




RESEARCH ARTICLE

NIH Toolbox performance of persons with Parkinson's disease according to *GBA1* and STN-DBS status

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Introduction

Deep brain stimulation (DBS) is a well-established treatment for persons with Parkinson's disease (PwP). Studies have suggested that genetic subtyping of PwP may be

Abstract

Objective: Mutations in the *glucocerebrosidase* (*GBA1*) gene and subthalamic nucleus deep brain stimulation (STN-DBS) are independently associated with cognitive dysfunction in persons with Parkinson's disease (PwP). We hypothesized that PwP with both *GBA1* mutations and STN-DBS are at greater risk of cognitive dysfunction than PwP with only *GBA1* mutations or STN-DBS, or neither. In this study, we determined the pattern of cognitive dysfunction in PwP based on *GBA1* mutation status and STN-DBS treatment. **Methods:** PwP who are *GBA1* mutation carriers with or without DBS (*GBA1*+DBS+, *GBA1*+DBS−), and noncarriers with or without DBS (*GBA1*−DBS+, *GBA1*−DBS−) were included. Using the NIH Toolbox, cross-sectional differences in response inhibition, processing speed, and episodic memory were compared using analysis of variance with adjustment for relevant covariates. **Results:** Data were available for 9 *GBA1*+DBS+, 14 *GBA1*+DBS−, 17 *GBA1*−DBS+, and 26 *GBA1*−DBS− PwP. In this cross-sectional study, after adjusting for covariates, we found that performance on the Flanker test (measure of response inhibition) was lower in *GBA1*+DBS+ PwP compared with *GBA1*−DBS+ PwP ($P = 0.030$). **Interpretation:** PwP who carry *GBA1* mutations and have STN-DBS have greater impaired response inhibition compared with PwP with STN-DBS but without *GBA1* mutations. Longitudinal data, including preoperative scores, are required to definitively determine whether *GBA1* mutation carriers respond differently to STN-DBS, particularly in the domain of response inhibition.

useful in understanding differential cognitive and motor outcomes of DBS.¹ In a nonrandomized study, we previously demonstrated that PwP with mutations in the *glucocerebrosidase* (*GBA1*) gene may be particularly susceptible to global cognitive deficit after subthalamic nucleus DBS

(STN-DBS).² PwP with *GBA1* mutations have reduced activity of the *glucocerebrosidase* (GCase) enzyme resulting in impaired sphingolipid metabolism³ with more rapid accumulation and spread of Lewy body pathology compared with non-*GBA1* PwP.⁴ Clinically, *GBA1* PwP are at increased risk for cognitive impairment and progress to dementia faster compared with non-*GBA1* patients.^{4–8} Importantly, STN-DBS itself can impair cognition, with a negative impact on verbal fluency,⁹ executive control of action,¹⁰ and inhibitory control.¹¹ This may be due to a micro-lesional effect^{12,13} and/or unintended current spread into adjacent associative and limbic subregions¹⁴ or other nearby nuclei such as the substantia nigra.¹⁵ Given that *GBA1* mutations and STN-DBS are independently associated with cognitive dysfunction in PwP, we hypothesized that PwP with both *GBA1* mutations and STN-DBS are at greater risk of cognitive dysfunction than PwP with only *GBA1* mutations or STN-DBS, or neither. The specific cognitive domains associated with cognitive dysfunction in PwP based on *GBA1* and DBS status, alone or in combination, remain unknown.

In this cross-sectional study, we used the NIH Toolbox to compare response inhibition (Flanker Inhibitory Control and Attention Test), processing speed (Pattern Comparison Processing Speed Test), and episodic memory (Picture Sequence Memory Test) in PwP who are *GBA1* carriers with or without STN-DBS (*GBA1*+DBS+, *GBA1*+DBS–), and noncarriers with or without STN-DBS (*GBA1*–DBS+, *GBA1*–DBS–). These tests were selected since response inhibition^{16,17} and processing speed¹⁸ may be impaired by STN-DBS (regardless of genetic status), and the combined effects of *GBA1* mutations and STN-DBS on these cognitive domains in PwP are unknown. The episodic memory task involves a visual memory component, and PwP with *GBA1* mutations are more likely to have visual memory dysfunction compared with nonmutation carriers.^{5,8} Given our prior findings that *GBA1*+DBS+ PwP are at greatest risk of global cognitive dysfunction compared with PwP without *GBA1* mutations and/or those without DBS,² we hypothesized that *GBA1*+DBS+ PwP would be the most impaired group in one or more of the above cognitive domains.

