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ORIGINAL COMMUNICATION

GBA moderates cognitive reserve's effect on cognitive function in patients with Parkinson's disease

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Abstract

Background Cognitive reserve (CR) involves an individual's ability to maintain cognitive vitality over their lifespan. Glucocerebrosidase (*GBA*) gene mutations contribute to additional effects on cognitive function in Parkinson's disease (PD) patients, but the interplay between *GBA* mutations and CR remains unclear. We investigated the interactions among CR, *GBA*, and diseases, aiming to examine whether the CR established at different stages interacts with specific genotypes to affect cognitive function.

Methods Three hundred and eighteen participants' CR indicators (i.e., education, occupation, and social function) and comprehensive neuropsychological function (i.e., tests for executive function, attention/working memory, visuospatial function, memory, and language) were evaluated.

Results We found that CR established in a specific life stage influences the individual's cognitive function, particularly in PD, based on their distinct *GBA* rs9628662 genotypes. Attention/working memory and memory performance are affected by occupational complexity in midlife in PD patients with the GG genotype ($q < 0.0001$; $q < 0.0001$) and healthy adults with the T genotype ($q = 0.0440$; $q < 0.0001$). Language is influenced by early education and occupation, and the effects of occupation are also observed in PD patients with the GG genotype ($q = 0.0040$) and in healthy adults carrying the T genotype ($q = 0.0040$).

Conclusions CR, established at different life stages, can be influenced by the *GBA* rs9628662 genotype, impacting later-life cognition. Validating genotypes and incorporating genotype information when assessing cognitive reserve effects is crucial and can enhance targeted cognitive training.

Keywords Parkinson's Disease · Cognitive Reserve · *GBA* mutations · Healthcare · Neuropsychological function

Introduction

Parkinson's disease (PD) is a prevalent neurodegenerative disorder [1] and is characterized by motor symptoms resulting from dopamine deficiency in the basal ganglia [2] and non-motor manifestations [3, 4], such as sleep disturbances [5, 6], cognitive impairment [7–14], disruptions in social cognition [15–18], neuropsychiatry symptoms [19], and social dysfunction [16, 20, 21]. Among these non-motor symptoms, dementia emerges as a particularly significant challenge in the progression of PD. Therefore, identifying risk and protective factors associated with dementia in PD patients holds the potential for facilitating earlier and more effective interventions.

The concept of "reserve" in the context of neurodegenerative diseases addresses the intriguing disparity between neuropathological traits and clinical manifestations and

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encompasses both active and passive forms [22, 23]. The passive form, called brain reserve, pertains to individual variations in brain structure that confer protection against disease-related impairments [23]. On the other hand, the active form, known as cognitive reserve (CR), involves the strategic utilization and compensation of cognitive resources to confront environmental challenges following brain injury [23]. CR is a dynamic and lifelong process influenced by myriad experiences [24] that mold brain processing [25], foster protective brain networks [26], and mitigate cognitive decline in later stages of life [27]. Various proxies, including education, occupational complexity, and social participation, can be employed to assess the impact of CR in patients with PD [28–31].

Among the identified CR factors, education in early life [32–34] and occupational complexity in mid-life [32, 33, 35] have been associated with cognitive function in PD patients. Although the impact of late-life CR proxies is still debatable, factors such as cognitive leisure activities, social participation, and telephone use have been considered. Older age, reduced social participation, and infrequent telephone use may potentially elevate the risk of dementia in PD patients [33]. Notably, creative and cognitive leisure activities, as opposed to physical activity, have demonstrated a correlation with general cognitive function [32]. The aforementioned studies have all used single indicators as measures of CR. However, subsequent research has emphasized the importance of combining different indicators, such as education, occupational activity, and leisure time activities, as indicators of CR [36]. The study found that CR's protective effects on neuropsychological functions not only extend to preserving cognitive performance but may also encompass the preservation of patients' motor functions [36, 37]. CR's involvement in protecting cognitive domains may span various aspects, including overall cognitive performance, short-term memory, and executive functions. Moreover, the protective effects of CR on cognitive functions may vary with the progression of the disease. These effects might not fully manifest in the early stages but gradually strengthen over time until reaching a turning point where the impact of neuropathology overwhelms CR's ability to protect cognitive functions [36, 37]. These findings underscore the substantial influence of CR on cognitive functions in individuals with PD.

The glucocerebrosidase (*GBA*) gene encodes glucocerebrosidase (GCase) [38], impacting PD patients' onset and severity of motor/nonmotor symptoms, including cognitive decline [39]. *GBA* mutation carriers have a two-fold increased risk of dementia [40], and the severity of disease or symptoms associated with *the GBA* genotype correlates with the rate of progression of cognitive impairment [39]. In a cross-sectional study, an association was found between *GBA* polymorphisms and cognitive performance in patients with Parkinson's disease [41]. Pathogenic mutations within the *GBA* gene, as well as a polymorphism (e.g., rs2230288), were associated with a higher prevalence of dementia and declines in working memory, executive function, and visuospatial abilities [41]. The study suggests that different *GBA* variants may have heterogeneous effects on the motor and cognitive phenotypes of Parkinson's disease [41]. In other words, different *GBA* mutations may also play varying roles in the cognitive impairment of *GBA*-PD patients [42], warranting further investigation in future studies.

GBA mutations can impair GCase activity and disrupt lysosomal function, potentially interfering with α-synuclein metabolism [43]. Experimental models have demonstrated that increased expression of α-synuclein can lead to decreased GCase activity. A malfunctioning *GBA* leads to increased α-synuclein levels, fostering its prion-like propagation and accumulation, consequently playing a role in the progression of cognitive impairment [43]. Toxic forms of α-synuclein, including oligomers and fibrils, can accumulate in presynaptic terminals of PD patients years before symptom onset [44]. This accumulation of toxic α-synuclein disrupts levels of synaptic proteins, leading to synaptic dysfunction. Consequently, synaptic transmission and plasticity are affected in PD [45]. These findings underscore the impact of *GBA* mutations on GCase activity, which contributes to the accumulation of α-synuclein and may influence synaptic plasticity in PD patients.

