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ORIGINAL RESEARCH

Association Between Pain Subtypes and Cognitive Impairment in Parkinson's Disease

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Purpose: To investigate the impact of different pain subtypes on cognitive function in patients with Parkinson's disease (PD).

Patients and Methods: A total of 344 patients with PD were enrolled in this cross-sectional study, comprising 187 males (54.4%) and 157 females (45.6%), with ages ranging from 32 to 84 years old. Demographic and clinical data were collected, including age, disease duration, levodopa equivalent daily dose (LEDD), and scores on the Unified Parkinson's Disease Rating Scale part III (UPDRS-III), Hoehn and Yahr (H&Y) scale, Pittsburgh Sleep Quality Index (PSQI), King's Parkinson's Disease Pain Scale (KPPS), Visual Analogue Scale (VAS), Mini-Mental State Examination (MMSE), Activities of Daily Living (ADL) scale, Hamilton Depression Rating Scale (HAMD), and Hamilton Anxiety Rating Scale (HAMA).

Results: Cognitive impairment was present in 56.4% of patients with PD. Compared with those with normal cognition, patients with cognitive impairment were older, had a later age at onset, more severe motor symptoms, higher levels of anxiety and depression, and greater pain severity. Specifically, they reported more chronic pain, central pain, visceral pain, "off" period dystonia, discoloration/swelling, and generalized lower abdominal pain ($p < 0.05$). Moreover, MMSE scores were positively correlated with chronic pain, radicular pain, and visceral pain ($p < 0.05$).

Conclusion: Cognitive impairment in PD is closely associated with pain severity, with certain pain subtypes exerting a stronger influence on cognition.

Keywords: parkinson's disease, pain, cognitive impairment, mini-mental state examination, king's parkinson's disease pain scale

Introduction

Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by both motor symptoms (resting tremor, rigidity, bradykinesia, and postural instability) and a wide range of non-motor symptoms (cognitive impairment, pain, sleep disturbances, anxiety, depression, autonomic dysfunction, behavioral abnormalities, and fatigue).[1] Among these, pain and cognitive impairment are increasingly recognized as prevalent and disabling non-motor symptoms that significantly reduce the quality of life in patients with PD.[2,3]

Approximately 40–85% of patients with PD experience different types of pain, including musculoskeletal pain, chronic pain, fluctuation-related pain, nocturnal pain, orofacial pain, discoloration/swelling, and radicular pain.[2] However, appropriate management is often lacking because PD-related pain remains poorly understood. To address this gap, the King's Parkinson's Disease Pain Scale (KPPS) was developed as the first disease-specific tool for assessing pain in PD and demonstrates greater validity across various PD-related pain types compared with the Visual Analogue Scale (VAS). KPPS not only enables characterization, scoring, and longitudinal monitoring of pain but also allows discrimination between different levels of pain severity.[4] Known clinical risk factors for PD-related pain include female sex, greater disease severity, and sleep disturbances.[2]

Cognitive impairment is also common in PD. At diagnosis, 15–35% of PD patients meet the criteria for mild cognitive impairment (PD-MCI), and longitudinal studies suggest that up to 80% of PD patients eventually progress to Parkinson's disease dementia (PDD).[5] Risk factors for cognitive decline include older age, later age at disease onset, greater disease

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severity, postural instability-gait disorder subtype, and the presence of features such as rapid eye movement sleep behavior disorder (RBD), psychosis, depression, and anxiety.[6]

Pain and cognitive impairment frequently co-occur in PD. Increasing evidence suggests that pain is closely associated with cognitive dysfunction, particularly impairments in memory, attention, executive function, and decision-making. These two conditions may interact bidirectionally, exacerbating one another.[7–10] The potential neurobiological mechanisms linking pain and cognition may involve shared neurotransmitter systems (including dopamine and acetylcholine) as well as overlapping anatomical structures, such as the limbic system and thalamus.

