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ORIGINAL ARTICLE

Correlation of Plasma Neuropeptide Y with Specific Cognitive Domains in Patients with Parkinson's Disease Cognitive Impairment

Ai-Rong Zhang [1, *], Min-Lu Wu [2, *], Wen-Jun Pang [3], Xian-Bin Ning [4], Yu-Jun Wu [2], Jin-Feng Pang [4]

[*] *These authors contributed equally to this work*
[1] *Reproductive Medicine Center, The Affiliated Hospital of Beihua University, Jilin City, Jilin Province, China*
[2] *Department of Neurology, No. 905 Hospital of PLA Navy, Shanghai City, China*
[3] *Department of Neurology, The Second Norman Bethune Hospital of Jilin University, Changchun City, Jilin Province, China*
[4] *Department of Neurosurgery, The Affiliated Hospital of Beihua University, Jilin City, Jilin Province, China*

SUMMARY

Background: **We aimed to investigate the correlation of plasma neuropeptide Y (NPY) with specific cognitive domains in patients with Parkinson's disease (PD) cognitive impairment (CI).**
Methods: **The study included thirty-six PD patients with normal cognitive function (PD-NC), 57 PD patients with mild cognitive impairment (PD-MCI), 30 PD patients with dementia (PDD), and 46 healthy individuals. Every patient underwent thorough clinical evaluations and neuropsychological examinations. Plasma NPY expression was assessed using ELISA. The effects of plasma NYP levels on PD-CI events or PDD were analyzed using univariate and multivariate logistic models. Multiple linear regression analyses were constructed to assess the independent associations of plasma NYP levels with z scores in 5 cognitive domains.**
Results: **Plasma NYP levels were reduced in patients with PD compared with healthy controls ($p < 0.001$). Plasma NYP levels were the highest in PD-NC patients and decreased with increasing CI, with the PDD group having the lowest plasma NYP levels. Multivariate logistic regression adjusted for years of education and UPDRS-III subscores showed a significant correlation between NYP and CI ($p = 0.005$). Plasma NYP was significantly correlated with a linear model between each of the 5 cognitive domains, including attention, executive function, language, memory, and visuospatial function.**
Conclusions: **Reduced plasma NPY levels are associated with CI in PD patients and are strongly correlated with 5 cognitive domains.**
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Correspondence:
Jin-Feng Pang
Department of Neurosurgery
The Affiliated Hospital of Beihua University
No. 12, Jiefang Middle Road
Jilin City, Jilin Province, 132011
China
Email: neurosurgeryp@sina.com

KEYWORDS

neuropeptide Y, Parkinson's disease, cognitive function, cognitive impairment, cognitive domains

INTRODUCTION

PD, or Parkinson's disease, is a condition that progressively degenerates the nervous system, affecting adults in middle and older age. Its main clinical symptoms are motor disorder and cognitive impairment (CI) [1]. CI manifests as mild CI (MCI) or dementia [2]. MCI can be present early in PD, and even in newly diagnosed PD

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patients, about 20% to 30% have comorbid MCI. It predicts future CI, including progression to Parkinson's disease dementia (PDD). In PD patients, the risk of developing dementia grows as the disease progresses, with rates as high as 30% at 5 years [3] and more than 80% at 20 years [4]. Early cognitive function screening in PD patients aids in detecting high-risk individuals for PDD, which may enable early diagnosis and intervention.

Clinically, simple and rapid screening tools for cognitive function include the mini mental state examination (MMSE), but it lacks assessments of executive functioning and attention [5]. Incorporating items that assess visuospatial, executive, and attention functions, Montreal cognitive assessment (MoCA) is more apt for screening CI in PD patients, but it emphasizes the sensitive detection of MCI [6]. Comprehensive neuropsychological suites of tests containing multiple cognitive domains can provide comprehensive and in-depth information. These tests typically contain multiple subtests, each of which provides an in-depth assessment of a cognitive domain, such as memory, executive function, language, attention, etc. [7].