The presence of a high CR alone does not provide a guarantee of protection against dementia, as genetic factors exert a significant influence on an individual's susceptibility to developing dementia [46]. Several investigations have examined the ramifications of CR and gene interactions on cognitive function within various diseases and the context of healthy aging, and have manifested the salient role of nature-nurture interplay in influencing cognitive function [47, 48]. Nevertheless, it is noteworthy to mention that, to the best of our knowledge, no such investigations have been undertaken within the PD population.

First, our research embraces life as an ongoing continuum, delineated into three distinct phases: early, middle, and late life. These phases correspond to key cognitive influences throughout the aging process, encompassing education, occupation, and social engagement. Next, the literature review reveals that *GBA* mutations may indirectly impact the buildup of toxic α-synuclein, so synaptic plasticity may gradually deteriorate with age. Notably, there are divergent gene expression patterns between Europeans and Asians in *GBA* rs9628662. Therefore, we hypothesized that *GBA* variants may affect synaptic plasticity, and their effects may interact with cognitive reserve to affect cognitive performance, and this effect may be particularly present in Asian patients with Parkinson's disease. We will use the moderation model to study genetic predisposition and acquired CR in shaping the cognitive performance of PD

patients. Our primary goal is to uncover potential variations in the impact of different stage's CR on cognitive function among PD patients, with careful consideration of their specific *GBA* genotypes.

Methods

We employed a cross-sectional study approach, conducting interviews with all participants. During these interviews, we gathered comprehensive data on participants' CR, cognitive abilities, demographic details, and clinical information, including the Levodopa equivalent daily dosage and disease duration (from the onset of symptoms to the day of neuropsychological testing) for PD patients.

Participants

A total of 318 participants were recruited for this study, categorized into two groups: 150 healthy controls (HC) and 168 PD patients. PD patients were included based on outpatient diagnoses by neurologists following the Movement Disorder Society PD Criteria [49], excluding those with atypical parkinsonism features or an onset age below 50 years. The HC group comprised community-recruited adults aged 50 or older. Both groups excluded participants with a history of brain surgery, comorbid psychiatric or neurological disorders, and inability to provide informed consent.

Measurement of CR

We conceptualized an individual's lifespan as consisting of three distinct stages: early, middle, and late life, each associated with significant CR factors.

Early life: We employed the years of formal education an individual had completed to gauge their early CR.

Middle life: We utilized the complexity of an individual's work responsibilities as the index for CR during middle age. The Standard Occupational Classification of the Republic of China[50] was employed to assess the level of CR. Taiwan's unique occupational classification system categorizes professions according to their technical complexity and professional expertise. It comprises four distinct categories, spanning from level 1, which encompasses fundamental labor roles, to level 4, which encompasses positions requiring high expertise and intricate problem-solving capabilities.

Late life: The Social Functioning Scale for Patients with PD (PDSFS) [50] was used to evaluate late-life CR. This scale was filled out by either the patients themselves or, in cases where patients were incapacitated (e.g., illiterate or the patient moves slowly, and the examiner is worried that the patient will be too tired if the time is too long), by their primary caregivers, usually family members. The majority of participants have retired, with a few having reached retirement age. The PDSFS primarily assesses the participants' experiences over the past month. In this study, three factors of the PDSFS were employed: Family Life, Hobbies and Self-Care (FHS); Interpersonal Relationship and Recreational Leisure (IRRL); and Social Bond (SB). Additionally, the total PDSFS scores were considered a measure of our study's late-life CR.

Neuropsychological assessment

In addition to taking the Mini-Mental State Examination (MMSE) [51] to assess general cognitive function, all participants also underwent neuropsychological testing covering five cognitive domains: executive function, attention/working memory, visuospatial function, memory, and language [52]. The categories and perseverative errors of the Modified Wisconsin Card Sorting Test (M-WCST) [51] and Category Verbal Fluency (fruit, fish, and vegetable) measured executive function. The attention and working memory assessment was conducted using the digit span subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) [51] and the attention subtest of the MMSE. A pentagon copy test of MMSE measured the visuospatial function. Immediate and delayed recall memory functions were assessed using the Logical Memory and Visual Reproduction subtests of the Chinese version of the Wechsler Memory Scale-Third Edition (WMS-III) [51]. The assessment of language ability, encompassing naming, repetition, verbal comprehension, and writing, was conducted using the language subtest of the MMSE. Scale scores were employed for the subtests of the WAIS-III and WMS-III, while corrected scores were applied in the M-WCST. Raw scores were utilized for statistical analysis in all other relevant assessments.

Genetic analysis

Peripheral blood leukocytes were obtained from all participants for genomic DNA extraction. Genotyping of selected Single-Nucleotide Polymorphisms (SNPs) was conducted using the C2-58 Axiom Genome-Wide TWB 2.0 Array Plate on the Affymetrix GeneChip platform, following a previously established protocol [53].

Data analysis

The normality of the variables was assessed using the Kolmogorov–Smirnov test. T-tests were used for normally distributed variables, while Mann–Whitney U-tests were used for non-normally distributed variables. Chi-square

tests were used for categorical variables such as gender and occupational level. The significance of statistical analysis results other than Hardy–Weinberg equilibrium (HWE) will be corrected by Benjamini–Hochberg correction and displayed in tables and figures with q-values, and the q-value < 0.05 was significant.

HWE was used to identify genotyping or sampling errors of all SNPs (Supplementary Table S1). Meanwhile, minor allele frequency (MAF) was calculated, and SNPs with MAF > 10% were included as target SNPs. According to Supplementary Table S1, the SNP rs9628662 of *GBA* with an MAF of 31.108% was selected, and the rs9628662 genotype was categorized as TT + TG and GG.

In our study, we utilized PROCESS 4.2 for linear regression analysis to investigate how cognitive function is influenced by the interaction between CR and genotype (TT + TG/GG), and to assess if these interactions vary between PD and HC groups. Model 3 positions CR as the independent variable, with rs9628662 genotype and study group (PD vs. HC) as moderators. The neuropsychological test scores were used as the dependent variable.