Studies examining the association between pain and cognition in PD patients have produced inconsistent findings. While two studies reported no significant relationship, a more recent investigation showed that PD patients with poorer executive function experienced greater pain interference.[11–13] Another study demonstrated that reduced amplitudes of pain-related somatosensory evoked potentials (SEPs) were associated with impairments in attention and memory.[14] Nevertheless, few studies have investigated the relationship between different pain subtypes and cognitive impairment in PD. Moreover, our previous research demonstrated that PD-related pain is associated with sleep, which may in turn influences cognitive function.[15] Therefore, using the Mini-Mental State Examination (MMSE) and the KPPS, the present study aimed to examine the association between specific pain subtypes and cognitive function, and to identify pain-related predictors of cognitive impairment in patients with PD.

Materials and Methods

Participants

This cross-sectional observational study enrolled 344 patients with PD who attended the Department of Neurology at the First Affiliated Hospital of Nanchang University between March 2019 and March 2024, comprising 187 males (54.4%) and 157 females (45.6%), with ages ranging from 32 to 84 years old. All participants, recruited from both outpatient clinics and inpatient wards, were evaluated by experienced neurologists and met the Movement Disorder Society (MDS) Clinical Diagnostic Criteria for Parkinson's Disease (MDS-PD Criteria).[16] Patients with atypical or secondary parkinsonism, pain of known etiology, or a history of neurosurgery were excluded. Individuals diagnosed with other parkinsonian syndromes, including progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration, as well as those with severe systemic diseases or psychiatric disorders, were also excluded. Written informed consent was obtained from all subjects before participation in the study. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (2020956).

Clinical Assessment Protocol

Demographic and clinical data, including age, sex, disease duration, and use of antiparkinsonian medications, were collected by movement disorder specialists through standardized face-to-face interviews. Motor disability was assessed using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III), and disease severity was staged with the Hoehn and Yahr (H&Y) scale. Pain was evaluated using the KPPS and the VAS. Global cognitive function was assessed using the MMSE. Depression and anxiety symptoms were evaluated with the Hamilton Depression Rating Scale (HAMD) and Hamilton Anxiety Rating Scale (HAMA), respectively. Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI), and functional status in activities of daily living was measured with the activities of daily life (ADL) scale. Participants were divided into two groups based on cognitive status: normal cognition (MMSE score 27–30) and cognitive impairment (MMSE score 0–26).

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD). Homogeneity of variance was assessed using Levene's test. Between-group differences in demographic and clinical characteristics were analyzed using independent two-tailed *t*-tests. The magnitude of differences between groups was quantified using Cohen's d, with thresholds of 0.2 (small), 0.5 (medium), and 0.8 (large). Categorical variables were presented as frequencies and percentages, and comparisons between groups

were made using the chi-square test. Correlations between MMSE and KPPS scores were evaluated using Pearson's correlation coefficient. Generalized linear regression was applied to identify potential risk factors for cognitive impairment. A two-tailed *p*-value of <0.05 was considered statistically significant.

Results

Clinical Characteristics

Table 1 summarizes the demographic and clinical characteristics of PD patients enrolled in this study. The mean MMSE score was 24.75 ± 4.02. Among them, 150 patients (43.6%) had normal cognition, while 194 patients (56.4%) exhibited cognitive impairment. There were no significant between-group differences in disease duration, levodopa equivalent daily dose (LEDD), or ADL scores. However, cognitive impairment was more common in females ($p < 0.001$). Patients with cognitive impairment were significantly older ($t = 3.127$, $p = 0.001$) and had a higher age at disease onset ($t = 2.630$, $p = 0.009$) compared with the normal cognition group. Motor disability, as measured by UPDRS-III ($t = 4.148$, $p < 0.001$) and H&Y scale ($t = 2.934$, $p = 0.004$), was more severe in patients with cognitive impairment. Furthermore, patients with cognitive impairment scored significantly higher on the HAMA ($t = 4.665$, $p < 0.001$), HAMD ($t = 3.002$, $p = 0.003$), and PSQI ($t = 2.254$, $p = 0.025$). A medium effect size was observed for HAMA (Cohen's d = 0.507), whereas small effect sizes were found for all other measures (Cohen's d < 0.5).

