HHS Public Access

Author manuscript

Neurobiol Aging. Author manuscript; available in PMC 2018 October 01.

Published in final edited form as:

Neurobiol Aging. 2017 October ; 58: 239.e1–239.e7. doi:10.1016/j.neurobiolaging.2017.06.010.

Cognitive and motor functioning in elderly *glucocerebrosidase* mutation carriers

Eileen E. Moran[a,*], **Cuiling Wang**[b,c], **Mindy Katz**[b], **Laurie Ozelius**[d], **Alison Schwartz**[e], **Jelena Pavlovic**[b], **Roberto A. Ortega**[e], **Richard B. Lipton**[b], **Molly E. Zimmerman**[a,b], and **Rachel Saunders-Pullman**[b,e]

[a]Department of Psychology, Fordham University, Bronx, NY, USA

[b]Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA

[c]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA

[d]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[e]Department of Neurology, Mount Sinai Beth Israel, New York, NY, USA

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 (≥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

*Corresponding author at: Department of Psychology, Fordham University, 441 E Fordham Rd, Bronx, NY 10458, USA. Tel.: +1-718-817-3835; fax: +1-718-817-3785. emoran@fordham.edu (E.E. Moran).

Disclosure statement

RS-P states that the study was in part funded through grant funding by the Gaucher Generations Program from Genzyme-Sanofi (no personal compensation was received). RS-P Pullman also receives research support from the National Institutes of Health, National Institute on Aging NIA (AG03949), National Institutes of Health, and National Institute of Neurological Disorders and Stroke (U01NS094148-01). RBL 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), and 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 National Headache Foundation. 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 the 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, and Vedanta. He receives royalties from Wolff's Headache, 8th Edition, Oxford Press University, 2009, Wiley and Informa. MEZ is a coinvestigator on NIH P01AG003949. The remaining authors declare no conflicts of interest.

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 disease; Cognition

1. Introduction

Biallelic mutations in the *glucocerebrosidase* gene (*GBA*) cause Gaucher disease, 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 2 disorders of synuclein accumulation form the core of a spectrum that includes parkinsonism and dementia (Wales et al., 2013). Worldwide, 2.9%–8% of the cases of PD are associated with *GBA* mutations (Clark et al., 2007; Mata et al., 2008; Sidransky et al., 2009) and *GBA* mutations are associated with an 8-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%–15% by the age of 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; Sidransky et al., 2009; Winder-Rhodes et al., 2013), including an increased risk for both mild cognitive impairment (Alcalay et al., 2012) and dementia (Brockmann et 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; Brockmann et al., 2011), and more specifically, deficits in visual short-term memory (Zokaei et al., 2014), memory and visuospatial functioning (Alcalay et al., 2012; Mata et al., 2016), and executive functioning and working memory (Mata et al., 2016). In addition, *GBA*-PD is related to neuropsychiatric symptoms such as depression and anxiety (Brockmann et al., 2011; Swan et al., 2016), 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 nonmanifesting 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 before 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 "preclinical 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., 2011). 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,b), 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, USA) A Sequenom Compact Mass Array Spectrometer was used to perform (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 (Katz et 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; Harold et al., 2009; Lambert et al., 2009; Verghese et 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 15-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, NC, USA) and SPSS 20 (SPSS INC, Chicago, IL, USA). 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 noncarriers (75.0% vs. 27.7%, $p < 0.001$). There were significantly more follow-up visits for noncarriers than carriers (mean 6.13 vs. 3.72, $p < 0.001$). Of all, 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 black ($p < 0.001$) were associated with worse performance. There was no significant difference in free recall performance between *GBA* mutation carriers and noncarriers at baseline. However, the rate of decline in free recall among mutation carriers was

significantly faster than that among noncarriers (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 noncarriers (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 was assessed and is presented in Table 3. When adjusting for ApoE4, the rate of decline in free recall among mutation carriers remained significantly faster than noncarriers (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 was 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 with 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 post hoc 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 nonmanifesting 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.