Considering the complexity of these interactions, our analysis encompassed six independent variables for cognitive reserve (Education, Occupational Level, PDSFS-FHS, PDSFS-IRRL, PDSFS-SB, and PDSFS-total score) and 12 neurocognitive test performances as dependent variables. This resulted in a comprehensive set of 72 analyses, factoring in genotypes (TT + TG, GG) and disease status (HC group and PD group), without modifying the moderator variables. Because we undertook a total of 72 interaction analyses, we also employed the Benjamini–Hochberg correction method to address the challenge of multiple comparisons inherent in such a comprehensive analysis. Mean-centering was applied to the continuous variables to minimize multicollinearity, and gender was included as a control variable due to significant group differences (as shown in Table 1). All statistical analyses were performed using SPSS version 26.

Results

Characteristics, cognitive reserve, and cognitive functions of participants with different *GBA* SNPs

Table 1 shows the demographic information, including gender, age, disease duration, Levodopa equivalent dosage, cognitive reserve index, and the performance of various cognitive functions for each group. Additionally, the ranges of minimum and maximum values for age and disease duration are provided.

In the comparison between the two groups, there were significant differences between the two groups in terms of gender, occupational level, score of the PDSFS [50], and most of the cognitive function performance. The PD cohort exhibited significantly inferior cognitive function (Table 1).

Data stratified by genotype within different groups were presented in Table 2. Most demographic variables, clinical characteristics, and cognitive functions did not significantly differ between the groups, except for the performance of the language subtest test of MMSE in the HC group and Logical Memory II of WMS-III in the 168 PD patients.

Supplementary Table S1 provides an overview of our study's examined SNPs. Except for SNPs for which HWE cannot be calculated, the remaining SNPs, including rs9628662, demonstrated genotype frequencies consistent with HWE.

Interaction between cognitive reserve, rs9628662 genotype, and group

A total of seventy-two interaction analyses were performed, examining the influence of CRs as independent variables and *GBA* genotypes and disease status as moderators on various cognitive functions as dependent variables. Out of the seventy-two analyses conducted, a subset of six analyses revealed significant interactions, as highlighted in Table 3. Table 4 provided a comprehensive overview of the six significant interactions identified in Table 3, and each model presented constant, main effects of independent and moderator variables, the interaction of pairwise variables, and control variables (i.e., gender).

Effect of CR on cognitive function in different groups and different *GBA* genotypes

Following identifying a statistically significant q-value indicating the interaction between CR, *GBA* genotypes, and disease status, the Fig. 1 was employed to elucidate the effects of this interaction on cognitive function. Notably, the Fig. 1 offers valuable insights by emphasizing the influence of CR within specific genotype-based groups, thereby enhancing our understanding of the intricate relationships between these variables and their impact on cognitive outcomes.

Our results are categorized by CR during three life stages, offering a comprehensive overview:

Early life: Education significantly impacts the language performance of individuals with TT + TG and GG genotypes in PD ($q = 0.0020$, $q < 0.0001$) and HC ($q < 0.0001$, $q = 0.0170$). People with better education will have better language performance.

Middle life: The higher the Occupational level, the better the cognitive function performance, and this performance mainly occurs in the following situations.

Table 1 Demographic information, clinical characteristics, and cognitive functions in study groups

	HC ($n=150$)		PD ($n=168$)		PD ($n=94$)[±]		q-value[‡]	Post Hoc[‡]	q-value[†]	Post Hoc[†]
	Mean	SD	Mean	SD	Mean	SD				
Male%	25.3%		68.5%		69.1%		**0.002**[a]		**0.002**[a]	
Age, years (range)	65.42 (50–82)	6.84	66.66 (52–84)	7.12	66.83 (52–84)	7.21	0.133[b]		0.141[b]	
Disease Duration, years (range)	–	–	5.26 (0–23)	4.50	5.04 (0–23)	4.51				
Levodopa equivalent dosage	–	–	512.85	405.86	477.29	422.80				
MMSE (range)	27.51 (16–30)	2.04	26.71 (13–30)	3.11	26.14 (13–30)	3.00	0.090[c]		**0.002**[c]	HC > PD
Education, years (range)	12.81 (0–20)	3.40	12.09 (0–23)	4.13	12.08 (0–18)	4.15	0.264[c]		0.390[c]	
Occupational Level%							**0.009**[a]		**0.023**[a]	
Level I	3.3%		3.0%		5.3%			HC > PD		HC < PD
Level II	46.0%		48.8%		52.1%			HC < PD		HC < PD
Level III	29.3%		14.9%		12.8%			HC > PD		HC > PD
Level IV	21.3%		33.3%		29.8%			HC < PD		HC < PD
Social Function										
PDSFS-FHS	24.68	3.83	–	–	23.53	4.64	–	–	0.076[c]	
PDSFS-IRRL	21.79	4.53	–	–	23.20	4.00	–	–	**0.019**[c]	HC < PD
PDSFS-SB	8.19	3.37	–	–	5.64	3.21	–	–	**0.002**[c]	HC > PD
PDSFS-Total score	54.66	9.14	–	–	52.37	8.69	–	–	**0.029**[c]	HC > PD
Executive Function										
M-WCST-Category	4.94	1.51	3.73	1.90	3.52	1.79	**0.002**[c]	HC > PD	**0.002**[c]	HC > PD
M-WCST-preservative error	4.50	4.78	8.06	9.35	9.45	10.50	**0.002**[c]	HC > PD	**0.002**[c]	HC > PD
Category fluency	39.82	8.41	32.45	8.31	32.69	8.17	**0.002**[c]	HC > PD	**0.002**[c]	HC > PD
Attention/Working Memory										
Digit span of the WAIS-III	12.63	2.65	11.14	2.84	11.27	2.91	**0.002**[c]	HC > PD	**0.002**[c]	HC > PD
Attention subtest of MMSE	7.59	0.73	7.20	1.14	7.12	1.16	**0.003**[c]	HC > PD	**0.002**[c]	HC > PD
Visuospatial Function										
Pentagon copy subtest of MMSE	0.95	0.21	0.85	0.36	0.82	0.39	**0.004**[c]	HC > PD	**0.002**[c]	HC > PD
Memory										
LM-I of the WMS-III	12.39	2.83	10.17	3.34	10.14	3.39	**0.002**[c]	HC > PD	**0.002**[c]	HC > PD
LM-II of the WMS-III	12.79	2.66	9.85	3.89	10.03	3.90	**0.002**[c]	HC > PD	**0.002**[c]	HC > PD
VR-I of the WMS-III	11.35	2.72	10.01	3.09	10.01	3.09	**0.002**[c]	HC > PD	**0.002**[c]	HC > PD
VR-I of the WMS-III	10.93	2.47	9.55	2.67	9.50	2.75	**0.002**[c]	HC > PD	**0.002**[c]	HC > PD
Language										
Language subtest of MMSE	4.75	0.53	4.76	0.56	4.66	0.67	0.599[c]		0.458[c]	

