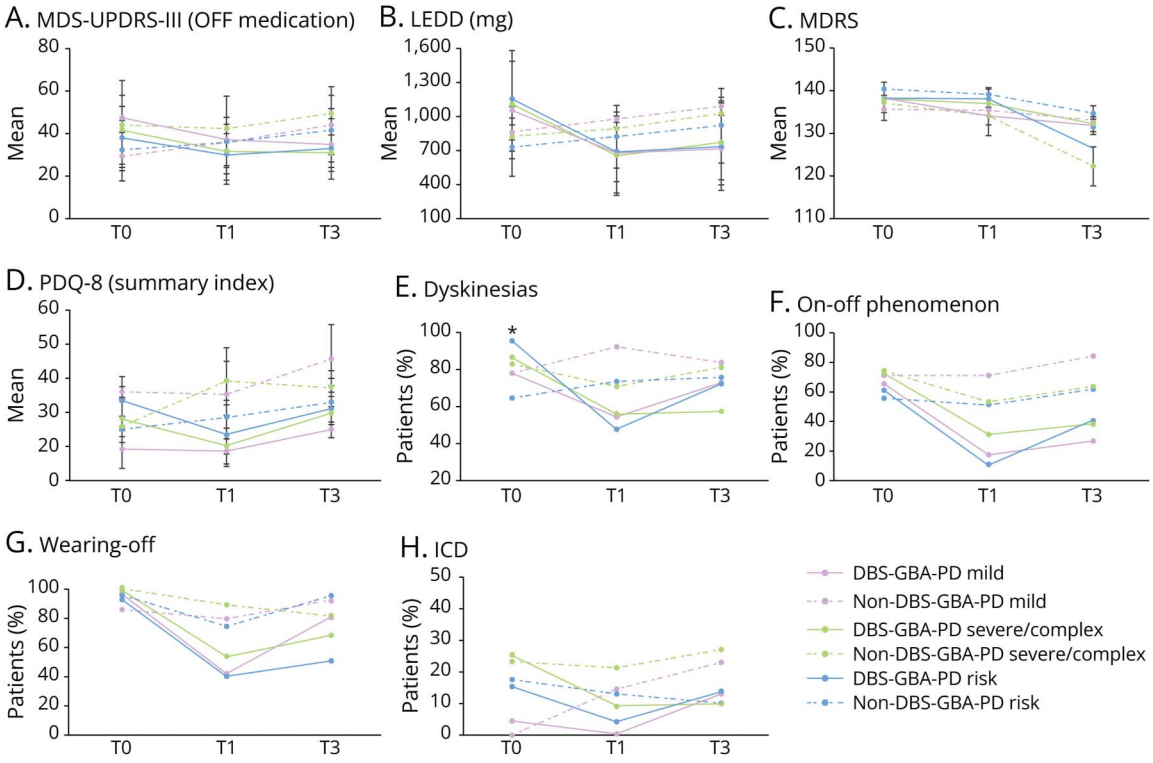
At baseline, the 3 cohorts were remarkably similar in motor, cognitive, and other nonmotor symptoms such as motor fluctuations, which represented the most prevalent indication for DBS surgery. The shorter disease duration, lower LEDD, and reduced freezing of gait shown by the nonDBS-GBA-PD group may be partly explained by the fact that the operated participants were evaluated just before surgery, whereas for nonDBS participants, the baseline was set at the time when patients were considered eligible for surgery, and thus potentially earlier than the operated groups.

Evaluation up to 5 years confirmed the well described DBS-related motor improvement, which was comparable in both operated groups regardless of *GBA1* genotype, with reduced motor fluctuations and lower LEDD intake. Conversely, nonDBS-GBA-PD participants exhibited a global decline in motor performance, which became more pronounced with time.

The most relevant finding of this study emerged when comparing the cognitive outcomes. Cognitive impairment of DBS-GBA-PD was in line with previous data.[7,10,11,26] Nonoperated GBA-PD also showed significantly lower cognitive scores than nonmutated participants already after 1 year, progressively worsening at longer follow-ups.