Neuropeptide Y (NPY) is a hormone found extensively in both the central and peripheral systems [8], particularly in the brain, where it significantly influences appetite regulation, stress response, and cognitive functions. In the central system, NPY secretion is closely associated with several cognition-related brain regions (e.g., hippocampus, frontal cortex, etc.), which are closely related to cognitive functions such as learning and memory, and emotion regulation [9]. In addition, NPY has neuroprotective effects on the brain through mechanisms such as inhibiting neuronal apoptosis and promoting neuronal growth [10]. This protective effect may help to maintain the stability of cognitive functions. The action of NPY is mainly accomplished by binding to its receptors. These receptors are widely distributed in the brain and are involved in a variety of physiological and pathological processes. Binding of NPY to its receptors may affect cognitive function by regulating mechanisms such as neurotransmitter release and signaling. A recent study has shown that elevated plasma NPY is associated with a reduced risk of CI. However, few studies have reported the relevance of NPY to specific cognitive domains.

Therefore, the aim of this study was to assess the correlation of CI and NYP levels in patients with PD and to analyze the linear relationship between NYP and specific cognitive domains.

MATERIALS AND METHODS

Subjects

In this prospective study, 147 patients with PD aged 50 - 85 years, who agreed to participate in this study, were finally recruited from January 2018 through March 2024 at the Affiliated Hospital of Beihua University. The diagnosis of PD for each participant was determined according to the Diagnostic criteria for Parkinson's disease in China (2016 edition). Individuals who had experienced stroke, encephalitis, epilepsy, traumatic brain injury, cancer, significant cardiovascular events, or severe mental health issues were excluded from the patient group. Furthermore, 46 healthy controls matched by age and gender were recruited, with no history of neurological or psychiatric disorders.

Data collection and clinical assessment

Patients' age, gender, years of education, and disease duration (from diagnosis of PD to inclusion in this study) were obtained from electronic repository information. Motor dysfunction was evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS) [11]. PD severity was evaluated based on the Hoehn and Yahr stage [12] at the point of maximum severity, usually when the medication's effects had subsided. The degree to which an individual is predisposed to excessive daytime sleepiness (total score > 6, predisposition to sleepiness; > 11, excessive sleepiness; > 16, dangerous sleepiness) was assessed using Epworth sleepiness scale (ESS) [13]. Depressive symptoms (0 - 10, normal; 11 - 20, mild; 21 - 30, moderate-severe) were assessed using the geriatric depression scale [14].

For cognitive assessment, the MMSE [5] and the following comprehensive neuropsychological suite of tests in five cognitive domains were utilized. Attention and working memory were evaluated using symbol digit modalities test [15] and trail making test A (TMT-A) [16]. Executive function was judged by Stroop color-word test and TMT-B [17]. Language was assessed using Boston naming test and animal fluency test [18]. Memory was determined by auditory verbal learning test [19] and Rey-Osterrieth complex figure test (ROCF) [20]. Visuospatial function was evaluated by clock drawing test [21] and ROCF [20]. All participants remained on state (i.e., under their regular dopaminergic medication) during the cognitive assessment to lessen motor-related confounding effects. In addition, 80 age-, education-, and gender-matched healthy controls were recruited to obtain population normative data (Supplementary Table 1).

Using the National Mortality Surveillance System (NMSS), patients were evaluated for non-motor symptoms, which included cardiovascular, sleep, and fatigue issues, mood and cognitive changes, perception and hallucinations, attention and memory, and gastrointestinal and urinary symptoms [22]. PD patients ticked off the scores corresponding to the severity and frequency of each of the symptoms according to their own situation. The severity of each of these items is graded on a scale of 0 to 3, and the frequency is graded on a scale of 0 to 4. The final score is determined by multiplying severity and frequency, with higher scores reflecting more severe symptoms. All tests were carried out by specialized physicians or personnel skilled in testing, who were unaware of the patient's clinical details.

Measurement of NPY

Fasting blood samples of 5 mL were treated with anticoagulant and centrifuged for 25 minutes (800 g, 4°C), with the supernatant centrifuged again for 10 minutes (1,600 g, 4°C). Plasma was stored frozen at -80°C to measure NPY using ELISA kit (R&D Systems, MN, USA). Intra- and inter-variation coefficients were under 3.0% and 5.2%, respectively. The lab technicians conducting the measurements were unaware of the clinical results for all study participants.