All q-values presented in the table is the significance after Benjamini–Hochberg correction

Bold values represent statistically significant findings that have been adjusted for multiple comparisons

HC healthy control, *PD* Parkinson's disease, *PDSFS* Social Functioning Scale for Patients with PD, *FHS* Family Life Hobbies and Self-Care, *IRRL* Interpersonal Relationship and Recreational Leisure, *SB* Social Bond, *M-WCST* Modified Wisconsin Card Sorting Test, *WAIS-III* Wechsler Adult Intelligence Scale-Third Edition, *MMSE* Mini-Mental State Examination, *LM* Logical memory, *WMS-III* Wechsler Memory Scale-Third Edition, *VR* Visual Reproduction

[a]Chi-square

[b]*T*-test; [c]Mann–Whitney U-test

[±]all participants have PDSFS score; [‡]Comparison of two groups between all HC and 168 PD. Patients

[†]Comparison of two groups between HC and 94 PD patients

Occupational level significantly influenced the digit span performance on WAIS-III in the GG genotype of the PD group ($q<0.0001$) and the TT + TG genotype of the HC group ($q=0.0440$). Additionally, the occupational level had a significant impact on WMS-III Logical Memory I performance in the GG genotype of the PD group

Table 2 Demographic information, clinical characteristics, and cognitive function stratified by *GBA* genotypes of each group

	HC				PD				PD±							
	TT + TG (*n* = 76)		GG (n = 74)		TT + TG (*n* = 96)		GG (*n* = 72)		TT + TG (*n* = 57)		GG (*n* = 37)		*q*-value$^{\varphi}$	*q*-value$^{\psi}$	*q*-value$^{\phi}$	Post hoc
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD				
%Male	26.3%		24.3%		62.5%		76.4%		66.7%		73.0%		0.880[a]	0.290[a]	0.716[a]	
Age, years	66.36	6.97	64.46	6.61	66.14	6.73	67.36	7.61	66.54	6.58	67.27	8.16	0.385[b]	0.478[b]	0.716[b]	
Disease Duration, years	–	–	–	–	4.99	4.49	5.61	4.51	4.98	4.77	5.14	4.13		0.478[c]	0.716[c]	
LED	–	–	–	–	491.33	416.17	541.56	392.74	467.24	443.80	492.77	374.30		0.478[c]	0.716[c]	
MMSE	27.46	2.43	27.57	1.54	26.90	3.02	26.46	3.23	26.49	2.65	25.59	3.42	0.796[c]	0.478[c]	0.567[c]	
Education, years	12.82	3.33	12.81	3.49	12.77	3.57	11.18	4.65	12.76	3.48	11.03	4.87	0.880[c]	0.133[c]	0.567[c]	
Occupational Level%													0.876[a]	0.478[a]	0.716[a]	
Level I	3.9%		2.7%		2.1%		4.2%		3.5%		8.1%					
Level II	40.8%		51.4%		53.1%		43.1%		56.1%		45.9%					
Level III	32.9%		25.7%		11.5%		19.4%		10.5%		16.2%					
Level IV	22.4%		20.3%		33.3%		33.3%		29.8%		29.7%					
Social Function																
PDSFS-FHS	25.13	3.08	24.22	4.44	–	–	–	–	23.95	4.49	22.89	4.87	0.512[c]	–	0.698[c]	
PDSFS-IRRL	21.22	4.24	22.38	4.77	–	–	–	–	23.05	4.08	23.43	3.91	0.203[c]	–	0.716[c]	
PDSFS-SB	7.70	3.47	8.69	3.22	–	–	–	–	5.79	3.51	5.41	2.71	0.385[c]	–	0.855[c]	
PDSFS-Total score	54.05	8.13	55.28	10.10	–	–	–	–	52.79	8.87	51.73	8.49	0.385[c]	–	0.716[c]	
Executive Function																
M-WCST-Category	5.06	1.56	4.81	1.45	3.71	1.92	3.77	1.88	3.33	1.91	3.82	1.56	0.512[c]	0.999[c]	0.716[b]	
M-WCST-preservative error	4.29	4.29	4.72	5.25	8.27	9.68	7.78	8.96	9.46	10.73	9.43	10.30	0.876[c]	0.999[c]	0.716[c]	
Category fluency	40.18	8.99	39.45	7.81	32.97	8.90	31.75	7.45	33.23	9.10	31.86	6.53	0.876[b]	0.478[b]	0.716[c]	
Attention/ Working Memory																
Digit span of the WAIS-III	12.63	2.73	12.64	2.59	11.53	2.85	10.61	2.76	11.49	2.92	10.92	2.90	0.880[c]	0.228[c]	0.716[c]	
Attention subtest of MMSE	7.72	0.58	7.45	0.85	7.26	1.08	7.13	1.21	7.23	0.95	6.95	1.43	0.203[c]	0.680[c]	0.716[c]	
Visuospatial																
Pentagon copy of MMSE	0.95	0.22	0.96	0.20	0.88	0.33	0.82	0.39	0.84	0.37	0.78	0.42	0.880[c]	0.478[c]	0.716[c]	
Memory																
LM-I of the WMS-III	12.37	2.92	12.41	2.76	10.73	3.50	9.42	2.98	10.79	3.71	9.14	2.58	0.894[c]	0.124[c]	0.138[c]	

