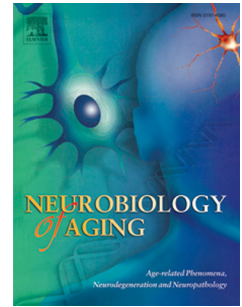# Accepted Manuscript

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Please cite this article as: Moran, E.E., Wang, C., Katz, M., Ozelius, L., Schwartz, A., Pavlovic, J., Ortega, R.A, Lipton, R.B., Zimmerman, M.E, Saunders-Pullman, R., Cognitive and Motor Functioning in Elderly Glucocerebrosidase (GBA) Mutation Carriers, *Neurobiology of Aging* (2017), doi: 10.1016/ j.neurobiolaging.2017.06.010.

Cognitive and Motor Functioning in Elderly Glucocerebrosidase (GBA) Mutation Carriers

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Abstract

Mutations in the glucocerebrosidase (*GBA*) gene are a strong genetic risk factor for the development of Parkinson's disease and dementia with Lewy Bodies. However the penetrance of *GBA* mutations is low for these diseases in heterozygous carriers. The aim of this study was to examine the relationship between mutation status and cognitive and motor functioning in a sample of community dwelling older adults. Using linear mixed effects models, we examined the effect of heterozygous mutation status on 736 community dwelling older adults ($\geq$70 years) without dementia or Parkinson's disease assessed over an average of 6 years, 28 of whom had a single *GBA* mutation (primarily N370S). Verbal memory was measured using the picture version of the Free and Cued Selective Reminding Test, and carriers showed significantly ($p<0.05$) greater decline in verbal memory over time. There was no difference in motor function or any other cognitive domain. Taken together, these results suggest an effect, but an overall limited burden, of harboring a single *GBA* mutation in aging mutation carriers.

Keywords: glucocerebrosidase, GBA, dementia, aging, Parkinson's, memory

1. Introduction

Biallelic mutations in the glucocerebrosidase gene (*GBA*) cause Gaucher Disease (GD), a multisystem disorder associated with hepatosplenomegaly, hematologic and bone changes (Pastores and Hughes, 1993). While carrying a single gene mutation historically was considered clinically insignificant, in the last decade, heterozygous mutations in the *GBA* gene have been established as the most frequent genetic contributors to the development of Parkinson's Disease (PD) and dementia with Lewy Bodies (DLB) (Lesage et al., 2011, Neumann et al., 2009, Sidransky et al., 2009). These two disorders of synuclein accumulation form the core of a spectrum that includes parkinsonism and dementia (Wales et al., 2013). Worldwide, 2.9 to 8% of cases of PD are associated with *GBA* mutations (Clark et al., 2007, Mata et al., 2008, Sidranskyet al., 2009) and *GBA* mutations are associated with an eight-fold increase in the risk for developing DLB (Clark et al., 2009, Nalls et al., 2013).

The full burden of harboring a single mutation, particularly on an aging brain, is not clear. The clinical manifestation of both PD and DLB is age-related, with prevalence of PD increasing from 1% of the population overall to 2% in the population age 80 and older (Pringsheim et al., 2014). It is estimated that the penetrance of a *GBA* mutation for PD by the age of 75 remains low, and this varies by the mutation. The risk of PD for heterozygous mutation carriers ranges from 2.2 to 5% by age 65 to 10.9 to 15% by age 85 (McNeill et al., 2012a, Rana et al., 2013). *GBA* related PD (GBA-PD) is overall associated with more prominent cognitive decline than idiopathic PD (Alcalay et al., 2012, Brockmann et al., 2011, Saunders-Pullman et al., 2010, Schapira, 2015, Sidranskyet al., 2009, Winder-Rhodes et al., 2013), including an increased risk for both mild cognitive impairment (Alcalayet al., 2012) and dementia (Brockmannet al., 2011, Crosiers et al., 2016, Mata et al., 2016, Seto-Salvia et al., 2012). This

includes worse performance on broad screening measures of cognitive functioning (e.g. the Montreal Cognitive Assessment, MoCA) (Brockmannet al., 2011), and more specifically, deficits in visual short-term memory (Zokaei et al., 2014), memory and visuospatial functioning (Alcalayet al., 2012, Mataet al., 2016), and executive functioning and working memory (Mataet al., 2016). Additionally, GBA-PD is related to neuropsychiatric symptoms such as depression and anxiety (Brockmannet al., 2011), and those with GBA-PD are more likely to have hallucinations and sustained cholinesterase inhibitor use (Barrett et al., 2014).