In addition, 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 that 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; Grober et al., 2000) and mild cognitive

impairment (Lemos et al., 2015a,b) 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 with idiopathic PD (Alcalay et al., 2012; Brockmann et al., 2011; Saunders-Pullman et al., 2010; Zokaei et 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 (Beavan et al., 2015) in nonmanifesting *GBA* carriers, and worse performance of *GBA* carriers on an experimental task of visual short-term memory relative to controls (Zokaei et 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 (Sardi et 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., 2017; Cilia et al., 2016). fMRI study of nonmanifesting heterozygous *GBA* carriers demonstrated that compared with noncarriers, those with *GBA* mutations showed greater activation during an executive functioning task (Bregman et al., 2017). 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 (Bregman et al., 2017) and thus may indicate impending cognitive changes.

In contrast to other studies (Beavan et al., 2015; Zokaei et 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 (Brockmann et al., 2011; Swan et al., 2016), and those with *GBA*-PD are more likely to have hallucinations and sustained cholinesterase inhibitor use (Barrett et al., 2014). However, we did not note differences on neuropsychiatric indicators in our nonmanifesting carriers. This is also in contrast to a British study which showed depressive symptoms to increase over time in a sample of nonmanifesting carriers (Beavan et 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 nontreatment seeking group. While we did not find early motor features, our sample may not have been large enough or proximal enough for the 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 (Lemos et al., 2015a,b), 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 noncarriers, 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 (Neumann et 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; Rana et 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 (224/3805

[5.89%]; Gan-Or et 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 nondemented 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 224/3805 (5.89%; Gan-Or et 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 nonmanifesting 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 noncarriers 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 with their nonmutation 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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, and National Institute of Neurological Disorders and Stroke (U01NS094148-01). The authors would like to thank April Russo, Diane Sparaccio, and Charlotte Magnotta for assistance with participant recruitment; Betty Forro, Wendy Ramratan, and Mary Joan Sebastian for assistance with clinical and neuropsychological assessment; Michael Potenza for assistance with data management; and all of the study participants who generously gave their time in support of this research.

References

Alcalay RN, Caccappolo E, Mejia-Santana H, Tang M, Rosado L, Orbe Reilly M, Orbe Reilly M, Ruiz D, Ross B, Vebitsky M, Kisseley S, Louis E, Comella C, Colcher A, Jennings D, Nance M, Bressman S, Scott WK, Tanner C, Mickel S, Andrews H, Waters C, Fahn S, Cote L, Frucht S, Ford B, Rezak M, Novak K, Friedman JH, Pfieffer R, Marsh L, Heiner B, Siderowf A, Payami H, Molho E, Factor S, Ottman R, Clark LN, Marder K. Cognitive performance of GBA mutation carriers with early-onset PD: the CORE-PD study. Neurology. 2012; 78:1434–1440. [PubMed: 22442429]

Almkvist O, Basun H, Backman L, Herlitz A, Lannfelt L, Small B, Viitanen M, Wahlund LO, Winbald B. Mild cognitive impairment–an early stage of Alzheimer's disease? J Neural Transm Suppl. 1998; 54:21–29. [PubMed: 9850912]

Anheim M, Elbaz A, Lesage S, Durr A, Condroyer C, Viallet F, Pollak P, Bonaïti-Pellié C, Brice A. French Parkinson Disease Genetic Group. Penetrance of Parkinson disease in glucocerebrosidase gene mutation carriers. Neurology. 2012; 78:417–420. [PubMed: 22282650]

Barrett MJ, Shanker VL, Severt WL, Raymond D, Gross SJ, Schreiber-Agus N, Kornreich R, Ozelius LJ, Bressman SB, Saunders-Pullman R. Cognitive and Antipsychotic Medication Use in Monoallelic GBA-related Parkinson disease. JIMD Rep. 2014; 16:31–38. [PubMed: 24850235]

Battery, A. Manual of Directions and Scoring. War Department, Adjunct Generals Office; Washington, D.C: 1944.