Data analysis

Statistical analysis was performed using SPSS 20.0 software. Categorical data were expressed as frequencies (n) and ratios (%) using the chi-squared test. Data normality was determined using the Shapiro-Wilk test. Continuous variables data were shown as mean ± standard deviation. Mann-Whitney U test was used for comparisons between two independent groups, and Kruskal-Wallis H test was used for multiple groups with post hoc Dunnett's multiple comparisons test. Correlations between continuous variables were analyzed using the Pearson test (normal distribution) or the Spearman test (skewed distribution). The effects of plasma NYP levels on PD-CI events or PDD were analyzed using univariate and multivariate logistic models, with years of education and UPDRS-III subscores included as confounders in multivariate logistic regression analyses. Multivariate linear regression analyses were constructed to assess the independent associations of plasma NYP levels with z scores for 5 cognitive domains. z score was calculated as (test score - $Mean_{control}$)/$SD_{control}$ [23]. Figures were plotted using GraphPad Prism 8. $p < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics and baseline clinical tests

The study enlisted 147 patients with PD and 46 healthy individuals. Patients with PD were divided into three categories: PD-NC (n = 36), PD-MCI (n = 57), and PDD (n = 30). The four cohorts had comparable age and gender distributions (all $p > 0.05$). Compared to other groups, the PDD group experienced a shorter period of education ($p < 0.001$), and those with more education were less likely to develop CI. The PDD group (UPDRS-III and Hoehn and Yahr stage) exhibited long disease duration and CI, with the PD-MCI group trailing behind ($p < 0.001$). The ESS showed no notable difference between the groups ($p = 0.329$). Those with CI in PD were more prone to depression (Table 1).

Assessment of specific cognitive domains and non-motor symptoms in PD

Table 2 shows the differences between the five cognitive domains and non-motor symptoms in different categories of PD patients. There was a statistically significant difference between the 3 cohorts on all aspects of cognitive domains (all $p < 0.001$). The worst cognitive functioning was found in the PDD group, followed by PD-MCI. Although the NMSS total score and multiple subtests score had higher mean values in the PDD group, no statistically significant differences between the three groups were observed ($p > 0.05$).

Correlation of plasma NYP levels with specific cognitive domains and non-motor symptoms

Plasma NYP levels were reduced in PD patients compared with healthy controls ($p < 0.001$, Figure 1A). Plasma NYP levels had the highest levels in PD-NC group and decreased with increasing CI, with the PDD group having the lowest plasma NYP levels (Figure 1B). A weak negative correlation was observed between attention/memory and plasma NYP levels ($p = 0.023$). However, after correction, the p-value was not significant (Supplementary Table 2). Plasma NYP was significantly associated with PD-CI (including PD-MCI and PDD) in univariate logistic regression analyses. Multivariate logistic regressions adjusted for years of education and UPDRS-III subscores showed significant correlations between NYP and CI severity ($p = 0.005$) (Table 3). Table 4 shows the linear models between plasma NYP and each of the five specific cognitive domains. Plasma NYP was correlated with each of these cognitive domains (β, 95% CI = 3.46 (1.48 - 5.44); β, 95% CI = 3.44 (1.94 - 3.05); β, 95% CI = 7.56 (1.05 - 20.35); β, 95% CI = 5.48 (4.76 - 10.25) β, 95% CI = 9.36 (1.25 - 25.35)).

DISCUSSION

This study compared plasma NYP levels in PD-NC, PD-MCI, PDD, and healthy controls. Reduced levels of NYP in PD patients were associated with CI in 5 specific cognitive domains of CI. In particular, elevated NYP was associated with a reduced probability of CI and progression of MCI to PDD in patients with PD.

The potential of biomarkers to identify CI early could assist in predicting dementia onset in PD and lead to timely intervention. Markers for the diagnosis of PD-CI have included quantitative electroencephalography [24], cerebrospinal fluid amyloid [25], and cerebral metabolism utilizing complex techniques [26]. Due to their invasive nature or steep expense, these methods have been routinely employed in large populations. In this research, circulating biomarkers continued to be selected as indicators. While serum/plasma markers are linked to CI, we believe this research is pioneering in investigating the correlation between plasma NPY and specific cognitive domains in PD patients.

CI in PD is markedly impaired in executive functions and visuospatial deficits [27]. Patients could eventually experience dementia as the disease develops. Therefore, patients in the PDD group had a longer disease duration (after diagnosis) and the most severe grade of the disease. PD involves a progressive and relatively selective

Table 1. Comparison of clinical characteristics between Parkinson's disease patients and healthy controls.