Studies in both homozygous and heterozygous *GBA* mutation carriers without clinical evidence of PD have demonstrated PD motor and cognitive changes (Beavan et al., 2015, Gatto et al., 2016, Goker-Alpan et al., 2004, McNeill et al., 2012b). However, much of what is currently known about the cognitive and motor profile of non-manifesting carriers has been evaluated in younger groups, and some studies used only broad screening measures for cognitive function. Because of the prominent cognitive burden in PD, as well as a posited prodromal period of Lewy body deposition prior to the development of motoric PD (Braak et al., 2003), the question arises as to whether heterozygous mutation carriers might demonstrate cognitive or motor changes in the absence of frank parkinsonism or dementia.   This is particularly relevant as potential disease modifying therapies for *GBA* related neurological diseases are on the horizon (Sardi et al., 2013).

Similar to AD, if there is a "pre-clinical window" that defines those early in the trajectory to PD or DLB, this group may, in theory, be more amenable to therapeutic intervention (Jack et al., 2010, Sperling et al., 2011b). The aim of this study was to investigate the cognitive and motor trajectories of older adult heterozygous non-manifesting *GBA* mutation carriers. In particular, we wished to focus on the burden of carrying a single mutation among a community

dwelling older adult sample using a comprehensive neuropsychological evaluation and motor assessment to determine if mutation status is related to cognitive and motor decline. As assessment tools sensitive to pre-clinical cognitive changes have demonstrated changes in verbal memory (Lemos et al., 2015a, Lemos et al., 2015b), we hypothesized that the effect of *GBA* status would be greatest on verbal memory decline.

2. Material and Methods

2.1 Participants

Participants were drawn from the Einstein Aging Study (EAS), a longitudinal prospective study that aims to identify risk factors for cognitive decline and dementia. The EAS study began in 1993 and follows an ethnically diverse, community dwelling sample of older adults who reside in Bronx County, New York. Systematic sampling procedures are used to recruit participants from Medicare enrollee lists and Bronx County voter registration lists. Participants were at least 70 years of age, community dwelling, ambulatory, English speaking, and provided informed consent at each annual visit to the clinic. Neuropsychological, psychosocial, and medical evaluations were completed annually. EAS recruitment and study procedures are described in more detail elsewhere (Katz et al., 2012). Subjects who meet DSM-IV criteria for dementia at baseline were excluded. A total of 736 participants who were enrolled in the EAS between 1993 and January 2016 and had consented to genotyping and had valid genotyping data were included in the following analyses.

2.2 Genotyping

The focus of this study was on the most common *GBA* mutations: N370S and L444P. In addition, we evaluated IVS2+1G>A, and V394L. The apolioprotein E4 (ApoE4) was also

genotyped as it has known associations with cognitive decline (Harold et al., 2009, Lambert et al., 2009, Verghese et al., 2013). For those participants who provided consent for genotyping, DNA was extracted from peripheral blood or saliva by standard techniques, and screened for SNPs corresponding to IVS2+1G>A, N370S, L444P, and V394L.

PCR and extension primers were designed from sequences containing each target SNP with 100 upstream and downstream bases using Assay Design Suite (a design tool hosted at www.mysequenom.com). Single base extension reactions were performed on the PCR reactions with the iPlex Gold Kit (Sequenom, San Diego, CA) A Sequenom Compact Mass Array Spectrometer was used to perform MALDI-TOF (matrix assisted laser desorption ionization time of flight) mass spectrometry according to the iPlex Gold Application Guide (Sequenom Document #11555, July 22, 2009 version.) The software package Typer 4 (Sequenom) was used to analyze the resulting spectra and the genotype of each SNP/sample was determined from the measured mass of each extended oligo.