It is most important that such cognitive deterioration was remarkably similar in the 2 GBA-PD groups regardless of

Figure 4 Evolution of Clinical Motor and Nonmotor Parameters of GBA-PD Subgroups According to Variant Classes



Line plots show the mean ± SE for (A) MDS-UPDRS-OFF med, (B) LEDD, (C) MDRS, and (D) PDQ-8-SI, as well as the percentage of patients with (E) dyskinesias, (F) on-off phenomenon, (G) wearing-off, and (H) ICD, at baseline (T0), T1, and T3. Unknown variants are not shown. Multiple comparisons were performed using post hoc pairwise tests with Bonferroni correction. Statistically significant *p* values ($p < 0.05$) are marked with (*). ICD = impulse control disorder; GBA-PD = PD participants carrying *GBA1* variants; LEDD = Levodopa Equivalent Daily Dose; MDRS = Mattis Dementia Rating Scale; MDS-UPDRS-III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III; OFF med = OFF medication; PD = Parkinson disease; PDQ-8-SI = Parkinson's Disease Questionnaire-8 Summary Index.

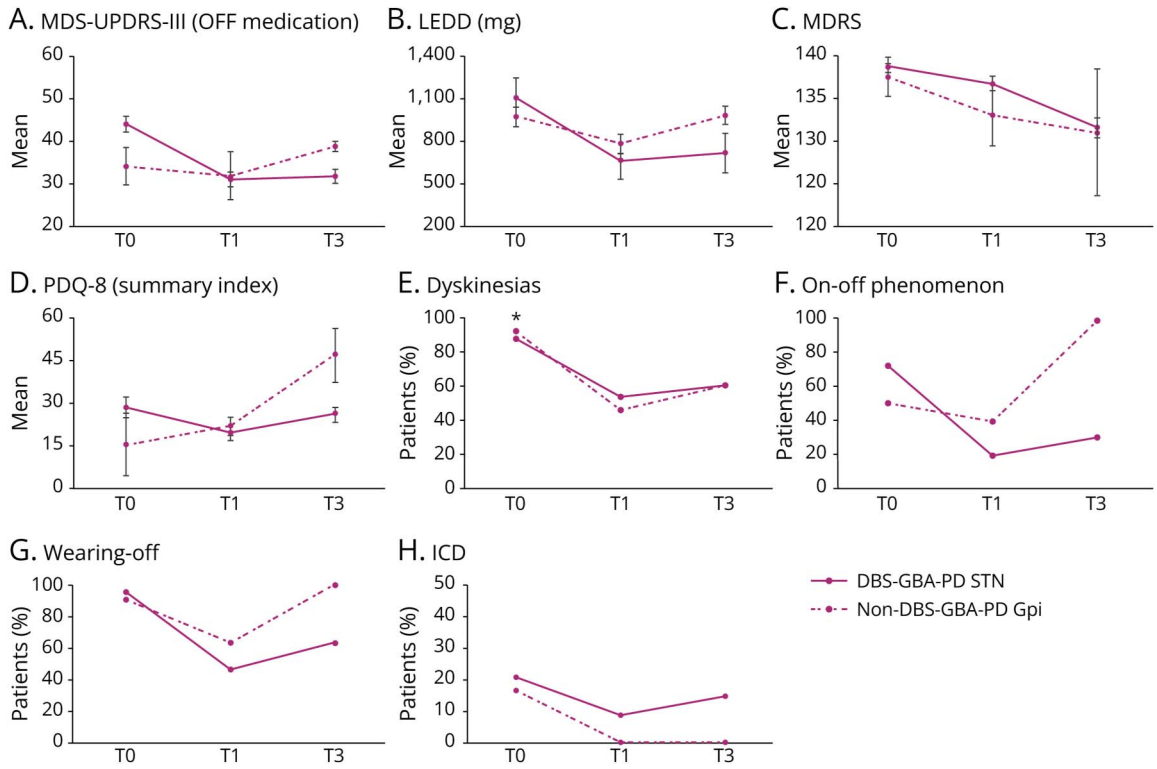
DBS, in sheer contrast with a previous study[10] that reported a significantly worse cognitive performance in DBS-GBA-PD compared with the nonoperated GBA-PD group. This discrepancy can possibly be explained by the different selection criteria adopted to recruit the nonDBS cohort. In the study by Pal et al.,[10] most nonDBS-GBA-PD patients were in a milder stage of disease, and therefore unmatched with the operated cohort, which included patients with more advanced PD.[27] Conversely, all nonoperated GBA-PD participants in our study fulfilled standard eligibility criteria for DBS.[17,18] Despite being considered appropriate candidates for DBS, these participants were not operated, primarily because they preferred to delay surgery or attempt alternative therapeutic strategies. Moreover, their phenotype at baseline was largely similar to that of the 2 operated groups. Indeed, replication of analyses on a strictly matched subgroup of patients confirmed the findings obtained in the whole cohort, demonstrating a more rapid cognitive deterioration in both GBA groups, regardless of DBS.