Table 2 (continued)

	HC				PD				PD±						
	TT + TG (n = 76)		GG (n = 74)		TT + TG (n = 96)		GG (n = 72)		TT + TG (n = 57)		GG (n = 37)		q-value$^{\varphi}$	q-value$^{\Psi}$	q-value$^{\phi}$	Post hoc
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD				
LM-II of the WMS-III	12.93	2.83	12.65	2.48	10.65	3.98	8.78	3.52	10.84	4.12	8.78	3.21	0.876[c]	**0.019**[c]	0.138[c]	TT + TG > GG$^{\Psi}$
VR-I of the WMS-III	11.54	2.49	11.15	2.95	10.16	3.00	9.82	3.21	10.35	3.01	9.49	3.14	0.793[c]	0.478[c]	0.567[c]	
VR-I of the WMS-III	11.04	2.40	10.82	2.56	9.72	2.80	9.33	2.50	9.79	2.94	9.05	2.39	0.876[c]	0.531[c]	0.698[c]	
Language																
Language subtest of MMSE	4.63	0.61	4.86	0.42	4.78	0.51	4.72	0.63	4.74	0.55	4.54	0.80	**0.042**[c]	0.800[c]	0.698[c]	TT + TG < GG$^{\varphi}$

Abbreviations: please see Table 1

Bold values represent statistically significant findings that have been adjusted for multiple comparisons

All q-values presented in the table is the significance after Benjamini–Hochberg correction

[a]Chi-square

[b]T-test

[c]Mann–Whitney U-test

[±]All participants have PDSFS score

[φ]Comparison of two genotypes within HC group; [Ψ]Comparison of two genotypes within 168 PD patients; [Φ]Comparison of two genotypes within 94 PD patients

($q < 0.0001$) and the TT + TG genotype of the HC group ($q < 0.0001$). Similarly, occupational level influenced the MMSE language performance in the GG genotype of the PD group ($q = 0.0040$) and the TT + TG genotype of the HC group ($q = 0.0040$).

Late life: Before the significance correction, the higher total score of PDSFS seemed to affect higher WMS-III Logical Memory I performance in the TT + TG genotype of the PD group ($p = 0.0133$); however, after the significance was corrected, it was not found that the total score of PDSFS affected any group's cognitive function. In addition, although the total score of PDSFS interacted with the two moderators on the MMSE pentagon copy, no significant results were observed in any group.

Discussion

Cognitive reserve refers to the accumulation of cognitive stimuli from life experiences, originating in early life and accumulating over time, which then influences the observed cognitive function in older age. Additionally, the genetic component is predetermined at birth, constituting inherent individual differences in humans, which also impact the expression of cognitive function. Taking all the above into consideration, our cognitive function performance is influenced by both cognitive reserve and genetics. This study explores how genes interact with a person's cognitive reserve in early, middle, and late life to affect a person's cognitive function, especially in PD patients. In our interaction results, we found that if we only explore the impact of cognitive reserve on overall cognitive function, there seems to be no result worthy of further investigation. Past studies have mentioned that there is heterogeneity in cognitive domains among PD patients [8]. The above findings make us more convinced that we need to explore the performance of different cognitive domains in PD patients. In our study, we found that education significantly affected the language function of all participants. Occupation history specifically affects the attention/working memory, memory, and language function of PD patients with GG genotype *GBA* rs9628662 and healthy elderly with genotype T. Such differences may be because *GBA* mutations begin to accumulate toxic α-synuclein in PD patients around middle age, affecting synaptic plasticity and whether cognitive reserve can be effectively established in middle age. Our research findings demonstrate that the establishment of cognitive reserve at various stages of life has an impact on the cognitive function of PD patients with distinct *GBA* genotypes.

Table 3 The interaction between cognitive reserve, rs9628662 and group (i.e., PD and HC) on cognitive function

Cognitive function (Outcome variable)		CR × rs9628662 × group					
		Education[a] × rs9628662 × group	Occupational Level[a] × rs9628662 × group	PDSFS-FHS[b] × rs9628662 × group	PDSFS-IRRL[b] × rs9628662 × group	PDSFS-SB[b] × rs9628662 × group	PDSFS-Total score[b] × rs9628662 × group
General cognition	MMSE	0.9050	0.2040	0.5020	0.9250	0.4890	0.5340
Executive function	M-WCST-Category	0.2510	0.7390	0.5930	0.5480	0.4730	0.9630
	M-WCST-preservative error	0.3530	0.7060	0.8720	0.1400	0.6500	0.5900
	Category fluency	0.9700	0.8720	0.4210	0.8870	0.2380	0.9380
Attention and Working memory	Digit span of the WAIS-III	0.5500	**0.0080***	0.8440	0.8870	0.1820	0.9690
	Attention subtest of MMSE	0.6120	0.6660	0.4100	0.8200	0.2630	0.2150
Visuospatial function	Pentagon copy subset of MMSE	0.3040	0.9200	0.1510	0.0740	0.5520	**0.0400***
Memory	LM-I of the WMS-III	0.7860	**0.0210***	0.1770	0.1680	0.1980	**0.0340***
	LM-II of the WMS-III	0.8870	0.0950	0.9800	0.3830	0.1080	0.3220
	VR-I of the WMS-III	0.2610	0.9320	0.5140	0.2210	0.2490	0.1500
	VR-II of the WMS-III	0.6650	0.4120	0.9750	0.9470	0.8870	0.9610
Language	Language subset of MMSE	**0.0380***	**0.0430***	0.1640	0.3700	0.9590	0.3790

Bold values represent statistically significant findings that have been adjusted for multiple comparisons

The significance presented in the table is the significance after Benjamini–Hochberg correction (*q*-value), and the results in this table were performed by PROCESS model 3; [a]150 HC participants & 168 PD patients; [b]150 HC participants & 94 PD patients

Moderator 1 is *GBA* rs9628662 and Moderator 2 is Group (PD/ HC)

Abbreviations: please see Table 1

CR affects cognitive function in the specific life stage according to the distinct *GBA* rs9628662 genotypes, especially in PD patients.