2.3 Primary Outcome Measures

2.3.1 Neuropsychological Assessment – Verbal Memory

Trained research assistants administered an extensive neuropsychological battery annually. This battery has been described in detail elsewhere (Katzet al., 2012). Diagnosis of dementia was based on criteria provided by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) and participants were evaluated annually at a diagnostic case conference attended by a neurologist and a neuropsychologist. If an individual developed dementia during the course of the study, the last visit without dementia was designated the final study visit.

The picture version of the Free and Cued Selective Reminding Test (FCSRT) was administered as a part of this battery. This task was selected for this study as a measure of verbal cued learning and memory as it has been shown to be a sensitive to preclinical dementia as well as a strong predictor of the development of dementia in older adults (Grober and Kawas, 1997, Grober et al., 2000). The primary variable of interest is the free recall score.

2.3.2 Motor Assessment

Annual neurological examinations conducted by physicians as part of the standard EAS clinical battery included the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Fahn and Elton, 1987). Based on history and examination, physicians rated presence of PD (none, possible, probable, or definite). Only individuals who were rated as not having PD were included in the study. If an individual developed PD during the course of the study, the last visit without PD was designated the final study visit.

2.4 Covariates

ApoE4 status and cardiovascular risk were measured and included as covariates due to their known impact on cognitive functioning in aging (Haan and Mayeda, 2010, Haroldet al., 2009, Lambertet al., 2009, Vergheseet al., 2013). Cardiovascular risk was assessed through combined history of hypertension, myocardial infarction, and stroke to measure a cardiovascular comorbidity index.

2.5 Secondary Outcome Measures

Visuospatial construction and nonverbal memory were assessed using the Repeatable Battery of Neuropsychological Status (RBANS) complex figure (Randolph et al., 1998).

Attention was assessed using Trail Making Test part A (TMTA) (Battery, 1944, Misdraji and Gass, 2010). To reduce skewness in TMTA time, the inverse transformation was used, which can be interpreted as speed in TMTA. Executive Functioning was assessed using Trail Making Test part B (TMTB) (Battery, 1944, Misdraji and Gass, 2010). Similar to TMTA, the inverse transformation was used for TMTB. The fifteen item Geriatric Depression Scale (GDS) was used to screen for depression (Yesavage et al., 1982), with a score of 6 or greater indicating clinical depression.

2.6 Statistical Analyses

All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, N.C.) and SPSS 20 (SPSS INC., Chicago, IL.) The sample, demographic and other baseline characteristics were assessed using summary statistics. Linear mixed effects models with random intercepts and random slopes were used to examine the effect of mutation status on cognitive and motor functioning over time. All analyses were adjusted for age, sex, education, and ethnicity.

Additional linear mixed effects models with random intercepts and random slopes were assessed to examine the effect of mutation status on cognitive functioning over time further adjusting for ApoE4 mutation status and cardiovascular risk.

As there are founder mutations for *GBA* among Ashkenazi Jews, sensitivity analyses including only those participants who self-identified with Jewish ancestry were performed.

3. Results

From a total of 736 individuals included in this study, 28 (3.8%) carried a *GBA* mutation. Of the 28 *GBA* carriers, 26 (92.9%) carried the N370S mutation, one carried the IVS2+1G>A mutation, and one carried the L444P mutation. Table 1 summarizes the demographic

characteristics of the sample. Groups did not differ by age or gender. Because there are founder mutations in *GBA* in Ashkenazi Jews, we examined the proportion of carriers self-identifying with Jewish heritage, and, as expected, a significantly greater proportion of carriers identified Jewish ancestry than non-carriers (75.0% vs. 27.7%, *p*<0.001). There were significantly more follow up visits for non-carriers than carriers (mean 6.13 vs. 3.72, *p*<0.001). 28.6% of carriers met criteria for dementia or PD, whereas 16.7% of controls met criteria for dementia or PD at their last follow up visit and therefore were not included forward. Overall prevalence of clinically significant depression (GDS score of 6 or greater) was 7.5%, and groups did not differ by rate of depression (7.5% of carriers vs. 7.7% of controls).

