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ORIGINAL RESEARCH

Effects of Rehabilitation Training on Cognitive Function in Parkinson's Disease with Subjective Cognitive Decline

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Purpose: To characterize Subjective Cognitive Decline (SCD) in Parkinson's disease (PD) and its progression, as well as to assess the impact of rehabilitation training programs on cognitive function in PD patients.

Patients and Methods: The study involved 42 patients diagnosed with PD. Participants underwent evaluation using a neuropsychological protocol and were subsequently classified into two groups: those with SCD (PD-SCD$^+$, n= 22) or those without (PD-SCD$^-$, n= 20). After an average follow-up period of 3.0 years (2.7–4.6 years), cognitive assessments were reiterated with the same group of subjects. Following the re-assessment, all 42 patients participated in a six-month rehabilitation training program, concluding with the reevaluation of cognitive performance.

Results: In the follow-up assessment, it was observed that PD-SCD$^+$ experienced a more pronounced annual decline in cognitive function, as measured by the Chinese-Beijing version of Montreal Cognitive Assessment (BJ-MoCA) test and semantic fluency, compared to PD-SCD$^-$. A stepwise logistic regression analysis identified low MMSE scores (P< 0.001), elevated HAMD scores (P= 0.008), male gender (P= 0.026), and the presence of SCD (P= 0.022) associated with diminished language skills in PD patients. Both groups of PD patients exhibited improvements in BJ-MoCA scores after participating a six-month rehabilitation training program. Particularly notable is the statistically significant improvement in language skills observed in patients with PD-SCD$^+$ compared to PD-SCD$^-$ patients following rehabilitation training.

Conclusion: As PD progresses, individuals with PD-SCD$^+$ tend to experience more pronounced cognitive decline compared to those with PD-SCD$^-$. Semantic fluency emerges as a crucial component for assessing the cognitive subset of PD, potentially serving as an indicator of cognitive decline in individuals with PD. Evidence suggests that rehabilitation training is a viable intervention for individuals diagnosed with PD. This intervention not only improves various cognitive domains but also leads to more substantial enhancements in language skills.

Keywords: Parkinson's disease, subjective cognitive decline, SCD, semantic fluency, rehabilitation training

Introduction

Parkinson's disease (PD) ranks as the second most prevalent neurodegenerative disorder. In China, the average prevalence of PD is approximately 3.8756‰.[1] By 2030, the number of PD patients is projected to reach 4.94 million.[2] Notably, cognitive impairment stands out as a prominent and significant symptom among the diverse manifestations of PD. Consequently, researchers have shown interest in this phenomenon.[3,4] The continuum of cognitive impairment in PD encompasses the range from normal cognition to subjective cognitive decline (SCD), mild cognitive impairment (MCI), and ultimately Parkinson's disease dementia (PDD).[5] PD-MCI is regarded an indicator for the early detection of PDD.[6] SCD is characterized by individuals personally noting a decline in memory and/or other cognitive abilities compared to

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their previous performance, despite the absence of evident neuropsychological deficits.[7] This phenomenon is frequently observed in the elderly, as well as in individuals diagnosed with Alzheimer's disease and PD.[8,9]

The onset of dementia in PD is indeed a notable concern for both patients and their caregivers. Cognitive impairment, including SCD, can significantly impact the quality of life and independence of individuals with PD.[10,11] Addressing cognitive impairment and the risk of dementia in individuals with PD stands as a priority in both research and clinical practice. Amid the ongoing exploration of various therapeutic approaches, it's crucial to customize interventions to the individual's specific cognitive profile and needs. Furthermore, adopting a holistic approach that encompasses both pharmacological and non-pharmacological strategies, in addition to caregiver support, is vital for enhancing the lives of individuals affected by PD-related cognitive impairment.[12]

Despite extensive research on Parkinson's disease and its motor symptoms, there has been comparatively less emphasis on the cognitive aspects, especially in the context of long-term follow-up studies. Cholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine are used to treat cognitive symptoms in Alzheimer's disease and may also be applied to manage dementia in PD. However, pharmacological treatments for PD-MCI are limited, with even fewer options available for PD-SCD.[6] Rehabilitation training can provide benefits to individuals with PD, especially those experiencing cognitive decline.[13] Cognitive rehabilitation programs, including memory training, attention exercises, and executive function training, have the potential to enhance cognitive function and improve the quality of life.[14] However, there is a limited number of studies that have specifically addressed SCD in individuals with PD through long-term follow-up study, and reports on rehabilitation training for PD patients with SCD are infrequent.[15–19] There is a critical need for additional research and rehabilitation efforts focused on cognitive decline in individual with PD, especially in the context of long-term follow-up studies. Effectively addressing cognitive issues in individuals with PD has the potential to significantly enhance the quality of life for affected individuals and may potentially decelerate the progression of cognitive decline.