Effects of Pain Subtypes on Cognition

Pain assessment with the KPPS ($t = 2.256$, $p = 0.025$) and VAS ($t = 2.954$, $p = 0.003$) revealed higher overall pain scores in PD patients with cognitive impairment (Table 1). Among the seven KPPS domains, patients with cognitive impairment had significantly higher scores for chronic pain ($t = 3.192$, $p = 0.002$) and discoloration/swelling ($t = 1.992$, $p = 0.047$). At the item level (14 KPPS items), patients with cognitive impairment showed higher scores for central pain ($t = 2.695$, $p = 0.007$), visceral pain ($t = 2.317$, $p = 0.021$), "off" period dystonia ($t = 2.114$, $p = 0.035$), and generalized lower abdominal pain ($t = 2.013$, $p = 0.045$) compared with patients with normal cognition (Table 2). However, the effect sizes were all small (Cohen's d < 0.5).

Table 1 Demographic and Clinical Features of Patients with Parkinson's Disease Related Pain in the Total Sample and Stratified by Cognition

	Total[a]	Normal Cognition[a]	Cognitive Impairment[a]	*Cohen's d*	*t value*	*p value*
Gender, male %	187 (54.4%)	98 (65.3%)	89 (45.9%)			<0.001[b]
Age, years	63.75±9.92	61.82±10.48	65.24±9.22	−0.350	3.217	0.001
Age at onset, years	59.44±10.80	57.71±11.23	60.77±10.30	−0.286	2.630	0.009
Disease duration, years	4.14±3.44	4.08±3.34	4.19±3.52	−0.034	0.313	0.755
LEDD, mg/d	368.24±268.61	369.93±271.08	366.94±267.38	0.011	−0.102	0.919
UPDRS III score	26.52±11.72	23.58±9.68	28.77±12.65	−0.453	4.148	<0.001
H&Y stage	2.26±0.90	2.10±0.80	2.38±0.96	−0.319	2.934	0.004
MMSE score	24.75±4.02	27.82±0.97	22.38±3.88	1.824	−16.772	<0.001
HAMD score	15.98±9.03	14.33±8.46	17.25±9.27	−0.326	3.002	0.003
HAMA score	13.53±6.25	11.80±5.35	14.88±6.57	−0.507	4.665	<0.001
ADL score	83.48±19.04	84.71±14.72	82.60±21.60	−0.111	−0.935	0.35
PSQI	8.67±5.03	7.98±4.94	9.21±5.05	−0.245	2.254	0.025
VAS score	2.10±2.67	1.56±2.21	2.48±2.90	−0.350	2.954	0.003
KPSS score	18.32±27.25	14.57±21.34	21.22±30.80	−0.245	2.256	0.025

Notes: Dose conversion: 100 mg levodopa = 1 mg pergolide = 10 mg bromocriptine = 50 mg piribedil = 1 mg pramipexole = 10 mg selegiline. [a]data are mean ± SD. [b]chi-square test.

Abbreviations: LEDD, levodopa equivalent daily dose; UPDRS-III, Unified Parkinson's Disease Rating Scale III; H&Y, Hoehn and Yahr scale; MMSE, Mini Mental State Examination; HAMD, Hamilton Depression Rating Scale; HAMA, Hamilton Anxiety Rating Scale; ADL, Activities of Daily Living; PSQI, Pittsburgh Sleep Quality Index; VAS, Visual Analogue Scale; KPPS, King's Parkinson's disease Pain Scale.