Beavan M, McNeill A, Proukakis C, Hughes DA, Mehta A, Schapira AH. Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. JAMA Neurol. 2015; 72:201–208. [PubMed: 25506732]

Blacker D, Lee H, Muzikansky A, Martin EC, Tanzi R, McArdle JJ, Moss M, Albert M. Neuropsychological measures in normal individuals that predict subsequent cognitive decline. Arch Neurol. 2007; 64:862–871. [PubMed: 17562935]

Braak H, Del Tredici K, Rub U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging. 2003; 24:197–211. [PubMed: 12498954]

Bregman N, Thaler A, Mirelman A, Helmich RC, Gurevich T, Orr-Urtreger A, Marder K, Bressman S, Bloem BR, Giladi N. LRRK2 Ashkenazi Jewish Consortium. A cognitive fMRI study in non-manifesting LRRK2 and GBA carriers. Brain Struct Funct. 2017; 222:1207–1218. [PubMed: 27401793]

Brockmann K, Srulijes K, Hauser AK, Schulte C, Csoti I, Gasser T, Berg D. GBA-associated PD presents with nonmotor characteristics. Neurology. 2011; 77:276–280. [PubMed: 21734182]

Cilia R, Tunesi S, Marotta G, Cereda E, Siri C, Tesei S, Zecchinelli AL, Canesi M, Mariani CB, Meucci N, Sacilotto G, Zini M, Barichella M, Magnani C, Duga S, Asselta R, Soldà G, Seresini A, Seia M, Pezzoli G, Goldwurm S. Survival and dementia in GBA-associated Parkinson's disease: the mutation matters. Ann Neurol. 2016; 80:662–673. [PubMed: 27632223]

Clark LN, Kartsaklis LA, Wolf Gilbert R, Dorado B, Ross BM, Kisselev S, Verbitsky M, Mejia-Santana H, Cote LJ, Andrews H, Vonsattel JP, Fahn S, Mayeux R, Honig LS, Marder K. Association of glucocerebrosidase mutations with dementia with lewy bodies. Arch Neurol. 2009; 66:578–583. [PubMed: 19433657]

Clark LN, Ross BM, Wang Y, Mejia-Santana H, Harris J, Louis ED, Cote LJ, Andrews H, Fahn S, Waters C, Ford B, Frucht S, Ottman R, Marder K. Mutations in the glucocerebrosidase gene are associated with early-onset Parkinson disease. Neurology. 2007; 69:1270–1277. [PubMed: 17875915]

Crosiers D, Verstraeten A, Wauters E, Engelborghs S, Peeters K, Mattheijssens M, De Deyn PP, Theuns J, Van Broeckhoven C, Cras P. Mutations in glucocerebrosidase are a major genetic risk factor for Parkinson's disease and increase susceptibility to dementia in a Flanders-Belgian cohort. Neurosci Lett. 2016; 629:160–164. [PubMed: 27397011]

Fahn, S., Elton, RL. Unified Parkinson's disease rating scale. In: Fahn, S.Marsden, CD.Clane, DB., Goldstein, M., editors. Recent Development in Parkinson's Disease. Macmillan Health Care Information; Florham Park, NJ: 1987. p. 153-164.

Gan-Or Z, Giladi N, Rozovski U, Shifrin C, Rosner S, Gurevich T, Bar-Shira A, Orr-Urteger A. Genotype-phenotype correlations between GBA mutations and Parkinson disease risk and onset. Neurology. 2008; 70:2277–2283. [PubMed: 18434642]

Gatto EM, Etcheverry JL, Sanguinetti A, Cesarini M, Fernandez Escobar N, Drelichman G. Prodromal clinical markers of Parkinson disease in Gaucher disease individuals. Eur Neurol. 2016; 76:19–21. [PubMed: 27344356]

Goker-Alpan O, Schiffmann R, LaMarca ME, Nussbaum RL, McInerney-Leo A, Sidransky E. Parkinsonism among Gaucher disease carriers. J Med Genet. 2004; 41:937–940. [PubMed: 15591280]

Goldman JG, Litvan I. Mild cognitive impairment in Parkinson's disease. Minerva Med. 2011; 102:441–459. [PubMed: 22193376]

Grober E, Kawas C. Learning and retention in preclinical and early Alzheimer's disease. Psychol Aging. 1997; 12:183–188. [PubMed: 9100279]