Methods

This prospective cross-sectional study was approved by the Institutional Review Board (IRB) at Rush University Medical Center and at Rutgers–Robert Wood Johnson Medical School, and informed consent was obtained from each participant. PwP were recruited based on convenience sampling from the Rush Movement Disorders clinic between July 2016 and March 2019 and at Rutgers University between July 2020 and March 2023. Furthermore, PwP with

known *GBA1* mutations were invited to participate. PwP were recruited if they carried a clinical diagnosis of PD by United Kingdom Parkinson Disease Society Brain Bank criteria,¹⁹ and STN-DBS PwP met standard criteria for implantation.²⁰ PwP with unknown *GBA1* status were fully sequenced for *GBA1* as previously described.²¹

Demographics and clinical data were collected in all PwP including baseline age, age at disease onset, sex, years since DBS procedure, most recent Unified Parkinson's Disease Rating Scale (UPDRS) Part-III or International Parkinson and Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS Part-III) scores, and levodopa equivalent daily dose (LEDD).²² UPDRS scores were converted to MDS-UPDRS scores where necessary.²³ A cross-sectional evaluation of cognition was performed using the NIH Toolbox. PwP completed three measures within the NIH Toolbox Cognitive Battery: (1) Flanker Inhibitory Control and Attention Test, to test response inhibition, (2) Pattern Comparison Processing Speed Test, to test processing speed, and (3) the Picture Sequence Memory Test, to test episodic memory.²⁴ DBS PwP were at least 1 year post implantation and in their optimally programmed state. All DBS PwP completed the evaluation in the ON medication/ON stimulation state, except for 1 *GBA1*+DBS PwP who completed the evaluation in the OFF medication/ON stimulation state (skipped Carbidopa/Levodopa 12.5/50 mg). Non-DBS PwP were tested in the ON medication state. Details regarding the test administration protocol have been previously described.²⁵

For each cognitive test, a fully adjusted *T*-score was calculated. This score compares the score of the test-taker to those in the NIH Toolbox nationally representative normative sample, while adjusting for key demographic variables collected during the Toolbox national norming study.²⁶ These variables include age, gender, 3 races (white, black, other), ethnicity (Hispanic vs. non-Hispanic), and educational attainment. The *T*-score is devised such that the mean is 50 and standard deviation is 10.²⁶

Age, age of onset, disease duration, and MDS-UPDRS were compared using one-way analysis of variance (ANOVA). For these variables, given the unequal sample sizes among groups, we performed Levene's test for homogeneity of variances, which was not significant ($P > 0.05$). However, Levene's test was significant ($P < 0.05$) when comparing years of DBS and LEDD, so Kruskal–Wallis test was performed. Sex was compared using the chi-squared test. *GBA1* mutations were subcategorized according to severity: risk variant, mild, or severe.²⁷ The number of *GBA1* PwP with risk variant, mild, and severe mutations was compared between the DBS and non-DBS groups using the chi-squared test.

For our cognitive tests (dependent variables), given the unequal sample sizes among groups, we performed

Table 1. Demographics and clinical characteristics according to GBA and DBS status