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Table 2 King's Parkinson's Disease Pain Scale Scores of Patients with Parkinson's Disease Related Pain in the Total Sample and Stratified by Cognition

Domain	Total[a]	Normal Cognition[a]	Cognitive Impairment[a]	*Cohen's d*	*t value*	*p* value
Domain 1: musculoskeletal pain	2.47±3.50	2.19±3.06	2.69±3.80	−0.144	1.326	0.186
Domain 2: chronic pain	1.97±4.07	1.18±2.67	2.57±4.80	−0.347	3.192	0.002
Central pain	1.61±3.32	1.07±2.44	2.03±3.82	–0.293	2.695	0.007
Visceral pain	0.29±1.28	0.11±0.54	0.43±1.62	-0.252	2.317	0.021
Domain 3: fluctuation related pain	4.99±7.76	4.21±6.50	5.60±8.58	−0.179	1.644	0.101
Dyskinetic pain	1.56±3.00	1.32±2.41	1.75±3.38	–0.144	1.323	0.187
"Off" period dystonia	2.28±3.48	1.83±2.90	2.63±3.83	-0.230	2.114	0.035
"Off" period pain	1.16±2.57	1.06±2.23	1.23±2.71	–0.068	0.623	0.533
Domain 4: nocturnal pain	2.71±5.30	2.27±4.63	3.05±5.76	−0.147	1.355	0.176
Restless leg syndrome	1.22±2.69	1.07±2.41	1.33±2.89	–0.095	0.877	0.381
Pain related to difficulty turning in bed	1.49±3.10	1.19±2.60	1.73±3.42	-0.173	1.587	0.113
Domain 5: oro-facial pain	0.69±2.53	0.59±1.90	0.77±2.93	−0.071	0.653	0.514
Pain when chewing	0.13±0.96	0.09±0.77	0.16±1.08	–0.082	0.751	0.453
Grinding their teeth during night	0.06±0.78	0.05±0.65	0.07±0.87	-0.024	0.221	0.825
Burning mouth syndrome	0.50±1.68	0.45±1.35	0.54±1.89	–0.049	0.454	0.650
Domain 6: discoloration; edema/swelling	1.35±3.54	0.95±2.45	1.67±3.89	−0.217	1.992	0.047
Burning pain in limbs	0.92±2.18	0.70±1.70	1.09±2.48	–0.178	1.640	0.102
Generalized lower abdominal pain	0.44±1.54	0.25±1.03	0.58±1.83	-0.156	2.013	0.045
Domain 7: radicular pain	2.34±3.54	1.96±3.10	2.64±3.83	−0.193	1.771	0.078

Notes: [a]Data are mean ± SD.

Association Between KPPS Subtypes and MMSE Scores

Pearson's correlation analysis showed that MMSE scores were correlated with both total KPPS ($r = 0.128$, $p = 0.018$) and VAS scores ($r = 0.176$, $p = 0.003$). Among the KPPS domains, MMSE scores were correlated with chronic pain ($r = 0.182$, $p = 0.001$) and radicular pain ($r = 0.138$, $p = 0.010$). At the item level, MMSE scores were positively correlated with visceral pain ($r = 0.213$, $p < 0.001$) (Table 3).

Table 3 Correlation of Mini Mental State Examination Scores with King's Parkinson's Disease Pain Scale Scores

Variable	MMSE Score	
	r (Correlation Coefficient)	*p* value
Domain 1: musculoskeletal pain	0.090	0.096
Domain 2: chronic pain	0.182	0.001
Central pain	0.101	0.062
Visceral pain	0.213	<0.001
Domain 3: fluctuation related pain	0.076	0.158
Dyskinetic pain	0.069	0.204
"Off" period dystonia	0.096	0.077
"Off" period pain	0.025	0.648
Domain 4: nocturnal pain	0.038	0.485
Restless leg syndrome	0.018	0.745
Pain related to difficulty turning in bed	0.050	0.351

(*Continued*)

Table 3 (Continued).

Variable	MMSE Score	
	***r* (Correlation Coefficient)**	***p* value**
Domain 5: oro-facial pain	0.104	0.054
Pain when chewing	0.100	0.065
Grinding their teeth during night	0.102	0.058
Burning mouth syndrome	0.052	0.333
Domain 6: discoloration; edema/swelling	0.076	0.160
Burning pain in limbs	0.053	0.325
Generalized lower abdominal pain	0.090	0.095
Domain 7: radicular pain	0.138	0.010
Total KPPS score	0.128	0.018
VAS score	0.176	0.003

Abbreviations: MMSE, Mini Mental State Examination; VAS, Visual Analogue Scale; KPPS, King's Parkinson's disease Pain Scale.