Factors	HC (n = 36)	PD-NC (n = 60)	PD-MCI (n = 57)	PDD (n = 30)	p (ALL)
Age, years	62.25 ± 7.68	61.20 ± 5.68	58.68 ± 7.05	60.58 ± 6.25	0.452
Gender					0.988
Female	16	28	27	11	
Male	20	32	30	14	
Education, years	-	11.82 ± 3.33	9.18 ± 3.16 ***	8.43 ± 3.86 *** #	< 0.001
Disease duration, months	-	32.35 ± 25.64	50.36 ± 38.64 ***	62.52 ± 45.35 *** ###	< 0.001
UPDRS-III subscore	-	26.11 ± 11.72	34.00 ± 12.69 ***	39.6 ± 13.51	< 0.001
Hoehn and Yahr stage	-	1.95 ± 0.82	2.53 ± 1.09 ***	2.92 ± 0.85 *** ##	< 0.001
ESS score	-	6.32 ± 5.89	7.05 ± 5.65 ***	6.68 ± 5.25 *** #	0.329
GDS score	-	11.6 ± 5.36	12.58 ± 6.52 ***	16.67 ± 5.69 *** ###	< 0.001
Levodopa equivalents (mg/day)	-	410.62 ± 215.53	685.25 ± 565.25 ***	669.65 ±402.3 ***	< 0.01

All measurement data are shown as X ± S, and categorical variables are shown as n (%). HC healthy control, PD-NC Parkinson's disease without cognitive impairment, PD-MCI Parkinson's disease with mild cognitive impairment, PDD Parkinson's disease with dementia, ESS Epworth sleepiness scale, GDS geriatric depression scale. For multiple comparisons of continuous values, the Kruskal-Wallis H test was used, and a post hoc Dunnett's multiple comparisons test was performed. * Compared with PD-NC, ** p < 0.01, *** p < 0.001; ## Compared with PD-MCI, ### p < 0.01, ### p < 0.001. Categorical variables were tested using the chi-squared test.

Table 2. Neuropsychological assessments related to specific cognitive domains and non-motor symptoms in Parkinson's disease patients.

Cognitive test	PD-NC (n = 60)	PD-MCI (n = 57)	PDD (n = 30)	p (ALL)
MMSE	28.48 ± 0.94	25.64 ± 2.75 ***	20.63 ± 4.49 *** ###	< 0.001
Attention and working memory				
SDMT	36.05 ± 13.12	22.51 ± 11.45 ***	16.70 ± 13.56 *** ###	< 0.001
TMT-A, seconds	59.25 ± 18.58	92.58 ± 43.58 ***	128.66 ± 60.6 *** ##	< 0.001
Executive function				
CWT-C time (seconds)	68.65 ± 17.56	90.60 ± 36.35 ***	55.65 ± 6.36 *** ###	< 0.001
CWT-C right	48.65 ± 4.25	45.56 ± 4.62 ***	39.65 ± 5.15 *** ##	< 0.001
TMT-B (seconds)	128.60 ± 42.33	189.64 ± 70.65 ***	238.14 ± 132.3 *** ##	< 0.001
Language				
BNT	26.64 ± 4.25	22.35 ± 4.02 ***	19.52 ± 4.64 *** ##	< 0.001
AFT	17.68 ± 4.31	14.30 ± 3.64 **	10.25 ± 4.58 *** ###	< 0.001
Memory				
AVLT-delay recall	5.83 ± 2.02	3.68 ± 2.15 ***	2.21 ± 1.21 *** ###	< 0.001
AVLT-T	28.65 ± 8.60	22.35 ± 8.68 ***	14.36 ± 8.69 *** ###	< 0.001
CFT-delay recall	16.84 ± 5.64	12.52 ± 8.42 ***	6.52 ± 5.32 *** ###	< 0.001
Visuospatial function				
CFT	35.25 ± 12.25	28.25 ± 10.64 ***	20.52 ± 12.35 *** ###	< 0.001
CDT	23.25 ± 6.25	17.89 ± 6.05 ***	12.85 ± 8.25 *** ##	< 0.001
NMSS total score	52.25 ± 45.31	57.10 ± 43.25	70.15 ± 55.37	0.297
Cardiovascular	8.15 ± 9.15	8.52 ± 10.36	10.25 ± 11.64	0.652
Sleep/Fatigue	20.35 ±18.56	22.54 ± 17.64	24.54 ± 22.32	0.527
Mood/Apathy	16.5 ± 15.65	15.52 ± 14.52	16.25 ± 18.52	0.54
Perceptual problems/Hallucinations	3.65 ± 10.54	4.05 ± 11.24	5.05 ± 10.28	0.201
Attention/Memory	14.25 ± 11.36	16.25 ± 10.26	18.52 ± 16.25	0.357
Gastrointestinal	12.25 ± 14.56	14.25 ± 12.25	15.25 ± 13.47	0.854
Urinary	27.69 ± 25.31	28.65 ± 21.26	30.25 ± 23.56	0.587
Sexual	28.27 ± 30.15	30.52 ± 32.52	40.52 ± 43.25	0.658
Miscellaneous	13.25 ± 10.25	15.35 ± 12.35	14.25 ± 11.35	0.158