Grober E, Lipton RB, Hall C, Crystal H. Memory impairment on free and cued selective reminding predicts dementia. Neurology. 2000; 54:827–832. [PubMed: 10690971]

Guarch J, Marcos T, Salamero M, Gasto C, Blesa R. Mild cognitive impairment: a risk indicator of later dementia, or a preclinical phase of the disease? Int J Geriatr Psychiatry. 2008; 23:257–265. [PubMed: 17668419]

Haan MN, Mayeda ER. Apolipoprotein E genotype and cardiovascular diseases in the elderly. Curr Cardiovasc Risk Rep. 2010; 4:361–368. [PubMed: 20694037]

Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Bill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Kraig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Hüll M, Rujescu D, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broechkoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliams R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Gurreiro R, Mühleisen TW, Nöthen MM, Moebus S, Jöckel KH, Klopp N, Wichmann HE, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ, Williams J. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet. 2009; 41:1088–1093. [PubMed: 19734902]

Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol. 2010; 9:119–128. [PubMed: 20083042]

Katz MJ, Lipton RB, Hall CB, Zimmerman ME, Sanders AE, Verghese J, Dickson DQ, Derby CA. Age-specific and sex-specific prevalence and incidence of mild cognitive impairment, dementia, and Alzheimer dementia in blacks and whites: a report from the Einstein Aging Study. Alzheimer Dis associated Disord. 2012; 26:335–343.

Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fiévet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossù P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Rictchie K, Blanché H, Dartiques JF, Tzourio C, Gut I, Van Broeckhoven C, Alpérovitch A, Lathrop M, Amouyel P. European Alzheimer's Disease Initiative Investigators. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet. 2009; 41:1094–1099. [PubMed: 19734903]

Lemos R, Cunha C, Maroco J, Afonso A, Simoes MR, Santana I. Free and cued selective reminding test is superior to the Wechsler memory scale in discriminating mild cognitive impairment from Alzheimer's disease. Geriatr Gerontol Int. 2015a; 15:961–968. [PubMed: 25243721]

Lemos R, Simoes MR, Santiago B, Santana I. The free and cued selective reminding test: validation for mild cognitive impairment and Alzheimer's disease. J Neuropsychol. 2015b; 9:242–257. [PubMed: 24894485]

Lesage S, Anheim M, Condroyer C, Pollak P, Durif F, Dupuits C, Viallet F, Lohmann E, Corvol JC, Honoré A, Rivaud S, Vidailhet M, Dürr A, Brice A. French Parkinson's Disease Genetics Study Group. Large-scale screening of the Gaucher's disease-related glucocerebrosidase gene in Europeans with Parkinson's disease. Hum Mol Genet. 2011; 20:202–210. [PubMed: 20947659]

Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, Rodriguez-Oroz MC, Tröster AL, Weintraub D. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord. 2011; 26:1814–1824. [PubMed: 21661055]

Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, Van Deerlin VM, Ritz B, Rausch R, Factor SA, Wood-Siverio C, Quinn JF, Chung KA, Peterson-Hiller AL, Goldman JG, Stebbins GT, Brenard B, Espay AJ, Revilla FJ, Devoto J, Rosenthal LS, Dawson TM, Albert MS, Tsuang D, Huston J, Yearout D, Hu SC, Cholerton BA, Montine TJ, Edwards KL, Zabetian CP. GBA Variants are associated with a distinct pattern of cognitive deficits in Parkinson's disease. Mov Disord. 2016; 31:95–102. [PubMed: 26296077]

Mata IF, Samii A, Schneer SH, Roberts JW, Griffith A, Leis BC, Schellenberg GD, Sidransky E, Bird TD, Leverenz JB, Zabetian CP. Glucocerebrosidase gene mutations: a risk factor for Lewy body disorders. Arch Neurol. 2008; 65:379–382. [PubMed: 18332251]

McNeill A, Duran R, Hughes DA, Mehta A, Schapira AH. A clinical and family history study of Parkinson's disease in heterozygous glucocerebrosidase mutation carriers. J Neurol Neurosurg Psychiatry. 2012a; 83:853–854. [PubMed: 22577228]