We observed that early-life educational attainment impacted the language abilities of all participants, irrespective of their genotype or group. During middle adulthood, occupation, a prominent cognitive stimulus during this stage, accumulated CR may influence attention/working memory, episodic memory, and language in PD patients with genotype GG in old age. In contrast, among healthy elderly participants, occupation affected attention/working memory, episodic memory, and language ability in genotype T carriers. CR established at different stages may have different protective effects on cognitive function in later life, and the impact of CR on cognitive function was also affected by different *GBA* genotypes in the PD cohort. Education may represent a particularly potent form of CR, influencing language function in all individuals. In middle adulthood, occupation aligned with this life phase impacted PD patients within the GG genotype group. However, social function may not offer the same protective effects in late adulthood.

In a previous genome-wide study involving Caucasians, the *GBA* rs9628662 gene was mentioned, but no association with PD was found [54]. Interestingly, data from the dbSNP website reveals that the major allele (T > G) in Europeans is opposite to the major allele (G > T) in Asians [55]. Given the absence of specific findings in the study conducted by Edward and colleagues (2010) [54] and the information available on the dbSNP, this research infers that the GG group of rs9628662 corresponds to the GCase low activity group. Our findings support our initial hypothesis, indicating that hypoactive genotypes (GG) may contribute to α-synuclein accumulation and impaired synaptic plasticity in

Table 4 Comprehensive model results of these six significant interactions in Table

Cognitive function (Outcome variable)	Parameters	$N^{\pm}$	Coefficient	se	*t*	*q*-value
Digit span of the WAIS-III	constant	318	12.7378***	0.7912	16.0994	**< 0.0001**
	occupational level	318	– 1.5677	0.8172	– 1.9184	0.0840
	rs9628662	318	– 1.1616*	0.5116	– 2.2703	**0.0430**
	group	318	0.0030	0.1874	0.0162	0.9870
	occupational level × rs9628662	318	1.6093**	0.5389	2.9864	**0.0090**
	occupational level × group	318	0.5632*	0.2104	2.6770	**0.0180**
	rs9628662 × group	318	0.1901	0.1214	1.5656	0.1520
	occupational level × rs9628662 × group	318	– 0.4311**	0.1363	– 3.1633	**0.0080**
	gender	318	– 0.3869	0.3444	– 1.1235	0.2950
Pentagon copy of MMSE	constant	244	1.3404	1.1446	1.1711	0.3620
	PDSFS-Total score	244	0.2971	0.1361	2.1836	0.0520
	rs9628662	244	– 0.7961	0.7660	– 1.0393	0.3840
	group	244	0.1913	0.3351	0.5707	0.5680
	PDSFS-Total score × rs9628662	244	– 0.2327	0.0991	– 2.3483	0.0520
	PDSFS-Total score × group	244	– 0.0863	0.0391	– 2.2074	0.0520
	rs9628662 × group	244	0.1887	0.2227	0.8472	0.4470
	PDSFS-Total score × rs9628662 × group	244	0.0631*	0.0242	2.6118	**0.0400**
	gender	244	1.4885*	0.5556	2.6790	**0.0400**
LM-I of the WMS-III	constant	318	12.3806***	0.8712	14.2118	**< 0.0001**
	occupational level	318	– 0.9052	0.8998	– 1.0060	0.3550
	rs9628662	318	– 1.6273*	0.5633	– 2.8887	**0.0180**
	group	318	0.0085	0.2063	0.0414	0.9670
	occupational level × rs9628662	318	1.2632	0.5933	2.1290	0.0510
	occupational level × group	318	0.6044 *	0.2317	2.6091	**0.0210**
	rs9628662 × group	318	0.2843	0.1337	2.1264	0.0510
	occupational level × rs9628662 × group	318	– 0.3927 *	0.1501	– 2.6168	**0.0210**
	gender	318	– 0.5267	0.3792	– 1.3889	0.2130
LM-I of the WMS-III	constant	244	12.8353***	1.1821	10.8578	**< 0.0001**
	PDSFS-Total score	244	0.3234*	0.1309	2.4716	**0.0340**
	rs9628662	244	– 2.1706*	0.7829	– 2.7727	**0.0270**
	group	244	– 0.0636	0.2461	– 0.2582	0.8580
	PDSFS-Total score × rs9628662	244	– 0.1847	0.0898	– 2.0576	0.0520
	PDSFS-Total score × group	244	– 0.0695*	0.0284	– 2.4511	**0.0340**
	rs9628662 × group	244	0.3517*	0.1628	2.1603	**0.0480**
	PDSFS-Total score × rs9628662 × group	244	0.0437*	0.0185	2.3634	**0.0340**
	gender	244	– 0.0776	0.4320	– 0.1797	0.8580
Language subset of MMSE	constant	318	4.8237***	0.1465	32.9192	**< 0.0001**
	education	318	– 0.0018	0.0380	– 0.0485	0.9610
	rs9628662	318	0.0064	0.0968	0.0657	0.9610
	group	318	– 0.0784	0.0348	– 2.2544	0.0560
	education × rs9628662	318	0.0379	0.0232	1.6296	0.1560
	education × group	318	0.0249*	0.0098	2.5398	**0.0380**
	rs9628662 × group	318	0.0412	0.0227	1.8103	0.1280
	education × rs9628662 × group	318	– 0.0153*	0.0061	– 2.5121	**0.0380**
	gender	318	– 0.0431	0.0632	– 0.6825	0.6370
Language subset of MMSE	constant	318	4.9523***	0.1568	31.5846	**< 0.0001**
	occupational level	318	– 0.1105	0.1620	– 0.6826	0.5570
	rs9628662	318	– 0.1332	0.1014	– 1.3133	0.2440
	group	318	– 0.0920*	0.0371	– 2.4762	**0.0410**
	occupational level × rs9628662	318	0.1779	0.1068	1.6663	0.1450

Table 4 (continued)