All measurements are shown as X ± S. PD-NC Parkinson's disease without cognitive impairment, PD-MCI Parkinson's disease with mild cognitive impairment, MMSE mini mental state examination, PDD Parkinson's disease with dementia, SDMT symbol digit modality test, TMT trail making test, CWT Stroop color-word test, BNT Boston naming test, AFT animal fluency test, AVLT auditory verbal learning test, CFT Rey-Osterrieth complex figure test, CDT clock drawing test. For multiple comparisons, the Kruskal-Wallis H test was used, and a post hoc Dunnett's multiple comparisons test was performed. * Compared with PD-NC, ** p < 0.01, *** p < 0.001; ## Compared with PD-MCI, ### p < 0.01, ### p < 0.001.

Table 3. Logistic regression analysis of the correlation between cognitive impairment and plasma NYP in patients with Parkinson's disease.

Variables	PD-Non vs. PD-CI				PD-MCI vs. PDD			
	β	S.E	p	OR (95% CI)	β	S.E	p	OR (95% CI)
Univariate analysis								
Plasma NYP	-1.25	0.09	< 0.001	0.99 (0.99 - 0.99)	-1.05	0.11	< 0.001	0.99 (0.99 - 0.99)
Multivariate analysis								
Plasma NYP	-0.98	0.01	< 0.001	0.99 (0.98 - 0.99)	-0.78	0.11	0.005	0.99 (0.98 - 0.99)

Analyses were conducted using univariate and multivariate logistic regression, respectively. Multivariate analyses incorporated years of education and UPDRS-III subscores for adjustment. OR odds ratio, CI confidence interval.

Table 4. Multivariate linear analysis model between plasma NYP and specific cognitive domains in Parkinson's disease patients.

Cognitive domain	β	S.E	p	B (95% CI)
Attention	3.46	1.01	< 0.001	3.46 (1.48 - 5.44)
Executive	3.44	0.68	< 0.001	3.44 (1.94 - 3.05)
Language	7.56	4.36	0.015	7.56 (1.05 - 20.35)
Memory	5.48	2.65	< 0.001	5.48 (4.76 - 10.25)
Visuospatial	9.35	3.65	0.002	9.36 (1.25 - 25.35)

Linear models were constructed for the five specific cognitive domains and plasma NYP, each of which was adjusted for years of education and UPDRS-III subscores, in addition to two or three psychological test results. All psychological test results were transformed by Z score. OR odds ratio, CI confidence interval.

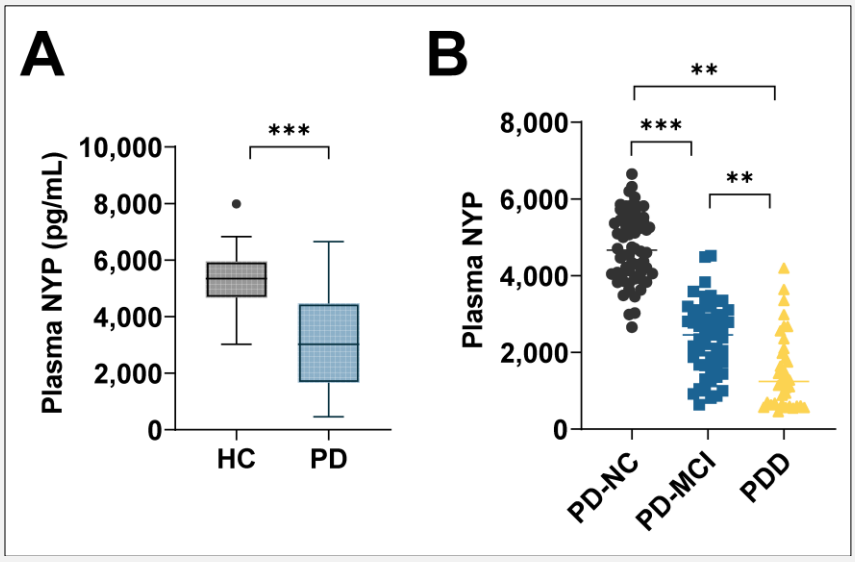

Figure 1. Comparison of plasma NYP levels in different cohorts.