Studies examining the correlation between SCD and performance on neuropsychological tests have produced mixed results. Findings from a decade-long study suggest a relationship between self-reported subjective memory issues and objective memory performance.[20] Individuals who reported more forgetting at the outset were prone to faster declines in their memory abilities over the decade, whereas those with higher baseline memory problems over time. A recent study indicates that SCD is relatively common among newly diagnosed, untreated patients with PD. More than half of individuals diagnosed mild cognitive impairment (PD-MCI) reported SCD, and even some PD patients with normal cognition reported experiencing SCD.[21] Ophey's study utilizing FDG-PET and voxel-wise regression analysis, specific brain regions, including the middle frontal, middle temporal, occipital areas, and the angular gyrus, exhibited reduced glucose metabolism in individuals with PD who reported SCD.[22] These identified regions may serve as potential neural correlates or markers of cognitive changes in individuals with PD who experience SCD. Findings from a diffusion tensor imaging (DTI) study suggest that individuals with SCD exhibit changes in the integrity of white matter tracts in the brain before displaying measurable objective cognitive deficits.[23] Collectively, these research findings suggest that SCD may serve as a crucial early indicator of cognitive decline in individuals with PD. Identifying and monitoring SCD in individuals with PD could potentially facilitate early intervention and the development of strategies to mitigate cognitive decline, ultimately enhancing the quality of life for these individuals. In contrast, specific studies have not identified a significant correlation between self-reported SCD and performance on neuropsychological tests.[17,24–26] A study focusing on non-demented patients with PD suggest the potential for a discrepancy between how individuals subjectively perceive their cognitive function and their actual cognitive performance on standardized tests.[27]

Therefore, the objectives of this study are (1) to review the cognitive and psychological aspects of individuals with PD and SCD; (2) track cognitive changes over time in individuals with PD; (3) and assess the potential benefits of rehabilitation training for individuals with this condition. These objectives provide a robust framework for our research, and achieving them will yield valuable insights into the field of Parkinson's Disease and cognitive decline.

Material and Methods

Patients

The study recruited patients with PD who were cognitively normal from First Hospital Affiliated of Harbin Medical University. All participants met the clinical diagnostic criteria for PD, newly established by the Movement Disorders Society in 2015.[28] A schematic representation of the study procedures is present in Figure 1.

Inclusion Criteria

The study relied on patients to self-report cognitive decline. We applied criteria based on the standards proposed by the Subject Cognitive Decline Initiative (SCD-I) Working Group in 2014 to assess SCD.[7] In the context of the study, individuals with PD who answered positively to at least one of these questions were categorized as PD-SCD$^+$ cases: (1) "Do you feel that you have a declining memory?"; (2) "Do you feel that you are no longer as competent as you used to be in your previous job or daily operations?"; (3) "Do you feel that your spoken language abilities have gotten worse?"; (4) "Do you feel that you have been a decline in your ability to recognize and interpret graphics and shapes?"; (5) "Do you feel that you are experiencing persistent distractions that you did not experience previously?".

Exclusion Criteria

Exclusion criteria encompassed the following: (1) Individuals who met the MDS Task Force proposed criteria for mild cognitive impairment in Parkinson's disease (PD-MCI) at level I or had dementia associated with Parkinson's disease (PDD) were excluded from the study;[29,30] (2) Individuals who had cognitive impairment due to reason other than PD (eg, stoke, adverse effects of medication, or head trauma) were excluded; (3) Individuals with comorbid conditions often associated with PD, such as psychosis, excessive daytime sleepiness, or depression, were excluded; (4) Laboratory tests, including thyroid function tests, human immunodeficiency syndrome(HIV) screening, and syphilis testing, were conducted to rule out comorbid conditions that could affect cognition; (5) Individuals with conditions other than typical idiopathic PD, such as secondary Parkinson's syndrome or Parkinsonism-Plus syndrome, were not included in the study.

As shown in Figure 1, 54 patients were considered eligible for the study initially. Out of these initial 54 eligible patients, 11 were lost to follow-up, and another patient underwent deep-brain stimulation during the study. Following the application of these exclusions, the study successfully recruited a final sample of 42 patients with PD. Participants were classified into two groups: PD-SCD$^-$ (n=20) and PD-SCD$^+$ (n=22) based on their responses. Initially, we assessed the cognitive performance of all participants and then re-evaluated cognitive performance at a mean follow-up of 3.0 years (2.7–4.6 years) from the baseline assessment. After the mean follow-up of 3.0 years for assessment and data collection, all 42 participants were encouraged to undergo cognitive training for six months, and we attempted to reevaluate their