	GBA1+DBS+	GBA1+DBS−	GBA1−DBS+	GBA1−DBS−
<i>n</i>	9	14	17	26
Demographics				
Age baseline	60.4 (7.50)	58.8 (7.6)	59.5 (16.8)	59.8 (6.2)
Age onset	48.3 (10.40)	43.4 (12.6)	49.4 (11.7)	47.5 (7.5)
Disease duration, years	12.1 (7.8)	15.4 (12.0)	10.1 (13.8)	12.3 (7.0)
Sex M/F	5/4	8/6	12/5	16/10
Years of DBS	2.0 (1.7)	0.0 (0.0)	1.9 (1.3)	0.0 (0.0)
MDS-UPDRS-III	28.9 (11.1) (<i>n</i> = 8)	24.6 (11.8)	27.7 (8.8)	27.2 (9.5)
LEDD	440.4 (301.2)	912.8 (650.3)	385.9 (265.9)	953.3 (693.6)
GBA1 mutation (<i>n</i>)	E326K (2), T369M (1), N370S (2), L279P (1), L444P (2), P134T (1)	E326K (3), T369M (1), G364R (1), G202R (1), D140H (1), H255Q (1), R159W (1), N370S (3), L444P (2)		
GBA1 mutation severity				
Risk variant (%)	3 (33.3)	4 (28.6)		
Mild (%)	2 (22.2)	4 (28.6)		
Severe (%)	4 (44.4)	6 (42.8)		

Levene's test for homogeneity of variances, which was significant ($P < 0.05$) for the Flanker test and the Pattern Comparison Processing Speed Test, but not the Picture Sequence Memory Test ($P > 0.05$). To account for this, a weighted least squares (WLS) adjustment was performed for Flanker scores and Pattern Comparison Processing Speed scores. Cognitive scores were compared using ANOVA with post hoc Bonferroni adjustment for pairwise comparisons ($P < 0.05$). Additional analysis was performed using analysis of covariance adjusting for disease duration, MDS-UPDRS Part III, and LEDD, using Bonferroni adjustment for pairwise comparisons ($P < 0.05$). Sex and age were already accounted for in the fully adjusted *T* score as described above.

Results

Baseline characteristics

A total of 66 PwP (9 GBA1+DBS+, 14 GBA1+DBS−, 17 GBA1−DBS+, and 26 GBA1−DBS−) were enrolled. Mean age, age of onset, sex, and MDS-UPDRS Part III scores were not significantly different among the 4 groups (Table 1). MDS-UPDRS Part III scores were consistent with historic values for PwP.²⁸ LEDD scores were > 50% lower in PwP with DBS compared to those without DBS, which can be considered a surrogate measure of effective STN-DBS response.² When examining GBA1 PwP, the number of PwP with risk variant, mild, or severe mutations was not significantly different between the DBS and non-DBS groups ($P = 0.9$). All GBA1 PwP were heterozygous mutation carriers, and thus, no PwP had Gaucher's disease (GD). Pattern Comparison Processing Speed scores were missing for 1 GBA1+DBS+ PwP. Picture

Sequence Memory test scores were missing for 2 GBA1+DBS+, 1 GBA1−DBS+, and 1 GBA1−DBS− PwP.

Comparison of NIH toolbox cognitive measures according to GBA1 and DBS status

Using ANOVA, Flanker scores were significantly different between GBA1+DBS+ vs. GBA1−DBS− PwP ($P = 0.041$) and GBA1+DBS+ vs. GBA1−DBS+ groups ($P = 0.010$) (Tables 2 and 3, Fig. 1). Of note, when excluding the GBA1+DBS+ PwP who performed the Flanker test in OFF medication/ON stimulation state, significance was retained when comparing the GBA1+DBS+ vs. GBA1−DBS+ groups only ($P = 0.019$).

After adjusting for covariates including disease duration, MDS-UPDRS Part III, and LEDD, differences

Table 2. Performance on NIH toolbox measures according to GBA1 and DBS status

	GBA1+DBS+	GBA1+DBS−	GBA1−DBS+	GBA1−DBS−
<i>N</i>	9	14	17	26
Flanker score (SE)	29.88 (3.52)	37.14 (1.56)	46.30 (3.56)	40.35 (1.28)
PCPS score (SE)	44.55 (10.84)	44.36 (3.96)	37.39 (3.07)	41.89 (2.59)
PSMT Score (SE)	44.04 (4.79)	47.29 (3.39)	47.73 (3.07)	49.84 (2.53)
	(<i>n</i> = 8)			(<i>n</i> = 25)

PCPS, pattern comparison processing speed; PSMT, picture sequence memory test; WLS, weighted least square.