3.1 Primary Outcome Measures

Results of the linear mixed effects models with random intercept and random slope used to examine the association between *GBA* mutation status and rate of decline in FCSRT free recall and UPDRS-III, adjusting for baseline age, gender, race, and education are presented in Table 2. For free recall, at baseline, male participants (*p*<0.001), being older (*p*<0.001), and being black (*p*<0.001) were associated with worse performance. There is no significant difference in free recall performance between *GBA* mutation carriers and non-carriers at baseline. However, the rate of decline in free recall among mutation carriers was significantly faster than that among non-carriers (difference in slope = 0.42 points per year, SE= 0.20, *p*=0.03). Older baseline age and being female were also associated with faster decline in free recall. Among male participants with average age at baseline, the expected rate of decline was 0.235 points per year among *GBA* mutation non-carriers (SE=0.066, *p*=0.0004) and 0.653 points per year among *GBA* mutation carriers (SE=0.199, *p*=0.001). An additional linear mixed effects model for free recall further adjusting for ApoE4 and cardiovascular risk is assessed and presented in table 3. When

adjusting for ApoE4, the rate of decline in free recall among mutation carriers remained significantly faster than non-carriers (difference in slope = 0.50 points per year, SE = 0.20, p = 0.011). The fact that further adjusting for ApoE4 and cardiovascular risk does not change the conclusion of the effect of GBA mutation on decline in verbal memory is not surprising given that GBA mutation status is not significantly associated with ApoE4 (p = 0.838) or cardiovascular risk (p =0.314).

No significant difference was found between carriers and controls on motor scores, as measured by the UPDRS-III.

3.2 Secondary Outcome Measures

No significant difference was found between carriers and non-carriers on baseline or the rate of decline in TMTA, TMTB, RBANS copy, RBANS recall, or GDS (Supplementary Table 1).

4. Discussion

We report greater longitudinal decline in verbal memory function, as measured by the Free and Cued Selective Reminding Test, in *GBA* mutation positive older adults compared to mutation negative peers. Our study is unique in that it evaluated a multiyear longitudinal community dwelling cohort of elderly in which genetic status was determined posthoc in the sample. The significantly greater decline in verbal memory among the mutation carriers supports the hypothesis that presentation of a mutation may represent a pathological burden even among non-manifesting heterozygous carriers. However, caution is warranted in interpreting this finding as no difference between carriers and controls were found in other cognitive domains, motor functioning, or depression.

Additionally, we found that carriers remained in the study for significantly fewer years than controls, with earlier study dropout or ineligibility. In light of the relationship between mutation status and decline in verbal memory, these findings may indicate the presence of a subclinical disease burden among *GBA* carriers. As decline in verbal memory is a robust early predictor of development of MCI and dementia (Almkvist et al., 1998, Blacker et al., 2007, Guarch et al., 2008, Rabin et al., 2009), the greater decline demonstrated in this group may indicate subclinical pathology. However, as no difference was found in any other cognitive domain assessed, the overall functioning of this older cohort indicates such pathology may remain mild into older adulthood.