Although some studies have implied a possible negative effect of STN-DBS on nonmotor symptoms in PD cohorts untested for *GBA1*,[28-31] others have suggested that the development of dementia may relate to the natural progression of the disease rather than the detrimental effects of DBS itself.[32-35] By longitudinally comparing 2 clinically matched cohorts of operated vs nonoperated GBA-PD participants, our data support the latter hypothesis, showing that DBS surgery does not contribute to the accelerated cognitive decline typical of the GBA-PD population.

Besides cognitive impairment, GBA-PD participants also manifested a significantly increased burden of hallucinations compared with nonmutated cases, which was also unrelated to DBS. Our data are consistent with previous findings reporting a higher occurrence of neuropsychiatric symptoms in GBA-PD,[13,19] suggesting that hallucinations may develop concurrently with the deterioration of cognitive functions. This observation corroborates the reported nonmotor clinical similarities of GBA-PD and dementia with Lewy bodies (DLB),[36] and the recent finding in GBA-PD of a significant reduction in resting activity in the posterolateral parieto-occipital cortical regions (a typical pattern of DLB), as well as the presence of a larger proportion of neocortical Lewy body pathology, compared with nonmutated cases.[37,38]

Although several studies suggested that depression is more prevalent in GBA-PD,[3,13,19] the 3 groups did not differ in the

Figure 5 Evolution of Clinical Motor and Nonmotor Parameters of DBS-GBA-PD According to DBS Target



Line plots show the mean ± SE for (A) MDS-UPDRS-OFF med, (B) LEDD, (C) MDRS, and (D) PDQ-8-SI, as well as the percentage of patients with (E) dyskinesias, (F) on-off phenomenon, (G) wearing-off, and (H) ICD, at baseline (T0), T1, and T3. Multiple comparisons were performed using post hoc pairwise tests with Bonferroni correction. Statistically significant p values ($p < 0.05$) are marked with (*). DBS = deep brain stimulation; GBA-PD = PD participants carrying *GBA1* variants; ICD = impulse control disorder; LEDD = Levodopa Equivalent Daily Dose; MDRS = Mattis Dementia Rating Scale; MDS-UPDRS-III = Movement Disorders Society-Unified Parkinson's Disease Rating Scale part III; OFF med = OFF medication; PD = Parkinson disease; PDQ-8-SI = Parkinson's Disease Questionnaire-8 Summary Index; STN = subthalamic nuclei.

prevalence of depressive symptoms at baseline, likely because participants with overt or poorly controlled depressive symptoms were excluded because of the DBS selection criteria. However, it is worth noting that, after 5 years, depression and ICD were significantly more pronounced in the nonDBS-GBA group compared with both operated groups, possibly reflecting the progressive worsening of motor function and the need for LEDD increase in patients who did not benefit from DBS treatment.[39,40]