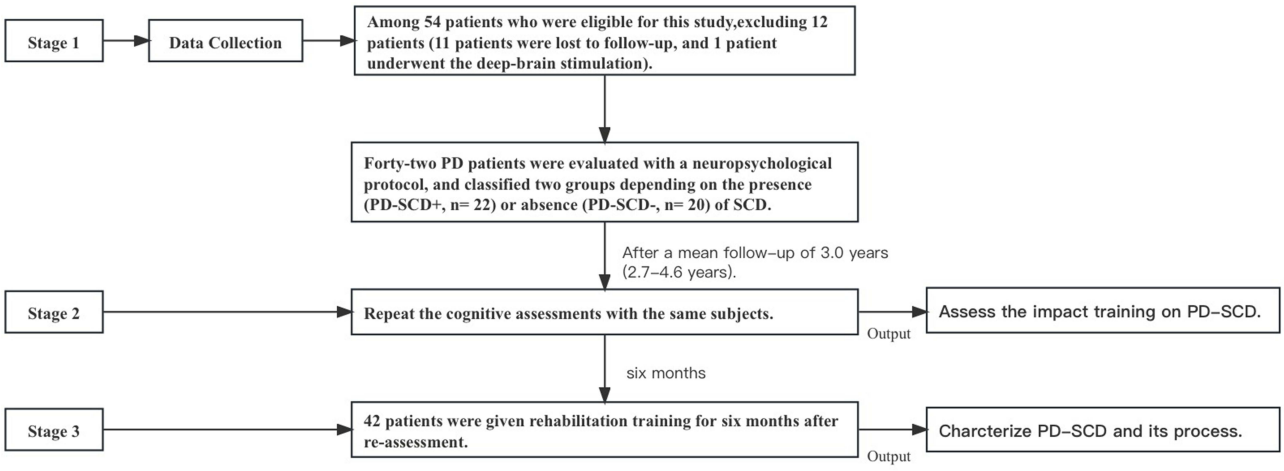

Figure 1 A process flow chart of the study.

cognitive performance after this training. However, 7 out of the 42 participants did not provide feedback scores after the training.

Our study complied with the Declaration of Helsinki. We received approval from the ethics committee of First Affiliated Hospital of Harbin Medical University for our study (V1.0,2019.02.01) and obtained written informed consent from all study participants (V1.0,2019.06.01).

Clinical Assessment

Demographic and clinical information were collected. The Unified Parkinson's Disease Rating Scale Part III(UPDRS-III) was employed to assess motor symptoms, and the Hoehn and Yahr Scale was utilized to categorize the overall stage and severity of PD. The Fazekas score was used to grade the degree of white matter hyperintensities (WMHs) in periventricular and subcortical white matter. Additionally, the Hamilton Depression Scale (HAMD) was utilized to evaluate the severity of depressive symptoms in individuals.

Neuropsychological Assessment

All patients underwent a neuropsychological assessment conducted by trained researchers. Global cognitive assessments of patients were evaluated using the Chinese Mini-Mental State Examination(C-MMSE)[31] and the Beijing version of the Montreal Cognitive Assessment (BJ-MoCA). The neuropsychological battery includes six cognitive domains, each assessed by one or two tests. The attention task is examined using digits forward and backward, as well as a serial subtraction task. Executive function is assessed using an alternation task, following the 1-A-2-B-3-C-4-D-5-E connection. Language and related functions consist of a phonemic fluency task (quickly evoke animal names in one minute), naming, and repetition. Memory is examined using immediate and delayed recall 1 (involving two learning trials of three nouns and delayed recall after approximately 5 minutes), and immediate and delayed recall 2 (involving two learning trials of five nouns and delayed recall after approximately 5 minutes). Orientation assessment involves spatial and temporal orienting. Visuospatial abilities are evaluated using the clock-drawing task (CDT) and cross pentagon copy. All assessments were conducted in the "on state". Additionally, we calculated annual cognitive decline by comparing the performance scores of baseline and follow-up assessments and dividing the difference by the time interval between the two assessments. The formula for calculating annual cognitive decline is: Annual Cognitive Decline = (Baseline Score-Follow-up Score)/Time Interval (in years).

Rehabilitation Training

Recognizing that no single task can sufficiently enhance a specific cognitive domain, this study adopted a holistic approach to promote cognitive health and prevent cognitive decline. Intellectual training included activities such as reading (eg, reading books or newspapers for 15 minutes, five times a week; if the patient is unable to read or has vision impairments, caregivers will read aloud to them), communication, and fine motor skills exercises. The fine motor skills exercises involve nine specific actions, each performed for 8 beats and repeated three times, to be done five times a week. These exercises include: 1) Flexing the arm forward towards the chest while blending the fingers; 2)Extending the forearm forward while spreading the fingers; 3) Abducting both arms while stretching the fingers as much as possible; 4) Touching the fingers of both hands together; 5) Performing wrist rotation and extension movements; 6) Using the thumb and index finger of one hand to pinch the fingertips of the other hand sequentially; 7) Performing cross-finger touching with both hands; 8) Using the thumb and index finger of one hand to pull the fingers of the other hand sequentially; 9) Clapping the fingers of both hands together. Physical exercise, particularly aerobic training, involved walking under the supervision of a caregiver, with the heart rate reaching 60% of the peak heart rate.[32] This was usually performed three times per week for about 30 minutes each session. A healthy diet, including smoking cessation and limited alcohol intake to under 20 grams of pure alcohol per day, was recommended. The researchers conducted monthly follow-up visits. Participants demonstrated high adherence to the program. The rehabilitation training lasted 6 months, followed by a reevaluation of cognitive performance. All assessments were conducted in the "on state".