McNeill A, Duran R, Proukakis C, Bras J, Hughes D, Mehta A, Hardy J, Wood NW, Schapira AH. Hyposmia and cognitive impairment in Gaucher disease patients and carriers. Mov Disord. 2012b; 27:526–532. [PubMed: 22344629]

McNeill A, Magalhaes J, Shen C, Chau KY, Hughes D, Mehta A, Foltynie T, Cooper JM, Abramov AY, Gegg M, Schapira AH. Ambroxol improves lysosomal biochemistry in glucocerebrosidase mutation-linked Parkinson disease cells. Brain. 2014; 137(Pt 5):1481–1495. [PubMed: 24574503]

Migdalska-Richards A, Daly L, Bezard E, Schapira AH. Ambroxol effects in glucocerebrosidase and alpha-synuclein transgenic mice. Ann Neurol. 2016; 80:766–775. [PubMed: 27859541]

Misdraji EL, Gass CS. The Trail Making test and its neurobehavioral components. J Clin Exp Neuropsychol. 2010; 32:159–163. [PubMed: 19459077]

Nalls MA, Duran R, Lopez G, Kurzawa-Akanbi M, McKeith IG, Chinnery PF, Morris CM, Theuns J, Crosiers D, Cras P, Engelborghs S, De Deyn PP, Van Broeckhoven C, Mann DM, Snowden J, Pickering-Brown S, Halliwell N, Davidson Y, Gibbons L, Harris J, Sherrin UM, Bras J, Hardy J, Clark L, Marder K, Honig LS, Berg D, Maetzler W, Brockmann K, Gasser T, Novellino F, Quattrone A, Annesli G, De Marco EV, Rogaeva E, Masellis M, Black SE, Bilbao JM, Foroud T, Ghetti B, Nichols WC, Pankratz N, Halliday G, Lesage S, Klebe S, Durr A, Duyckaerts C, Brice A, Giasson BI, Trojanowski JQ, Hurtig HI, Tayebi N, Landazabal C, Knight MA, Keller M, Singleton AB, Wolfsberg TG, Sidransky E. A multicenter study of glucocerebrosidase mutations in dementia with Lewy bodies. JAMA Neurol. 2013; 70:727–735. [PubMed: 23588557]

Narita A, Shirai K, Itamura S, Matsuda A, Ishihara A, Matsushita K, Fukuda C, Kubota N, Takayama R, Shigematsu H, Hayashi A, Kumada T, Yuge K, Watanabe Y, Kosugi S, Nishida H, Himura Y, Endo Y, Higaki K, Nanbe E, Nishimura Y, Tamasaki A, Togawa M, Saito Y, Maegaki Y, Ohno K, Suzuki Y. Ambroxol chaperone therapy for neuronopathic Gaucher disease: a pilot study. Ann Clin Translational Neurol. 2016; 3:200–215.

Neumann J, Bras J, Deas E, O'Sullivan SS, Parkkinen L, Lachmann RH, Li A, Guerreiro R, Paudel R, Segarane B, Singleton A, Lees A, Hardy J, Houlden H, Revesz T, Wood NW. Glucocerebrosidase mutations in clinical and pathologically proven Parkinson's disease. Brain. 2009; 132(Pt 7):1783–1794. [PubMed: 19286695]

Nichols WC, Pankratz N, Marek DK, Pauciulo MW, Elsaesser VE, Halter CA, Rudolph A, Wojcieszek J, Pfeiffer RF, Foroud T. Parkinson Study Group-PROGENI Investigators. Mutations in GBA are associated with familial Parkinson disease susceptibility and age at onset. Neurology. 2009; 72:310–316. [PubMed: 18987351]

Pastores, GM., Hughes, DA. Gaucher disease. In: Pagon, RA.Adam, MP.Ardinger, HH.Wallace, SE.Amemiya, A.Bean, LJH., et al., editors. Gen-eReviews(R). University of Washington; Seattle, Seattle (WA): 1993. All rights reserved

Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. Mov Disord. 2014; 29:1583–1590. [PubMed: 24976103]

Rabin LA, Pare N, Saykin AJ, Brown MJ, Wishart HA, Flashman LA, Santulli RB. Differential memory test sensitivity for diagnosing amnestic mild cognitive impairment and predicting conversion to Alzheimer's disease. Neuropsychol Dev Cogn Sec B Aging Neuropsychol Cogn. 2009; 16:357–376.