Cognitive function (Outcome variable)	Parameters	$N^{\pm}$	Coefficient	se	*t*	*q*-value
	occupational level × group	318	0.0911	0.0417	2.1850	0.0530
	rs9628662 × group	318	0.0614*	0.0241	2.5526	**0.0410**
	occupational level × rs9628662 × group	318	– 0.0636*	0.0270	– 2.3562	**0.0430**
	gender	318	– 0.0151	0.0683	– 0.2208	0.8250

Bold values represent statistically significant findings that have been adjusted for multiple comparisons

The analysis results in this table were performed by PROCESS model 3, and the *q*-values presented in the table is the significance after the Benjamini–Hochberg correction. ±The study encompassed a cohort of 318 individuals, comprised of 150 HC participants and 168 individuals diagnosed with PD. Furthermore, within the total count of 244 individuals, there were 150 HC participants and 94 PD patients

Abbreviations: please see Table 1

*q < 0.05, **q < 0.01, ***q < 0.001

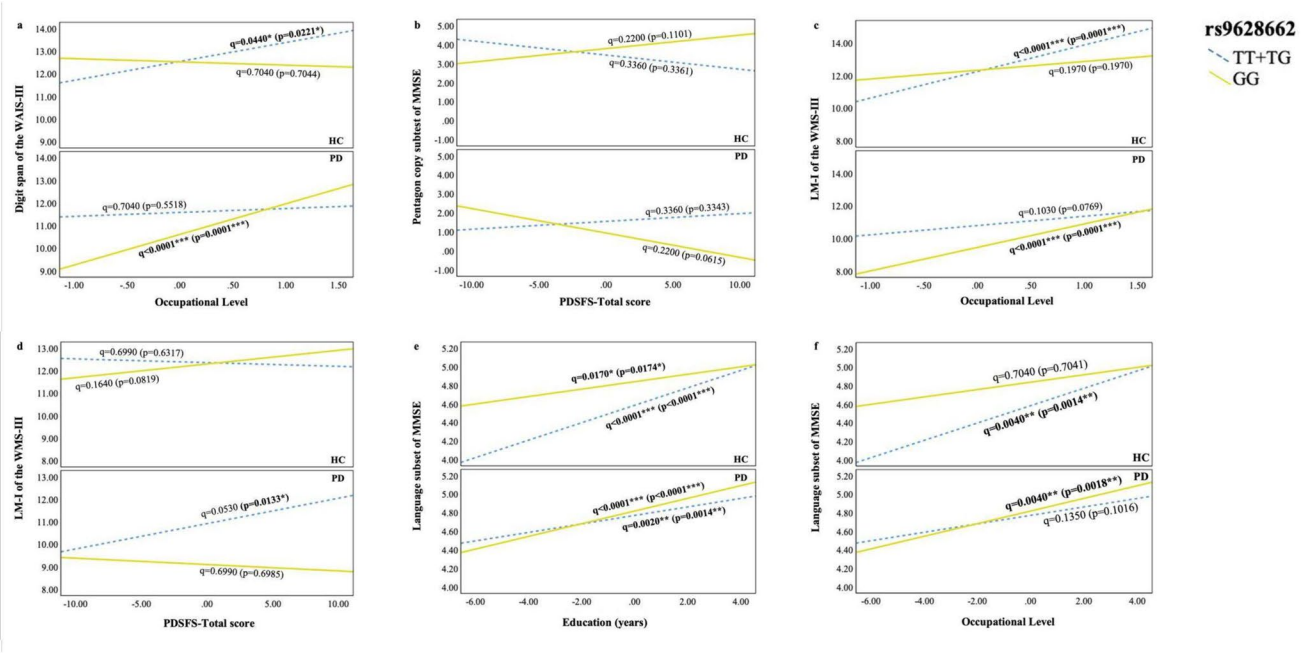

Fig. 1 Conditional direct effect of cognitive reserve on cognitive function in different genotypes (TT + TG/ GG) in each group (PD/HC).The variability in the influence of cognitive reserve on cognitive function across different life stages (i.e., early, middle, and late stage), considering the distinctions of the group (i.e., PD and HC) and genotype (i.e., TT + TG and GG). In terms of attention/working memory performance, **a** mid-life occupational complexity affected the performance of PD patients belonging to the GG gene and healthy participants carrying the T genotype. Regarding visuospatial performance, **b** social function did not affect the performance. Turning to memory performance, **c** mid-life occupational complexity influenced performance in PD patients with GG genes and healthy participants with T genotypes, and **d** the p-value before correction showed that in the late stage, social function only affected episodic memory performance in patients with PD with T carriers. Finally, in language performance it was found that **e** early education affected language performance in all participants, **f** mid-life occupational complexity demonstrated its influence on the performance of PD patients with GG genes and healthy individuals with T genotypes. All *q*-values reported in the table underwent the Benjamini–Hochberg correction, while the uncorrected p-values are presented in parentheses. It should be noted that PROCESS will further analyze the conditional direct effect only when the three variables interact. Therefore, only analyzes with significant results for the interaction of the three variables are shown in the figure. *q < 0.05, **q < 0.01, ***q < 0.001; *p < 0.05, **p < 0.01, ***p < 0.001

PD patients. Subsequently, compromised synaptic plasticity affects the role of CR. The accumulation of α-synuclein typically initiates during middle adulthood in PD patients [44], a phase where occupation plays a pivotal role as a form of CR. We postulate that the onset of α-synuclein accumulation and the subsequent decline in synaptic plasticity necessitate sufficient job complexity to manifest the impact of occupation on cognitive function. As a result, the influence of CR on cognitive function becomes apparent during this particular life stage. Hence, we speculate that this is why late-life cognitive performance in the GG genotype group of PD patients is influenced by midlife occupational level,

as evidenced by our results. It is speculated that in terms of *GBA* rs9628662 activity, CR is more able to establish its protection in individuals with T carriers. Our research findings also revealed differences between the HC group and the PD group.