Statistical Analysis

To compare demographic and clinical characteristics between two groups, Student's *t*-test and Mann–Whitney *U*-test were employed for group differences in continuous variables, and the chi-square test was used for group differences in categorical variables. Stepwise multiple regression analysis was employed to examine the contribution of SCD at the baseline to cognitive performance. Repeated-measures multivariate analysis of variance was used to compare pre- and post-intervention data between groups. SPSS software (version 25.0) was utilized for data analysis, and a p-value<0.05 was considered statistically significant.

Results

Baseline Demographic and Neuropsychological Characteristics

A total of 42 PD patients with normal cognition were included in the study at baseline, with 22 of them classified as PD-SCD$^+$. The demographic and clinical characteristics of the study participants at the baseline are detailed in Table 1. There were no statistically significant differences between the two groups in terms of age, sex, and years of education. The mean duration from the onset of PD was 7.10 years (ranging from 3.0 to 34.0 years). The average motor part (Part III) scores of the Unified Parkinson's Disease Rating Scale (UPDRS) for our study subjects were 18.5 points (ranging from 4 to 51 points). The duration of motor symptoms, HAMD score, UPDRS motor score, baseline C-MMSE, and BJ-MoCA scores did not exhibit statistically significant differences between the PD-SCD$^+$ and PD-SCD$^-$ groups. For most cognitive domains, there were no statistically significant differences in baseline comprehensive neuropsychological tests between

Table 1 Baseline Demographic Data and Clinical Characteristics of PD-SCD$^+$ or PD-SCD

	PD-SCD$^-$ (n=20)	PD-SCD$^+$ (n=22)	*p* Value
Age	64.10±7.20	66.45±8.71	0.348[a]
Number of males, n (%)	10(50.0)	9(40.9)	0.550[c]
Duration of motor symptom, (y)	6.06±2.27	8.05±6.29	0.197[b]
Years of education	9.75±4.83	10.86±4.54	0.377[b]
HAMD score	3.45±1.91	4.23±1.45	0.179[b]
White matter hyperintensity score	0.70±0.47	0.95±0.49	0.121[b]
UPDRS motor score	18.05±10.22	18.82±12.21	0.827[b]
Baseline C-MMSE score	28.30±2.11	27.83±2.67	0.549[b]
Baseline BJ-MoCA score	24.85±4.49	24.68±3.40	0.891[b]
Attention task			
Digits forward and backward	1.80±0.41	1.86±0.35	0.691[b]
Serial subtraction task	4.20±1.40	3.96±1.56	0.655[b]
Executive function			
Alternation task	0.70±0.47	0.64±0.49	0.750[b]
Language and related functions			
Phonemic fluency task	1.00±0.00	0.95±0.21	NS[b]
Naming and repeat	2.90±0.31	2.68±0.57	0.213[b]
Memory			
Immediate and delayed recall 1	4.90±0.45	4.86±0.47	Ns[b]
Immediate and delayed recall 2	3.35±1.60	2.32±1.64	0.033*[b]
Orientation	9.65±0.49	9.77±0.61	0.214[b]
Visuospatial abilities			
Clock-drawing task	8.45±1.88	7.64±2.82	0.354[b]
Cross pentagon copy	0.85±0.37	0.86±0.35	NS[b]

Notes: Data are expressed as mean± SD. NS, nonsignificant effect. [a] Student's *t* test, [b] Mann–Whitney *U*-test, [c] χ^2 test, *$p<0.05$.

Abbreviations: HAMD, Hamilton Depression Scale; UPDRS, Unified Parkinson's Disease Rating Scale; C-MMSE, Chinese Mini-Mental State Examination; BJ-MoCA, the Beijing version of the Montreal Cognitive Assessment.

the two groups, except for immediate and delayed recall 2. A noteworthy proportion of the patients reported SCD. Specifically, 100% reported subjective memory decline, 59.1% reported poor attention, 50.0% reported language complaints, 36.4% reported executive function decline, and 4.5% reported impaired visuospatial function.

Longitudinal Assessment of Cognitive Function

The mean follow-up duration in our study was 3.0 years. Out of the initial 20 patients classified as PD-SCD$^-$ at the baseline, 12 of them (60%) were newly diagnosed with PD-SCD$^+$ during the follow-up period based on the same SCD assessment procedure used in this study. In contrast, no patients initially classified as PD-SCD$^+$ reverted back to the PD-SCD$^-$ category during the follow-up. Furthermore, no patients in our study converted to MCI during the follow-up period.