Greater verbal memory decline on the FCSRT, which has been shown to be sensitive to preclinical dementia (Grober and Kawas, 1997, Groberet al., 2000) and mild cognitive impairment (Lemoset al., 2015a, Lemoset al., 2015b) may be indicative of the same processes that impact cognition in GBA-PD. The FCSRT was our primary cognitive outcome measure as it has robust psychometric properties and is sensitive to early cognitive changes associated with preclinical dementia. Mild cognitive impairment is commonly seen in PD, with approximately 20-50% of individuals meeting criteria for PD-MCI (Goldman and Litvan, 2011, Litvan et al., 2011), and such cognitive changes may precede motor symptoms. More prominent cognitive impairment has been demonstrated in those with GBA-PD compared to idiopathic PD (Alcalayet al., 2012, Brockmannet al., 2011, Saunders-Pullmanet al., 2010, Zokaeiet al., 2014). Our finding of verbal memory changes is consistent with prior studies including those showing greater decline in global cognition as well as increased parkinsonian features (Beavanet al., 2015) in non-manifesting *GBA* carriers, and worse performance of *GBA* carriers on an experimental task of visual short-term memory relative to controls (Zokaeiet al., 2014).

Homozygous mutations in *GBA* cause decreased glucocerebrosidase (GCase) activity and an accumulation of the substrate, glucosylceramide as well as glucosylsphingosine. The mechanism by which *GBA* mutations lead to PD and DLB is debated, although overall it is generally considered a loss of function disorder, whereby improving GCase transcription/folding, increasing GCase activity (McNeill et al., 2014, Migdalska-Richards et al., 2016, Narita et al., 2016), and reducing substrate accumulation may be avenues for intervention (Sardiet al., 2013). On a cellular level, GBA-PD has been proposed primarily to be a loss-of function effect, whereby enzyme deficiency feeds a cycle of poor alpha-synuclein processing, leading to oligomeric alpha-synuclein, which in turn decreases GCase activity (Sardi et al., 2015). On a systems level, there is not only nigral dopaminergic loss and synuclein deposition but cortical frontal and parietal circuits are implicated as well (Bregman et al., 2016, Cilia et al., 2016). fMRI study of non-manifesting heterozygous *GBA* carriers demonstrated that compared to non-carriers, those with *GBA* mutations showed greater activation during an executive functioning task (Bregmanet al., 2016). Although no difference in behavioral task performance was demonstrated, the increased activation among *GBA* carriers may reflect neural compensatory mechanisms that allowed this group to perform the cognitive task as well as the control group (Bregmanet al., 2016) and thus may indicate impending cognitive changes.

In contrast to other studies (Beavanet al., 2015, Zokaeiet al., 2014), we did not find differences between carriers and non-carriers on executive functioning, visuospatial, nonverbal memory tasks, or depression either cross-sectionally or longitudinally. There were important differences between these cohorts and ours: our cohort represented an older sample of individuals with *GBA* mutations, and our cohort was derived from a community based sample. In the previously mentioned studies, participants were all recruited from clinical settings,

including relatives of those who were treatment seeking, and thus they might harbor additional genetic modifiers that predispose to disease. Perhaps more importantly, our sample was almost exclusively N370S mutation carriers. Presence of different *GBA* mutations confers different risk for developing PD. Severe mutations (e.g. IVS2+1G>A, L444P) confer a 13.6 fold increased risk, whereas presence of mild mutations (e.g. N370S) confer a 2.2 fold increased risk (Gan-Or et al., 2008). Because more severe mutations are associated with greater cognitive decline in PD cases, and mixed European samples tend to have a greater proportion of severe, especially L444P carriers, the differences might also be attributed to mutation type.

GBA-PD is also related to neuropsychiatric symptoms such as depression and anxiety (Brockmannet al., 2011), and those with GBA-PD are more likely to have hallucinations and sustained cholinesterase inhibitor use (Barrettet al., 2014). However, we did not note differences on neuropsychiatric indicators in our non-manifesting carriers. This is also in contrast to a British study which showed depressive symptoms to increase over time in a sample of non-manifesting carriers (Beavanet al., 2015). Differences may be attributed to mutations, as described above. It is also important to note that prevalence of clinically significant depressive symptoms was low in our sample. Perhaps given that this sample was recruited from the community, rather than from a clinical setting, the lower rates of depression may reflect the sampling procedure used and consequent lower rates of depression among this non-treatment seeking group. While we did not find early motor features, our sample may not have been large enough or proximal enough to potential development of symptoms to detect a difference in motoric change. Alternately, this may reflect the relatively mild burden of the predominant N370S mutation in our sample.