Table 4 Generalized Linear Regression Analysis of Risk Factors for Cognitive Impairment in Parkinson's Disease

Model Dependent Variable	*B*	S.E.	*β*	*t*	*p* value
Constant	29.154	0.616		47.352	<0.001
UPDRS III score	−0.127	0.021	−0.348	−5.942	<0.001
HAMA score	−0.161	0.038	−0.247	−4.251	<0.001
Disease duration	0.253	0.065	0.221	3.897	<0.001

Abbreviations: B, unstandardized regression coefficient; SE, standard error; β, standardized regression coefficient; UPDRS-III, Unified Parkinson's Disease Rating Scale III; HAMA, Hamilton Anxiety Rating Scale; MMSE, Mini Mental State Examination.

Table 5 Summary Results of Generalized Linear Models (Stepwise Including Method) Assessing the Effect of UPDRS III Score, HAMA Score and Disease Duration on MMSE Score

Model	R	R^2	Adjusted R^2	SE of the Estimate
1	0.372	0.138	0.135	3.686
2	0.414	0.172	0.166	3.620
3	0.462	0.213	0.205	3.534

Notes: Model 1 includes UPDRS-III; model 2 contains Model 1 plus HAMA; model 3 includes Model 2 plus disease duration; MMSE is a dependent variable. **Abbreviations**: R, the square root of R^2; R^2, variance portion in the dependent variable, which can be predicted using the independent variables; SE, standard error; UPDRS-III, Unified Parkinson's Disease Rating Scale III; HAMA, Hamilton Anxiety Rating Scale; MMSE, Mini Mental State Examination.

Risk Factors for Cognitive Impairment

Regression analysis identified UPDRS III score ($\beta = -0.348$, $p < 0.001$), HAMA score ($\beta = -0.247$, $p < 0.001$), and disease duration ($\beta = 0.221$, $p < 0.001$) as independent predictors of cognitive impairment in PD (Tables 4 and 5).

Discussion

This is the first study to investigate the association between specific pain subtypes and cognitive impairment in PD using the KPPS. Our findings demonstrate that patients with cognitive impairment experience greater pain severity than those

with normal cognition, and patients with cognitive impairment are more prone to develop chronic pain, central pain, visceral pain, "off" period dystonia, discoloration/swelling, and generalized lower abdominal pain in PD.

In line with previous studies,[5,17] the prevalence of cognitive impairment in our cohort was 56.4%, and female patients were more likely to develop cognitive deficits. Additionally, patients with cognitive impairment were older, had a higher age at disease onset, more severe motor symptoms, and higher levels of anxiety, depression, and sleep disturbances, which is also consistent with prior reports.[6]

Pain severity was significantly higher in patients with cognitive impairment. Neurophysiological studies support this finding; for instance, Okada et al reported reduced amplitudes of pain-related somatosensory evoked potentials and impaired attention and memory in PD patients.[13] Cruz-Almeida et al found that deficits in working memory and inhibitory function were associated with higher pain interference, possibly due to altered frontal lobe integrity.[14] However, other studies, such as that by Engels et al, found no direct relationship between cognition and pain, instead attributing variance in pain perception primarily to depression and anxiety symptoms.[12]

In our study, chronic pain including central and visceral pain was more common in patients with cognitive impairment. Epidemiological data suggest that over half of individuals with chronic pain also experience cognitive deficits.[18] Several mechanisms may explain this relationship. The neural resource hypothesis posits that persistent pain consumes neural resources, limiting capacity for cognitive processing.[10] Chronic pain also alters activity in the dorsolateral prefrontal cortex, medial prefrontal cortex, and default mode network.[19] The gate control theory proposed by Melzack and Wall further suggests that persistent activation of pain "gates" amplifies nociceptive input, increasing cognitive load.[20] Neuroimaging studies have shown cortical thinning and disrupted connectivity in chronic pain-related networks, particularly in the insula and anterior cingulate cortex.[8] Finally, chronic pain and PD share mechanisms of neuroinflammation and dopaminergic dysfunction, potentially accelerating neuronal decline in regions involved in both pain modulation and cognition.[21]