As shown in Table 2, in the PD-SCD$^+$ group, the mean annual change from baseline in the BJ-MoCA score was −0.48 points. In contrast, the PD-SCD$^-$ group had a mean annual change of 0.07 points in the BJ-MoCA score. The difference between these two groups in terms of the annual change in the BJ-MoCA score was statistically significant (p=0.038). This indicates that the PD-SCD$^+$ group experienced a decline in their cognitive performance over time, as evidenced by the negative annual change in BJ-MoCA score, whereas the PD-SCD$^-$ group did not show a significant decline. For the semantic fluency score, the PD-SCD$^+$ group had a mean annual change of −0.14 points. In comparison, the PD-SCD$^-$ group had a mean change of −0.03 points in the semantic fluency score. The difference between these two groups in terms of annual change in semantic fluency score was statistically significant (p=0.035). This suggests that the PD-SCD$^+$ group experienced a greater decline in semantic fluency over time compared to the PD-SCD$^-$ group. No statistically significant difference in cognitive performance were observed between the two groups for other cognitive domains assessed in our study.

Stepwise logistic regression analyses were employed to predict poor cognitive functioning in various cognitive domains. Age, sex, UPDRS score, years of education, duration of motor symptoms, HAMD scores, degree of WMHS, presence or absence of SCD, baseline C-MMSE scores, and baseline BJ-MoCA scores were included as independent variables in the logistic regression analysis. The dependent variable in the analysis was different cognitive domains, and the aim was to predict poor cognitive functioning in these domains. The model's goodness-of-fit was assessed with a multicollinearity index variance inflation factor (VIF)<5, R-square= 0.583, and adjusted R square= 0.538. These results indicated that the model had a good fit. As shown in Table 3, the results of the multivariate analysis for predicting poor language functions are as follows. Being male was associated with an increased odds ratio (OR) of 1.30, with a p-value

Table 2 Annual Changes of Neuropsychological Performance in Patients with PD-SCD$^+$ or PD-SCD

Assessment	PD-SCD$^-$ (n=20)	PD-SCD$^+$ (n=22)	*p* Value
BJ-MoCA score	0.07±1.00	−0.48±1.08	0.038*
C-MMSE score	−0.31±0.58	−0.14±0.83	0.985
Attention task	−0.14±0.42	−0.15±0.37	0.723
Executive function			
Alternation task	0.07±0.18	−0.06±0.13	0.853
Language and related functions			
Phonemic fluency task	−0.03±0.10	−0.14±0.17	0.035*
Naming and repeat	−0.02±0.17	−0.09±0.15	0.207
Memory			
Immediate and delayed recall 1	0.01±0.05	0.00±0.18	0.630
Immediate and delayed recall 2	−0.20±0.40	−0.08±0.59	0.653
Orientation	0.05±0.20	−0.05±0.37	0.273
Visuospatial abilities	−0.17±0.37	−0.23±0.44	0.555

Note: * $p<0.05$.
Abbreviations: BJ-MoCA, the Beijing version of the Montreal Cognitive Assessment; C-MMSE, Chinese Mini-Mental State Examination.

Table 3 Stepwise Logistic Regression Analysis of Language and Related Function

Factors	OR	95% CI	P Value
Male	1.30	1.03–1.63	0.026
HAMD	1.10	1.03–1.19	0.001
C-MMSE	1.14	1.09–1.20	0.000
SCD^+	1.32	1.03–1.66	0.022

Abbreviations: HAMD, Hamilton Depression Scale; C-MMSE, Chinese Mini-Mental State Examination; SCD, subjective cognitive decline; OR, odds ratio; CI, Confidence Interval.

of 0.026. This suggests that being male was a significant predictor of poor language functioning. Lower C-MMSE scores were associated with an increased OR of 1.14, with a p-value of <0.001. This indicates that lower C-MMSE scores significantly contributed to the prediction of poor language functions. Higher HAMD scores were associated with an increased OR of 1.10, with a p-value of 0.001. This suggests that higher levels of depression significantly contributed to the prediction of poor language functions. The presence of SCD was associated with an increased OR of 1.32, with a p-value of 0.022. This indicates that the presence of SCD significantly contributed to the prediction of poor language functions. In summary, this logistic regression analysis found that being male, having lower C-MMSE scores, higher HAMD scores, and the presence of SCD were all significant predictors of poor language functioning in the cognitive domain.

Reassessment of Cognitive Function After Rehabilitation Training

After the mean of 3.0 years follow-up for assessment and data collection, all 42 patients received appropriate therapeutic interventions. At the end of the 6-month rehabilitation period (post-intervention), cognitive assessment information was collected from 35 participants. Seven patients were lost to follow-up during the study ($PD\text{-}SCD^-$: 2 patients, $PD\text{-}SCD^+$: 5 patients). It is regrettable that we could not obtain data from the seven patients lost to follow-up after rehabilitation, so we are unable to compare the differences between completers and non-completers. Pre- and post- rehabilitation training cognitive test scores were presented in Table 4. Both the $PD\text{-}SCD^-$ group (p=0.001) and the $PD\text{-}SCD^+$ group (p=0.009) showed a significant improvement in BJ-MoCA scores after the 6-month rehabilitation training period. In the $PD\text{-}SCD^-$ group, there was statistically significant improvement in C-MMSE scores (p=0.004) and memory scores (p=0.005) after the rehabilitation training period. Repeated measurement data analysis of language showed that the $PD\text{-}SCD^+$ group exhibited significant improvement compared to the $PD\text{-}SCD^-$ group after rehabilitation training. This implies that the $PD\text{-}SCD^+$ group exhibited greater improvement in language skills.