Table 3. Pairwise comparisons without adjustment for covariates

Measure	Overall	<i>GBA1</i> +DBS+ vs.	<i>GBA1</i> +DBS+ vs.	<i>GBA1</i> +DBS+ vs.	<i>GBA1</i> +DBS- vs.	<i>GBA1</i> -DBS+ vs.	<i>GBA1</i> +DBS- vs.
		<i>GBA1</i> -DBS+	<i>GBA1</i> -DBS-	<i>GBA1</i> +DBS-	<i>GBA1</i> -DBS-	<i>GBA1</i> -DBS-	<i>GBA1</i> -DBS+
Flanker score	0.007	0.010	0.041	0.382	0.711	0.722	0.129
PCPS score	0.513	1.000	1.000	1.000	1.000	1.000	1.000
PSMT score	0.739	1.000	1.000	1.000	1.000	1.000	1.000

Above *P* values are reflective of Bonferroni adjustment for pairwise comparisons. Of note, the comparison between PD patients in the *GBA1*+DBS+ vs. *GBA1*-DBS+ groups remained statistically significant (*P* = 0.030) after adjustment for covariates. PCPS, pattern comparison processing speed; PSMT, picture sequence memory test.

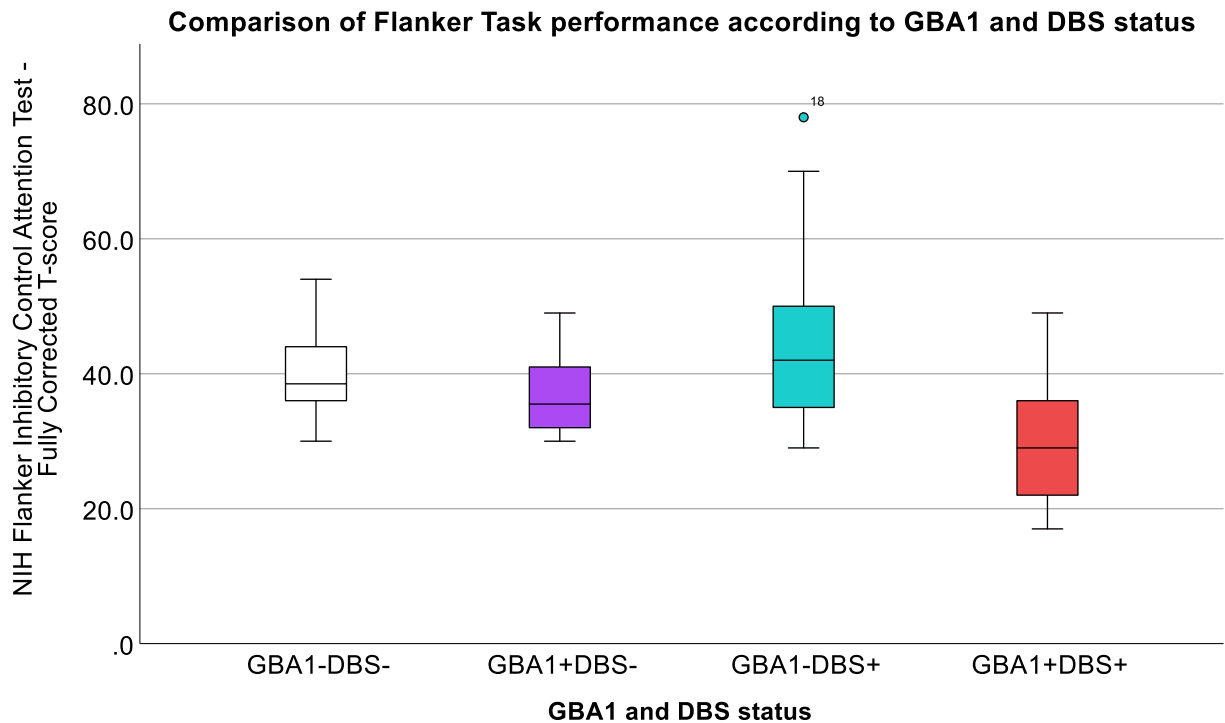


Figure 1. Comparison of Flanker Task performance according to *GBA1* and DBS status. In persons with Parkinson's disease (PwP), Flanker scores were significantly different between *GBA1*+DBS+ (red) vs. *GBA1*-DBS- (white) groups (*P* = 0.041). Flanker scores were also significantly different between *GBA1*+DBS+ (red) vs. *GBA1*-DBS+ (teal) groups (*P* = 0.010). After adjustment for covariates, group differences in Flanker scores remained significant when comparing *GBA1*+DBS+ vs. *GBA1*-DBS+ PwP only (*P* = 0.030).