Strengths of our study include that the community dwelling elderly cohort that is more representative of a group that might eventually receive an intervention, the rigorous neuropsychological methods which are more sensitive to detection of change (Lemoset al., 2015a, Lemoset al., 2015b), inclusion of other factors which impact cognitive decline in aging (e.g. ApoE4 status, cardiovascular risk), and the longitudinal nature of the study. The latter enables us to capture slopes of progression and is more reliable than a single cross-sectional time point. While it is an advantage that our cohort is focused primarily on a homogenous mutation type (93% of carriers have N370S mutations), the effect may be less than that observed with severe mutations. Potential disadvantages include that our assessment of *GBA* mutations was limited to major mutations, and effects of mutations may be underestimated as carriers of mutations outside of our screen would have been classified as non-carriers, leading to a diminution of the finding.

Further study in elderly cohorts such as ours is warranted with larger samples of individuals with *GBA* mutations. GBA-PD is associated with an earlier age of onset than idiopathic PD (Neumannet al., 2009, Nichols et al., 2009), with average age of onset for GBA-PD between 50 and 60 years of age (Swan and Saunders-Pullman, 2013). In contrast, participants in our study have survived into their 70s(+) without having developed PD, and thus this may represent a group with relatively increased protective factors or decreased burden of potential pathological mechanisms. While penetrance estimates suggest that the burden increases with age (Anheim et al., 2012, Ranaet al., 2013), further longitudinal study is warranted to determine whether these individuals remain at risk for PD and DLB or whether there is a window of susceptibility which can close and individuals are no longer at increased risk.

Supporting the overall low mid-life burden of N370S mutations is that the frequency of the N370S mutation is not significantly lower in our community-dwelling elderly Ashkenazi Jewish population (9.68%) than in published younger control frequencies (224/3,805 (5.89%)) (Gan-Oret al., 2008). A lower frequency would be expected if there is a strong disease effect such that N370S led to mid-life disease with a higher rate of dementia and/or PD, as affected individuals should be underrepresented in an elderly home-dwelling non-demented cohort. However, our absolute number of carriers was small, as was also noted in another elderly Ashkenazi Jewish control population where the frequency of carriers was lower 3.3% (11/333) compared with younger controls 224/3,805 (5.89%) (Gan-Oret al., 2008), but this difference was also not significant.

The data from this cohort suggest that among a sample of community dwelling older adults who are non-manifesting carriers, there is evidence of a cognitive burden associated with a single *GBA* mutation. It is of interest that the *GBA* cohort had shorter duration of follow-up, as follow-up is determined in part by functional cognitive status, and while not significant, there was a higher proportion of *GBA* individuals who discontinued the study because they met criteria for dementia. The recruitment strategies used in this study may have led to a sample with a mild burden of mutation status. Carriers in our sample had significantly fewer follow up visits than non-carriers and were nearly twice as likely as controls to meet criteria for dementia or PD, consistent with findings indicating a burden of *GBA* mutation status. Nevertheless, this study provided evidence of relative cognitive decline in verbal memory in this group using a comprehensive neuropsychological battery. Further prospective evaluation will allow for the determination of the relative impact of mutation status in different age groups as well as improved understanding of the aspects of cognition most likely to be affected and functional

consequences.   These will help set the stage to consider potential disease modifying agents and early interventions in at risk groups.

5. Conclusions

Individuals who were followed longitudinally as part of a community dwelling cohort were subsequently determined to have *GBA* mutations. Compared to their non-mutation peers, *GBA* carriers were found to have more rapid decline in verbal memory even when controlling for ApoE4 and cardiovascular risk, yet no differences were found in any other cognitive domain, motor functioning, or depression. As decline in verbal memory is predictive of overall cognitive decline, these findings suggests that harboring a single N370S *GBA* mutation may be associated with cognitive decline in aging. However, the overall burden of cognitive and motoric disease was low, as it was limited to one domain and was not associated with difference in motor performance or depression.