Table 4 Changes in Cognitive Test Scores of Patients at Pre- and Post- Intervention

Assessment	$PD\text{-}SCD^-$ (n=18)			$PD\text{-}SCD^+$ (n=17)			$PD\text{-}SCD^-$ (n=18)	$PD\text{-}SCD^+$ (n=17)	
	Pre-	Post-	*p* Value[a]	Pre-	Post-	*p* Value[a]	D-Value	D-Value	*p* Value[a]
BJ-MoCA	24.67±4.35	26.94±2.41	0.001*	23.59±3.16	25.41±2.98	0.009*	2.23±2.52	1.82±2.53	0.598
C-MMSE	27.22±2.34	28.17±1.89	0.004*	27.29±1.96	27.94±1.95	0.274	0.94±1.16	0.65±2.37	0.638
Attention	5.44±2.18	6.06±1.35	0.094	5.47±2.07	6.00±1.28	0.281	0.61±1.42	0.53±1.55	0.872
Executive	0.50±0.51	0.56±0.51	>0.999	0.47±0.51	0.71±0.47	0.125	0.06±0.24	0.24±0.44	0.137
Language	3.72±0.46	3.83±0.38	0.625	2.94±0.75	3.71±0.47	0.002*	0.11±0.47	0.76±0.75	0.004*
Memory	7.83±1.76	8.50±1.34	0.005*	6.94±1.48	7.47±1.01	0.127	0.67±0.77	0.53±1.23	0.693
Orientation	9.78±0.43	9.78±0.55	>0.999	9.77±0.56	9.59±0.80	0.531	0.00±0.59	−0.18±0.73	0.436
Visuospatial	9.11±1.75	9.50±1.54	0.374	8.53±2.48	8.53±2.35	0.864	0.39±1.69	0.00±2.52	0.594

Notes: [a] repeated measures analysis of variance between $PD\text{-}SCD^+$ and $PD\text{-}SCD^-$ at pre- and post-intervention. *$p<0.05$.
Abbreviations: C-MMSE, Chinese Mini-Mental State Examination; BJ-MoCA, the Beijing version of the Montreal Cognitive Assessment.

Discussion

This study is a longitudinal follow-up cohort study focusing on PD patients, investigating the presence of SCD in this population and the effects of rehabilitation training on cognitive function. The primary objectives of this study are to assess the clinical value and progression characteristics of SCD in PD patients and evaluate the feasibility of rehabilitation training on cognitive functions in PD patients. The study indicates that the annual scores of cognitive declines in PD-SCD$^+$ group were greater than those in the PD-SCD$^-$ group. This suggests that PD patients with SCD may experience more significant cognitive decline over time compared to those without SCD. The study also indicates a significant improvement observed in PD patients over a 6-month period of rehabilitation training. This suggests that rehabilitation training may have a positive impact on cognitive function in PD patients, potentially slowing down cognitive decline or even improving cognitive abilities.

We conducted a 3-year follow-up investigation focused on PD patients (n=42) who, at the beginning of the investigation, were cognitively normal. The study revealed that SCD was common in this group of cognitively normal PD patients, with half of them reporting such complaints. SCD is recognized as a risk factor for the progression to dementia in PD patients. Several studies suggest that individuals with PD who report subjective cognitive complaints may be at an increased risk of developing more severe cognitive impairments over time.[5,9,20] Among the PD patients who reported SCD, the study identified the following cognitive domains that were most commonly affected. Memory problems (100%) were the most frequently reported cognitive complaint. Many patients also reported difficulties with attention and concentration (59.1%). Language-related cognitive complaints were reported by half of the patients. A significant proportion of patients experienced difficulties with executive functions (36.4%). While less common, some patients reported issues with visuospatial skills (4.5%). The study's findings indicate the complexity and heterogeneity of cognitive issues in PD; individuals with SCD do not just experience memory-related complaints but can have difficulties in a variety of cognitive domains.