Regarding the late adulthood stage, our findings indicate a diminished presence of the protective impact of social function on cognitive functioning as individuals transition into this phase of life. It is important to acknowledge that our study's available social function data was relatively limited, encompassing 94 PD patients. Despite the modest sample size, the significance of the results, as indicated by the uncorrected p-value, persisted below the conventional threshold of 0.05. This suggests that social function may exclusively influence episodic memory in PD patients carrying the genotype T during late adulthood. This observation implies that α-synuclein accumulation may have attained a substantial level, and PD patients within the GG genotype group consistently displayed impaired synaptic plasticity, resulting in reduced effectiveness of social functioning due to overall synaptic impairment. Consequently, the discernible influence of social functioning on episodic memory seems to be confined to patients with the genotype T. Drawing upon the synthesis of the outcomes mentioned above, and our research outcomes propose that the impact of *GBA* hypoactivity on synaptic plasticity is notably pronounced among individuals diagnosed with PD.

Cognitive reserve and its impact on language, memory, and attention in PD

Our research findings unveiled a noteworthy correlation between educational attainment and language proficiency, independent of group or genotype. Existing studies have proposed that individuals with higher levels of education may initially experience declines in memory or executive function while preserving their language ability, such as naming [28]. Moreover, CR exerts a pivotal influence on cognitive function, particularly when considering early-life stimuli such as educational attainment. The influence of educational attainment on cognitive function has consistently demonstrated its significance, both in healthy older individuals and those with PD [34]. We posit that education should be regarded not only as an early-life stimulus but also as one with enduring implications for cognitive function in later life [24]. Therefore, the effects of this stimulus may transcend specific disease or genotype groups.

Our study offers compelling evidence supporting the protective role of occupation in cognitive function, aligning with previous research conducted in this domain. Previous investigations have highlighted that engaging in intellectually demanding and complex work can positively influence cognitive performance among older individuals [31]. These effects have been observed regarding enhanced cognitive performance [33, 35] and positive correlations with memory, particularly in individuals diagnosed with PD [32]. To comprehensively examine the protective effects of occupation on working memory, episodic memory, and language performance, it is crucial to consider the concept of occupation level, which encompasses the job's content and requisite skills [56]. Occupations characterized by higher levels and greater complexity necessitate a wealth of experience, knowledge, and communication skills to accomplish tasks effectively. Regardless of the occupation level, most jobs involve receiving and processing tasks, temporary storage of work-related information in memory, retrieval of content and details from previous tasks, and engagement in team communication. We propose that working memory, episodic memory, and language abilities are actively employed across a spectrum of tasks, ranging from low to high complexity. The key distinguishing factor lies in the degree of complexity, which ultimately reflects variations in CR.

Within the scope of our study, social functions encompass various aspects, including FHS, IRRL, and SB. Before applying corrections, our preliminary findings revealed a noteworthy influence of social function on memory performance in individuals with PD. Previous research consistently underscores the association between leisure activities [30], social networks, social bond [29], and cognitive functions, such as global cognitive function, episodic memory, and executive function. This association may be attributed to the diverse range of social stimuli encountered, such as information, verbal and nonverbal messages, facial expressions, and language patterns [29]. Additionally, the sense of security, self-esteem, and control fostered by social bonding can counteract the detrimental effects of stress on the brain [29]. It is conceivable that, apart from the factors mentioned above, interactions within these domains involve the recollection of relationships, task completion, and the utilization of acquired experience and knowledge. A higher score in social function indicates more extensive stimulation across these dimensions, ultimately facilitating the preservation of cognitive abilities.

Our study mentioned how cognitive reserve affects the cognitive domain performance of PD patients. However, it still needs to be noted that cognitive reserve is not permanent for the cognitive function performance of PD patients [36, 37]. The protective effect of cognitive reserve on cognitive function is not fully apparent from the beginning of the disease, but increases over time and continues until the impact of neuropathology overwhelms the ability of CR to protect cognitive function [36, 37].Although cognitive reserves cannot prevent the inevitable decline, during the period when cognitive functions are still preserved, efforts

can be made to maintain the quality of life for patients and their families. This time also allows for preparation to face the disease and helps in reducing associated non-motor symptoms such as depression and anxiety. Therefore, we believe that a detailed understanding of cognitive reserve can still help future patient care.

Conclusion

We found that cognitive reserve established at different stages of life can be influenced by the *GBA* rs9628662 genotype and affect cognitive function in later years. We suggest that when investigating the impact of cognitive reserve on cognitive function, genotype information should be taken into comprehensive consideration. In the future, enhancing the precision of follow-up cognitive training becomes possible by validating the patient's genotype and assessing their cognitive reserve status. Furthermore, the *GBA* rs9628662 variant has received limited attention in the past, and there is an exact opposite gene expression pattern between Europeans and Asians. In other words, the *GBA* rs9628662 variant deserves further research in the Asian population.

Limitations

This study adopts a longitudinal perspective, viewing an individual's life as an ongoing performance. Nevertheless, it is important to exercise caution when interpreting the findings due to the cross-sectional design employed. Additionally, our study aimed to thoroughly investigate the relationship between cognitive reserve, genes, and cognitive function across different life stages; however, utilizing the MMSE as the assessment tool has limitations. Despite covering key cognitive domains relevant to our analysis, its brevity restricts the depth and breadth of cognitive assessment compared to more extensive neuropsychological batteries. This constraint may have hindered our ability to capture nuanced cognitive changes and correlations with genotype analyses accurately. Additionally, practical constraints in clinical research settings influenced our choice of assessment tools. Future research endeavors will incorporate a broader range of neuropsychological assessments to address these limitations and provide a more comprehensive understanding of the interplay between genetic factors, cognitive reserve, and cognitive functioning across different life stages.

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Data availability All the associated data not included in this paper are available upon reasonable request from Rwei-Ling Yu.

Declarations

Conflicts of interest The authors declare that there are no conflicts of interest relevant to this work.

Ethics approval Before enrollment, we ensured that all participants provided written informed consent in adherence to the ethical standards outlined in the 1964 Declaration of Helsinki. The research protocol and study procedures underwent rigorous scrutiny and received approval from the ethical research committees of Kaohsiung Medical University Hospital and National Cheng Kung University Hospital. All study aspects were conducted strictly with the approved guidelines and regulation.

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