Table 1

Participant characteristics by genetic status

	GBA carriers (n=28)	Non-carriers (n=708)	*p*-value
Gender (%Female)	61%	64.3%	.121[a]
Age at baseline, y, mean (SD)	77.4 (5.6)	78.5 (5.3)	.339[b]
Education, y, mean (SD)	14.6 (3.8)	14.0 (3.4)	.484[b]
Follow up visits, mean (SD), median	3.72(1.85), 4	6.13(3.80), 6	.000[b]
Follow up discontinued:	25 (89.3%)	594 (83.9%)	.444[a]
Developed Dementia	7 (25.0%)	107 (15.1%)	.156[a]
Developed PD	1 (3.7%)	11 (1.6%)	.408[a]
Deceased	7 (25.0%)	239 (33.8%)	.335[a]
Withdrew	9 (32.1%)	136 (19.2%)	.160[a]
Lost to follow up	1 (3.7%)	101 (14.3%)	.108[a]
FCSRT, mean (SD)	32.0 (5.1)	30.7 (6.3)	.172
UPDRS-III, mean (SD)	6.1 (6.0)	7.8 (6.9)	.431

[a]Chi-squared test, [b]Mann Whitney U test

Key: y, years; SD, standard deviation, FCSRT, free and cued selective reminding test; UPDRS-III, Unified Parkinson's Disease Rating Scale motor section.

Table 2

Fixed effects for model predicting verbal memory and motor change

Parameter	FCRST				UPDRS-III			
Effects	B	SE	95% CI	p-value	B	SE	95% CI	p-value
Intercept	26.86	0.99	24.92, 28.79	<0.01	9.71	1.23	7.30, 12.12	<0.01
Age	-0.31	0.04	-0.39, -0.23	<0.01	0.38	0.06	0.26, 0.50	<0.01
Gender	2.09	0.45	1.19, 2.96	<0.01	-1.20	0.58	-2.34, -0.06	0.04
Race	-1.61	0.50	0.46, 2.31	<0.01	0.60	0.60	-0.58, 1.78	0.32
Education	0.16	0.06	0.03, 0.28	0.01	-0.10	0.07	-0.24, 0.03	0.20
GBA status	-0.13	1.15	-2.40, 2.11	0.91	-1.49	1.04	-3.53, 0.55	0.15
Time	-0.23	0.06	-0.36, -0.10	<0.01	0.59	0.10	0.39, 0.79	<0.01
Age X Time	-0.03	0.01	-0.05, -0.02	<0.01	0.05	0.01	0.03, 0.06	<0.01
Gender X Time	-0.18	0.08	-0.35, -0.02	0.03	0.11	0.12	-0.13, 0.35	0.36
GBA status X Time	-0.42	0.20	-0.80, -0.03	0.03	0.17	0.29	-0.40, 0.74	0.56

Key: FCSRT, free and cued selective reminding test; UPDRS-III, unified Parkinson's disease rating scale motor section;

Note: The model for FCRST is a single model with all listed variables as covariates. The model for UPDRS-III is a single model with all listed variables as covariates. The effect 'Time' indicates the rate of change, i.e., slope, in points per year. The interaction terms with Time measure the effect of baseline age, gender and genetic status, respectively, on the rate of change in FCSRT and UPDRS-III

Table 3

Fixed effects model for predicting verbal memory change with additional covariates

Parameter		FCRST		
Effects	B	SE	95% CI	p-value
Intercept	26.90	1.02	24.90, 28.90	<0.001
Age	-0.31	0.04	-0.40, -0.23	<0.001
Gender	1.93	0.47	1.01, 2.85	<0.001
Race	1.09	0.48	0.15, 2.04	0.023
Education	0.18	0.06	0.06, 0.31	0.004
GBA status at baseline	-0.015	1.17	-2.30, 2.23	0.989
Time	-0.15	1.17	-0.29, -0.02	0.027
Age X Time	-0.036	0.01	-0.05, -0.02	<0.0001
Gender X Time	-0.18	0.08	-0.34, -0.01	0.035
ApoE4	-0.12	0.54	-1.16, 0.94	0.838
CV	-0.58	0.57	-1.70, 0.55	0.314
ApoE4 X Time	-0.40	0.10	-0.60, -0.20	<0.0001
GBA status X Time	-0.50	0.20	-0.88, -0.11	0.010

Key: ApoE4, apolipoprotein E4 genetic status; CV, cardiovascular risk score

Note: This is a single model with all listed variables as covariates.