The study revealed that PD-SCD$^+$ patients had significantly lower scores on both immediate and delayed recall of memory compared to PD-SCD$^-$ patients. This suggests that self-reported cognitive complaints are associated with measurable deficits in memory function. The findings align with our previous work[33] and with Pan's report,[21] demonstrating similar patterns of cognitive impairment in PD patients with SCD. There are conflicting results in previous studies regarding the relationship between subjective and objective cognitive functioning in PD. Some researchers, in line with our study's results, suggest that memory impairment is more likely to be a subjective complaint in early PD patients.[34] This means that individuals with early-stage PD may perceive memory problems but may not necessarily show significant objective deficits in memory on cognitive tests. On the other hand, other researchers have found that cognitive deficits in nondemented PD patients tend to affect executive and visuospatial functions more prominently.[35–37] This implies that while memory may remain relatively intact, other cognitive domains such as problem-solving, planning, and spatial perception may be more affected in early-stage PD. Another study found no statistically significant association between self-reported cognitive deficits and performance on cognitive tasks.[27] These differing findings highlight the heterogeneity of cognitive profiles in PD and underscore the need for individualized assessment and care. Not all PD patients will experience the same cognitive deficits, and the specific cognitive impairments may vary from person to person and at different stages of the disease. One reason for the conflicting results in SCD research could be differences in the assessment of SCD. Currently, there is not a standardized measurement for assessing SCD, and there is little consistency between studies. Most studies rely on brief questionnaires or simple yes/no questions to evaluate SCD.[24] Aiming to capture a broader range of cognitive complaints beyond a simple yes/no response, this study assessed SCD using a multiple-response test to provide a more detailed description. To date, the objective assessment of SCD is largely based on overall neuropsychological tests, and only a few cognitive subsets of SCD are assessed. This highlights the need for further research to establish standardized research methods, diagnostic criteria, and enlarge sample sizes to better understand and assess SCD in PD patients.

We employed annual cognitive performance scores and a longitudinal follow-up approach to investigate how cognitive changes unfold over time in individuals with PD. Our study showed that PD-SCD$^+$ patients experienced a faster decline in BJ-MoCA scores and semantic fluency over time compared to PD-SCD$^-$ patients. This suggests that

individuals with self-reported cognitive complaints (SCD) may indeed exhibit a more rapid cognitive decline in specific cognitive domains. However, our study did not find a significant difference in the yearly fluctuations of C-MMSE scores between the two groups. This may imply that the C-MMSE is less sensitive to detecting cognitive changes in PD-SCD$^+$ individuals compared to the BJ-MoCA. The study highlights potential differences in sensitivity between cognitive assessment instruments. The BJ-MoCA appears to be more sensitive in detecting cognitive changes, especially in the early stages of cognitive decline (SCD stage), compared to the C-MMSE. A study by Hong, utilizing the Korean version of Mini-Mental State Examination (K-MMSE) for cognitive assessment, did not observe divergent declines in global cognitive function over time between PD-SCD$^+$ and PD-SCD$^-$ individuals.[16] This implies that the selection of assessment tools and cultural factors may impact research findings in this field. These results underscore the significance of choosing suitable cognitive assessment tools tailored to the specific cognitive domains of interest in research or clinical settings.

The study's findings align with prior research.[16] Specifically, both studies suggest that individuals with PD and SCD experience a more pronounced annual decline in semantic fluency. This implies a connection between SCD and worsening semantic fluency in Parkinson's Disease. Research has indicated that PD patients exhibit deficits in semantic fluency, impacting their quality of life.[38] Semantic fluency deficits are identified as a potential risk factor for Parkinson's Disease-related dementia. This indicates that alterations in semantic fluency could serve as an early indicator of cognitive decline in PD patients. Language output in PD patients is often less extensive and informative compared to that of healthy individuals. This distinction is evident not only in demented PD patients but also in non-demented PD patients and elderly controls.[39,40] Thus, language difficulties, including semantic fluency deficits, may emerge in various stages of Parkinson's Disease. The basal ganglia are highlighted for its central role in regulating semantic access. Semantic fluency deficits may signify impairments in the fronto-striatal loop, a neural circuit involving the frontal cortex and the striatum.[39–41] These early impairments may be relevant to understanding cognitive changes in PD. A study by Hedman et al showed that lower scores on an oral word test were correlated with age and education in PD patients.[38] This implies that demographic factors such as age and education may influence semantic fluency performance. The stepwise regression analysis in our study involving PD patients and their performance on semantic fluency tests revealed that lower C-MMSE scores, higher HAMD scores, male gender, and the presence of SCD as significant predictors of semantic fluency deficits in PD patients. Obeso et al reported similar findings, noting that non-motor features, depression (measured using HAMD), and global cognitive ability (measured using MMSE) influence semantic fluency in PD patients, aligning with our study.[42] However, gender did not impact semantic fluency scores in Obeso's study. In contrast, in our study, being male was identified as a predictor of semantic fluency deficits. Previous studies focusing on gender differences in PD cognitive are also inconsistent. A study did not find gender differences in the cognitive function of PD patients.[43] In line with our study, one systematic review found that women with PD have better cognitive levels,[44] while another meta-analysis showed that women with PD without dementia perform better than men in frontal executive functions.[45] These differing results may be due to the duration of PD. Chen et al suggested that shorter disease duration reveals gender differences in neurocognitive domains, whereas longer disease duration shows no differences. Men may be at greater risk for semantic fluency or other cognitive domain deficits, possibly because men with PD have lower dopamine concentrations compared to women with PD. On the other hand, gender differences in cognitive domains might also result from the protective effect of estrogen in women with PD.[43] Larger sample sizes and studies of patients with varying disease durations, along with investigations of estrogen and dopamine concentrations and fMRI studies will help us better understand gender differences in various cognitive domains and generalized cognitive function. Discrepancies in findings may be attributed to various factors, including variations in age, educational level, duration of motor symptoms, and disease stage among the study participants. Further research is essential to elucidate the role of key clinical features, such as gender and the presence of SCD, in predicting language complaints and semantic fluency deficits in PD patients. The disparities between studies underscore the heterogeneity of the PD population and the diverse factors influencing cognitive and language function.