Another poorly investigated critical issue is the long-term effect of DBS on QoL in GBA-PD. Several studies have shown an improvement of QoL soon after STN-DBS[41-43] and up to 5-year follow-up.[44] Only 1 former study evaluated QoL in a small cohort of DBS-GBA-PD patients, reporting worse scores compared with nonmutated participants.[26] Here, we observed that, at 5 years from surgery (~15 years from PD onset), QoL worsened significantly from baseline in nonoperated GBA-PD individuals, while it remained stable or even improved in the operated groups, regardless of the *GBA1* genotype. One possible explanation for the progressive worsening observed in the nonDBS-GBA-PD group is that unlike operated participants, their LEDD gradually increased, affecting the occurrence of dyskinesias and neuropsychiatric symptoms. However, further studies correlating QoL index with clinical features over time are needed to better address this important issue. Moreover, long-term motor complications (recurrent falls and inability to walk) were limited and comparable between DBS groups, likely contributing to the better QoL reported by these participants, while they worsened from baseline in the nonoperated group. Finally, we explored whether any demographic or baseline features could predict the risk of cognitive deterioration and worse QoL over time in GBA-PD. In line with our previous work,[11] an older age at PD onset seemed to be associated with dementia and a poorer QoL in both operated and nonoperated groups. Of interest, we found that lower QoL at follow-up was also predicted by male sex, a higher prevalence of the "on-off" phenomena, and the absence of DBS.

These evidence emphasize the relevance of long-term effects of DBS on GBA-PD patients. Thus, DBS should be considered as a viable therapeutic option also in this genetic group of patients, especially in those with an early disease onset who could benefit from the procedure for a longer period.

A secondary objective of this study was to disclose potential differences of long-term DBS outcome in carriers of distinct *GBA1* variant classes. Both operated and nonoperated GBA-PD participants carrying variants in different classes overall exhibited a similar clinical profile, characterized by a prolonged motor benefit after surgery, and a parallel deterioration of cognitive functions and other nonmotor symptoms. These observations suggest that the current classification of *GBA1* variant classes, "borrowed" from Gaucher disease,[20] may not be appropriate to define the pathogenic effect and prognostic implication of *GBA1* variants in the context of PD, and a novel, PD-specific classification is warranted.

Finally, our exploratory analysis comparing the long-term outcome of STN vs GPi targets in GBA-PD showed similar clinical trajectories in motor, cognitive, and other nonmotor symptoms up to 3-year postsurgery. STN was suggested to worsen cognitive deterioration and neuropsychiatric symptoms in general PD population compared with GPi[31,45]; however, a meta-analysis[46] and a more recent study[47] failed to detect significant differences between targets. Replication studies on larger GBA-PD cohorts comparing DBS targets are needed to confirm our observations.

We acknowledge some limitations in our study. First, the 3 groups were not perfectly matched at baseline because nonDBS-GBA-PD had slightly shorter disease duration, lower LEDD, and reduced freezing of gait compared with operated groups. However, we minimized this limitation by repeating longitudinal analyses across smaller subgroups selected through a 1:1 pair matching based on disease duration, obtaining similar results. Second, the sample size was still relatively small when stratifying GBA-PD according to different variant classes or to different DBS targets, particularly at long-term follow-up, hampering the detection of potential subtle differences across subgroups. A third limitation resides in the retrospective nature of the study. Cognitive decline was assessed based on a single cognitive scale, unable to assess subtle differences of selective cognitive domains; similarly, some clinical features such as symptomatic orthostatic hypotension and urinary incontinence were mainly recorded anamnestically, possibly leading to an overestimation or underestimation of their frequencies.[48]

In conclusion, we report the first systematic assessment of DBS long-term effects on GBA-PD, comparing DBS-treated participants with a comparable cohort who did not undergo surgery. We confirm a sustained benefit of DBS on motor features, with a general improvement of QoL. It is important that the accelerated cognitive decline of GBA-PD compared with nonmutated participants was fully comparable in the operated and non-operated groups regardless of surgery, *GBA1* variants class, and DBS target. Overall, these results indicate that DBS should be considered as a valid and safe therapeutic option for GBA-PD.

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