Supplementary Table 1

Summary of adjusted models comparing cognitive rates of change in *GBA* carriers versus controls

Outcome	B	SE	95% CI	p-value
RBANS Copy	-0.15	0.13	-0.40, 0.10	0.26
RBANS Recall	-0.09	0.12	-0.33, 0.15	0.40
TMTA	0.00	0.00	0.00, 0.00	0.90
TMTB	0.00	0.00	0.00, 0.00	0.98
GDS	0.05	0.04	-0.03, 0.13	0.24

Key: RBANS, repeatable battery of neuropsychological status complex figure test; TMTA, trail making test A; TMTB, trail making test B; GDS, geriatric depression scale.

Note: The B coefficients are the interaction terms of Time (rate of change) with genetic status in separate models in which baseline age, gender and education are covariates.

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Highlights

- In a community based sample of older adults, burden of *GBA* mutation was assessed.
- *GBA* mutation positive older adults showed greater decline in verbal memory.
- No difference was found in motor functioning or any other cognitive domain.
- Some burden was seen in a sample primarily consisting of the milder N370S mutation.

Verification Statement

1. Conflicts of Interest:

Eileen E. Moran: no conflicts of interest

Cuiling Wang: no conflicts of interest

Mindy Katz: no conflicts of interest

Laurie Ozelius: no conflicts of interest

Alison Schwartz: no conflicts of interest

Jelena Pavlovic: no conflicts of interst

Roberto A. Ortega: no conflicts of interest

Richard B. Lipton: Dr. Richard B. Lipton is the Edwin S. Lowe Professor of Neurology at the Albert Einstein College of Medicine in New York. He receives research support from the NIH: 2PO1 AG003949 (Program Director), 5U10 NS077308 (PI), 1RO1 AG042595 (Investigator), RO1 NS082432 (Investigator), K23 NS09610 (Mentor), K23AG049466 (Mentor). He also receives support from the Migraine Research Foundation and the National Headache Foundation. He serves on the editorial board of Neurology and as senior advisor to Headache. He has reviewed for the NIA and NINDS, holds stock options in eNeura Therapeutics; serves as consultant, advisory board member, or has received honoraria from: American Academy of Neurology, Alder, Allergan, American Headache Society, Amgen, Autonomic Technologies, Avanir, Biohaven, Biovision, Boston Scientific, Colucid, Dr. Reddy's, Electrocore, Eli Lilly, eNeura Therapeutics, GlaxoSmithKlein, Merck, Pernix, Pfizer, Supernus, Teva, Trigemina, Vector, Vedanta. He receives royalties from Wolff's Headache, 8th Edition, Oxford Press University, 2009, Wiley and Informa.

Molly E. Zimmerman: is a co-investigator on NIH P01AG003949

Rachel Saunders-Pullman: the study was in part funded through grant funding to the Gaucher Generations Program from Genzyme-Sanofi (no personal compensation was received)

2. This work was supported by the Gaucher Generations Program from Genzyme Sanofi; the National Institutes of Health, National Institute on Aging NIA [AG03949], National Institutes of Health, National Institute of Neurological Disorders and Stroke [U01NS094148-01].

3. The data contained in this manuscript have not been previously published, have not been submitted elsewhere, and will not be submitted elsewhere while under consideration at Neurobiology of Aging.

4. All participants provided informed consent at each study visit and study procedures were approved by the institutional review board at Albert Einstein Medical Center.

5. All authors have reviewed the contents of this manuscript and approve of its contents. All authors validate the accuracy of the data.