We also observed that "off" period dystonia was more severe in patients with cognitive impairment, likely reflecting overlapping dopaminergic dysfunction contributing to motor, cognitive, and pain-related symptoms.[3] Similarly, generalized lower abdominal pain was more frequent in cognitively impaired patients. Emerging evidence implicates the gut-brain-microbiota axis in PD pathogenesis.[22] For example, Shen et al reported altered gut microbiota composition in PD patients with cognitive impairment, including reduced short-chain fatty acid-producing bacteria and increased pathogenic species.[23] Microbiome dysbiosis may exacerbate pain and cognitive decline through systemic inflammation and altered neurotransmitter regulation.[24,25]

Additionally, we observed that MMSE scores were positively correlated with radicular pain, a neuropathic pain subtype. Previous studies have demonstrated that neuropathic pain progressively impairs both working and long-term memory, accompanied by hippocampal remodeling and microglial activation.[26] Huang et al identified circuitry abnormalities in patients with neuropathic pain using transcranial magnetic stimulation (TMS) combined with electroencephalogram co-registration (TMS-EEG), and reported increased activity within attentional-cognitive regions, including the anterior insula and supracallosal anterior cingulate cortex, compared with healthy controls.[27] Furthermore, neuropathic pain has been shown to disrupt glutamatergic and GABAergic neurotransmission as well as brain-derived neurotrophic factor (BDNF) expression in the hippocampus.[28] In addition, CXCL12-mediated monocyte recruitment into the perivascular space has been identified as a critical mechanism underlying neuroinflammation and the associated cognitive impairment observed in neuropathic pain.[29]

While our study identified a statistically significant association between pain and cognitive impairment in patients with PD, the effect size was relatively small, suggesting a modest strength of association.[30,31] Further analysis of the risk factors for cognitive impairment indicated that the UPDRS Part III score, the HAMA score, and disease duration were the primary factors influencing cognitive function in these patients. Therefore, caution is warranted when interpreting the relationship between pain and cognitive function in PD, and any overinterpretation or exaggeration of their association should be avoided.

Moreover, our study has several limitations. First, the cohort predominantly comprised patients at moderate disease stages, and the use of analgesic medications was not recorded, which may have influenced the results. Second, the MMSE, while widely used, is not disease-specific and may underestimate certain cognitive domains. Future studies should incorporate Montreal Cognitive Assessment (MoCA) and PD-specific cognitive scales such as the Parkinson's

Disease Cognitive Rating Scale (PD-CRS). Third, our study found that PD patients with cognitive impairment had higher levels of anxiety, depression, sleep disturbances and disease severity. Therefore, when evaluating the relationship between pain and cognition, the potential mediating effects of mood disorders and disease severity should be taken into account. Finally, this study is a cross-sectional observational design; therefore, it cannot establish a causal relationship between pain and cognitive function in PD patients. Future larger cohort studies are needed to further clarify this association and improve the statistical power of these findings.

Conclusion

Cognitive impairment is highly prevalent in PD and is associated with increased overall pain severity. Crucially, our findings suggest a specific association between cognitive impairment and certain PD-related pain subtypes, particularly chronic pain (including central and visceral pain), "off" period dystonia, discoloration/swelling, generalized lower abdominal pain, and radicular pain. These associations may arise from shared pathophysiological mechanisms involving neural resource competition, structural and functional brain alterations, dopaminergic dysfunction, neuroinflammation, and gut-brain axis dysregulation. Future longitudinal studies utilizing PD-specific cognitive assessments and larger cohorts are needed to elucidate causal relationships and underlying mechanisms.

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An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (https://www.parinc.com). The authors thank the patients and their families for their participation in the study.

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Disclosure

The authors report no conflicts of interest in this work.

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