Rana HQ, Balwani M, Bier L, Alcalay RN. Age-specific Parkinson disease risk in GBA mutation carriers: information for genetic counseling. Genet Med. 2013; 15:146–149. [PubMed: 22935721]

Randolph C, Tierney MC, Mohr E, Chase TN. The Repeatable battery for the assessment of neuropsychological status (RBANS): preliminary clinical validity. J Clin Exp Neuropsychol. 1998; 20:310–319. [PubMed: 9845158]

Sardi SP, Cheng SH, Shihabuddin LS. Gaucher-related synucleinopathies: the examination of sporadic neurodegeneration from a rare (disease) angle. Prog Neurobiol. 2015; 125:47–62. [PubMed: 25573151]

Sardi SP, Clarke J, Viel C, Chan M, Tamsett TJ, Treleaven CM, Bu J, Sweet L, Passini MA, Dodge JC, Yu WH, Sidman RL, Cheng SH, Shihabuddin LS. Augmenting CNS glucocerebrosidase activity as a therapeutic strategy for parkinsonism and other Gaucher-related synucleinopathies. Proc Natl Acad Sci U S A. 2013; 110:3537–3542. [PubMed: 23297226]

Saunders-Pullman R, Hagenah J, Dhawan V, Stanley K, Pastores G, Sathe S, Tagliati M, Condefer K, Palmese C, Brüggemann N, Klein C, Roe A, Kornreich R, Ozelius L, Bressman S. Gaucher disease ascertained through a Parkinson's center: imaging and clinical characterization. Mov Disord. 2010; 25:1364–1372. [PubMed: 20629126]

Schapira AH. Glucocerebrosidase and Parkinson disease: Recent advances. Mol Cell Neurosci. 2015; 66(Pt A):37–42. [PubMed: 25802027]

Seto-Salvia N, Pagonabarraga J, Houlden H, Pascual-Sedano B, Dols-Icardo O, Tucci A, Paisán-Ruiz C, Campolongo A, Antón-Aguirre S, Martín I, Muñoz L, Bufill E, Bilageliu L, Grinberg D, Cozar M, Blesa R, Lleó A, Hardy J, Kulisevsky J, Clarimón J. Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. Mov Disord. 2012; 27:393–399. [PubMed: 22173904]

Sidransky E, Nalls MA, Aasly JO, Aharon-Peretz J, Annesi G, Barbosa ER, Bar-Shira A, Berg D, Bras J, Brice A, Chen CM, Clark LN, Condroyer C, De Marco EV, Dürr A, Eblan MJ, Fahn S, Farrer MJ, Fung HC, Gan-Or Z, Gasser T, Gershoni-Baruch R, Giladi N, Griffith A, Gurevich T, Januario C, Kropp P, Lang AE, Lee-Chen GJ, Lesage S, Marder K, Mata IF, Mirelman A, Mitsui J, Mizuta I, Nicoletti G, Oliveira C, Ottman R, Orr-Urteer A, Pereira LV, Quattrone A, Rogaeva E, Rolfs A, Rosenbaum H, Rozenberg R, Samii A, Samaddar T, Schulte C, Sharma M, Singleton A, Spitz M, Tan EK, Tayebi N, Toda T, Troiano AR, Tsuji S, Wittstock M, Wolfsberg TG, Wu YR, Zabetian CP, Zhao Y, Ziegler SG. Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. New Engl J Med. 2009; 361:1651–1661. [PubMed: 19846850]

Sperling RA, Jack CR Jr, Aisen PS. Testing the right target and right drug at the right stage. Sci Transl Med. 2011; 3:111cm33.