A) Healthy controls versus PD patients; B) comparison between PD patients with different levels of cognitive dysfunction. The Mann-Whitney U test was used for comparison between the two independent groups, and Dunnett's multiple comparisons test was used for two-by-two comparisons between the three groups.

reduction of dopaminergic neurons in the substantia nigra [28]. Dopaminergic neuron degeneration causes a decrease in dopamine in the striatum [29]. The number of cells expressing NPY mRNA is higher in the caudate nucleus of PD patients compared to healthy subjects [30]. In an animal model of PD, striatal injection of NPY blocks degeneration of the nigrostriatal pathway [31]. Decreased dopamine levels may lead to neurotransmitter imbalance, which in turn affects cognitive function. In addition, neurodegenerative lesions, neuroinflammation, and oxidative stress are also contributing factors for CI [32]. There is extensive neurodegeneration in the brain of patients with PD, including atrophy and neuronal loss in frontal, parietal, and temporal lobes [33]. Alterations in NPY expression or function may impact the degenerative process in these brain regions, which are closely tied to cognitive function. The role of neuropeptides in the central nervous system is significant in degenerative diseases [34]. Extensive destruction of neuropeptides has been demonstrated to be associated with pathophysiologic symptoms of PD, where impairment of motor function is associated with neuropeptide dysregulation in the substantia nigra [35]. However, the role of neuropeptides in non-motor symptoms was earlier reported to be more related to stress response, mood, appetite, and metabolism [36]. In an analysis based on 80 patients with dementia, a strong tendency for NPY to decrease in the cerebrospinal fluid was noted, and decreased NPY levels were associated with increased disease duration [37]. NPY has a region-dependent modulatory effect on hippocampal function and network excitability during normal and pathological oscillatory activity [9]. NYP injection into the dorsal hippocampus of rats modulates adaptive memory by activating NPY receptors [38]. A prospective study has demonstrated that NPY is associated with postischemic stroke CI [39]. Furthermore, increases in plasma NPY provide incremental predictive utility for PSCI beyond conventional risk factors. Our findings and available evidence support a neuroprotective effect of circulating NPY in patients with PD.

In the present study, plasma NPY was significantly lower in patients with PD compared to healthy controls. They were further categorized into 3 groups based on cognitive status. Reduced NPY levels were found to be associated with increased CI. In specific domains, NPY in plasma was consistently linked to z-scores in memory function. With the advancement of PD-NC to PDD, memory impairments emerge, hinting at an accidental malfunction of the temporal lobe. The connection between NPY and memory capabilities could stem from the elevated levels of NPY in the CNS, especially in hippocampal neurons. Furthermore, a decrease in NPY levels is linked to executive function, yet a deeper investigation into the fundamental processes is required. The link between NPY and language function and visuospatial function may be that NPY indirectly affects language function by modulating the activity of pathways or neurons associated with language function [31]. Currently, the mechanisms underlying the exact cognitive deficits in PD are unknown. The correlation of NYP with a variety of specific cognitive domains may provide a basis for the study of these pathologic mechanisms.

We acknowledge the limitations of our study. The study involves a small number of participants, and more are needed to substantiate the results. Secondly, the research employed a cross-sectional approach, which is limited to examining the relationship between current data and outcomes and is not suitable for assessing the long-term effects of NPY on cognitive function in PD. The cross-sectional nature of our study prevents causal conclusions, and the specific mechanisms of NPY require additional investigation.

In conclusion, plasma NPY correlates with PDCI, and it may be a potential biomarker for PD.

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Availability of Data and Materials:

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethical Approval Statement:

The present study was approved by the Ethics Committee of the Affiliated Hospital of Beihua University (no. 20240060), and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

Declaration of Interest:

The authors have no conflicts of interest to declare.

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