between group Flanker scores remained significant when comparing *GBA1*+DBS+ vs. *GBA1*-DBS+ PwP only (*P* = 0.030). Flanker scores and Picture Sequence Memory Test scores were lower in *GBA1*+DBS+ PwP compared with *GBA1*+DBS- PwP (Table 2), but these differences were not statistically significant. Overall, group comparisons of Pattern Comparison Processing Speed and Picture Sequence Memory test scores were not statistically different among the four groups (Table 3).

Discussion

In this study, we aimed to define the pattern of cognitive dysfunction in PwP based on *GBA1* and STN-DBS status. Pal et al² and Mangone et al²⁹ have previously demonstrated that *GBA1* PwP with STN-DBS are at risk of cognitive decline when examining global cognitive function. In this cross-sectional study, we found that *GBA1* PwP with STN-DBS may be more prone to impaired response

inhibition compared with PwP with STN-DBS but without *GBA1* mutations.

Several studies have identified the STN as playing an important role in response inhibition, a process involved in inhibiting choices and actions especially in the face of competing alternatives.³⁰ STN-DBS results in more impulsive decision making in high conflict tasks (such as Flanker or Stroop tasks). STN-DBS PwP may have a faster reaction time potentially leading to more errors.³⁰ Several brain regions have been implicated in this process³¹ including the inferior frontal cortex (IFC)³² and structures within the medial prefrontal cortex (mPFC), such as the anterior cingulate cortex (ACC) and the presupplementary motor area (pre-SMA).³³ *GBA1* mutations cause a deficiency in glucocerebrosidase (GCase) enzyme activity, and both the ACC and frontal cortex, regions involved in response inhibition, may have reduced GCase activity in *GBA1* carriers.^{34,35} Consequently, it is conceivable that *GBA1* carriers are at higher risk of worsening impulse control after STN-DBS than PwP without *GBA1* mutations. Anatomic and tractography studies would be useful in further exploring these associations but these data were not available in this study. However, as DBS manufacturers increasingly incorporate imaging with DBS programming,³⁶ these associations may be examined with greater ease in future studies.

Strengths of our study include use of validated measures from the NIH Toolbox cognition battery, comparison of several cognitive domains among the groups of interest, and comparable numbers of *GBA1* PwP with risk variant, mild, and severe mutations when comparing DBS and non-DBS groups. Limitations of this study include small sample size, cross-sectional evaluation, and some missing data. Flanker and Picture Sequence Memory Test scores were lower in *GBA1*+DBS+ PwP vs. *GBA1*+DBS−PwP, but did not achieve statistical significance, likely due to insufficient power. Also, we did not have preoperative cognitive scores, so we are not able to definitively determine whether the between group differences are related to DBS or are simply a reflection of baseline differences according to mutation status.

In conclusion, PwP who carry *GBA1* mutations and have STN-DBS have greater impaired response inhibition compared with PwP with STN-DBS but without *GBA1* mutations. The pattern of cognitive dysfunction according to *GBA1* status, mutation severity, and DBS implantation warrants further examination in a larger cohort of PwP.

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Author Contributions

Gian Pal (GP) was responsible for the research project conception, organization, execution, statistical analysis, editing, and critique. Ahmad Almelegy (AA) was responsible for data collection, writing of the first draft of the manuscript, and editing and critique of the manuscript. Srujanesh Gunda (SG) was involved in study design, data organization, and the editing of the manuscript. Steven Buyske (SB) was involved in study design, data analysis, and the editing of the manuscript. Marc Rosenbaum (MR), Sepehr Sani (SS), Mitra Afshari (MA), and Leo Verhagen Metman (LVM) were involved in study design, data collection, and the editing of the manuscript. Christopher G. Goetz (CGG), Deborah Hall (DH), and M. Maral Mouradian (MMM) were responsible for the study design and the editing of the manuscript.

Conflict of Interest

None.

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