Swan M, Doan N, Ortega RA, Barrett M, Nichols W, Ozelius L, Soto-Valencia J, Boschung S, Deik A, Sarva H, Cabassa J, Johannes B, Raymond D, Marder K, Giladi N, Miravite J, Severt W, Sachdev R, Shanker V, Bressman S, Saunders-Pullman R. Neuropsychiatric characteristics of GBA-associated Parkinson disease. J Neurol Sci. 2016; 370:63–69. [PubMed: 27772789]

Swan M, Saunders-Pullman R. The association between ss-glucocerebrosidase mutations and parkinsonism. Curr Neurol Neurosci Rep. 2013; 13:368. [PubMed: 23812893]

Verghese J, Holtzer R, Wang C, Katz MJ, Barzilai N, Lipton RB. Role of APOE genotype in gait decline and disability in aging. J Gerontol Ser A Biol Sci Med Sci. 2013; 68:1395–1401. [PubMed: 23902934]

Wales P, Pinho R, Lazaro DF, Outeiro TF. Limelight on alpha-synuclein: pathological and mechanistic implications in neurodegeneration. J Parkinson's Dis. 2013; 3:415–459. [PubMed: 24270242]

Winder-Rhodes SE, Evans JR, Ban M, Mason SL, Williams-Gray CH, Foltynie T, Duran R, Mencacci NE, Sawcer SJ, Barker RA. Glucocerebrosidase mutations influence the natural history of Parkinson's disease in a community-based incident cohort. Brain. 2013; 136(Pt 2):392–399. [PubMed: 23413260]

Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, Leirer VO. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res. 1982; 17:37–49. [PubMed: 7183759]

Zokaei N, McNeill A, Proukakis C, Beavan M, Jarman P, Korlipara P, Hughes D, Mehta A, Hu MT, Schapira AH, Husain M. Visual short-term memory deficits associated with GBA mutation and Parkinson's disease. Brain. 2014; 137(Pt 8):2303–2311. [PubMed: 24919969]

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2017.06.010.

Table 1

Participant characteristics by genetic status

Variable	*GBA* carriers (n = 28)	Noncarriers (n = 708)	*p*-value
Gender (%female)	61%	64.3%	0.121[a]
Age at baseline, y, mean (SD)	77.4 (5.6)	78.5 (5.3)	0.339[b]
Education, y, mean (SD)	14.6 (3.8)	14.0 (3.4)	0.484[b]
Follow-up visits, mean (SD), median	3.72 (1.85), 4	6.13 (3.80), 6	0.000[b]
Follow-up discontinued	25 (89.3%)	594 (83.9%)	0.444[a]
Developed dementia	7 (25.0%)	107 (15.1%)	0.156[a]
Developed PD	1 (3.7%)	11 (1.6%)	0.408[a]
Deceased	7 (25.0%)	239 (33.8%)	0.335[a]
Withdrew	9 (32.1%)	136 (19.2%)	0.160[a]
Lost to follow up	1 (3.7%)	101 (14.3%)	0.108[a]
FCSRT, mean (SD)	32.0 (5.1)	30.7 (6.3)	0.172
UPDRS-III, mean (SD)	6.1 (6.0)	7.8 (6.9)	0.431

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

[a] Chi-squared test.

[b] Mann Whitney *U* test.

Table 2

Fixed effects for model predicting verbal memory and motor change

Parameter, effects	FCSRT				UPDRS-III			
	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 × time	−0.03	0.01	−0.05, −0.02	<0.01	0.05	0.01	0.03, 0.06	<0.01
Gender × time	−0.18	0.08	−0.35, −0.02	0.03	0.11	0.12	−0.13, 0.35	0.36
GBA status × time	−0.42	0.20	−0.80, −0.03	0.03	0.17	0.29	−0.40, 0.74	0.56

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, that is, 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.

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

Table 3

Fixed effects model for predicting verbal memory change with additional covariates

Parameter, effects	FCSRT			
	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 × time	−0.036	0.01	−0.05, −0.02	<0.0001
Gender × 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 × time	−0.40	0.10	−0.60, −0.20	<0.0001
GBA status × time	−0.50	0.20	−0.88, −0.11	0.010

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

Key: ApoE4, apolipoprotein E4 genetic status; CV, cardiovascular risk score; FCSRT, free and cued selective reminding test.