There have been few clinical trials specifically addressing rehabilitation training strategies for individuals with SCD in the context of PD, indicating a research gap concerning effective interventions for this specific patient group. The present study aimed to assess the effects of rehabilitation training on SCD in patients with PD. Participants in the study

exhibited high levels of effort and adherence to homework assignments, showcasing a strong commitment to the rehabilitation program. Our study's results indicated that rehabilitation training had a positive impact on cognitive function, as demonstrated by improved BJ-MoCA scores for both PD-SCD^{+} and PD-SCD^{-}. This implies that the rehabilitation program effectively enhanced cognitive abilities in these individuals. Another study investigating the impact of tango dancing on PD patients reported significant improvements in global cognitive function, as measured by MoCA, compared to a control group.[46] However, a crucial distinction is that the participants in the present study were specifically diagnosed with SCD in PD, while the tango dancing study involved individuals with idiopathic PD. PD-SCD^{-} demonstrated significant improvement in C-MMSE and memory scores after rehabilitation training. Conversely, PD-SCD^{+} participants exhibited notable improvement in language skills compared to PD-SCD^{-}. This indicates that the effects of rehabilitation training may vary depending on the specific cognitive domain being assessed. The study demonstrated the feasibility and effectiveness of rehabilitation training in enhancing cognitive function in PD patients, with a particular emphasis on those with SCD. Our results underscore the potential benefits of tailored interventions for individuals with PD experiencing cognitive decline, recognizing that different cognitive domains may respond differently to such training. Montemurro et al found a significant correlation between language performance and the severity of motor impairment in PD patients.[47] This suggests that as motor symptoms worsen, language abilities may also decline. The same study proposed that modifying lifestyle factors could potentially compensate for language problems in PD patients, implying that certain lifestyle changes might help mitigate language deficits in individuals with PD. Another research demonstrated that aerobic exercise can have a positive impact on both cognitive function and language abilities in PD patients.[48] This highlights the potential benefits of physical activity for maintaining cognitive and language function in this population. Rösch et al proposed that deficits in speech and walking in PD patients may share common underlying mechanisms within the brain's cortical circuits.[49] This suggests that addressing one aspect, such as speech, could potentially have positive effects on the other, such as gait. Based on these research findings, individuals with PD who also experience SCD (PD-SCD^{+}) should consider participating in rehabilitation training interventions. Such interventions may help maintain overall cognitive function and prevent the continuous decline of language abilities. We did not investigate the long-term sustainability of cognitive improvements following rehabilitation. Balkom et al assessed changes in cognitive function after an eight-week cognitive training at one- and two-year follow-ups but did not find a significant long-term effect.[50] However, eight weeks may be too short for effective rehabilitation. Longer and more sustained rehabilitation might lead to greater cognitive improvements.

Several limitations exist in this study. Firstly, a limitation is related to the absence of consensus criteria for the diagnosis of PD-SCD. This lack of standardized criteria can introduce subjectivity and variability in the diagnosis and assessment of cognitive decline in PD patients. While the study aimed to comprehensively assess cognitive functioning in PD patients by covering five major cognitive domains (memory, attention, language, execution, and visuospatial function), this approach may have limitations or challenges. It's important to recognize that assessing cognitive function comprehensively can be complex and may not fully capture the nuances of cognitive decline in PD. Secondly, the research employed a small sample size. A limited sample size can restrict the generalizability of the findings and may not provide sufficient statistical power to detect subtle or less common effects. Thirdly, there are still some factors affecting cognitive function, such as genetic susceptibility, sleep disorders, and inflammatory markers,[51] that were not included in this study. Future research should consider these factors, as doing so will be more beneficial for developing personalized treatment plans. Fourthly, the follow-up period in the study was not sufficiently long. Longitudinal studies with extended follow-up periods are often needed to observe changes over time, especially in conditions like PD where cognitive decline may be progressive. However, as discussed above, our results are consistent with previous literature, providing some validation and context for the findings. Further research with larger sample sizes and longer follow-up periods would be conducted to confirm the findings and address some of the limitations mentioned.

Conclusions

In summary, the present study has yielded notable findings regarding PD patients, particularly those with SCD. The study offers valuable insights into the relationship between SCD, cognitive decline, and rehabilitation in patients with PD. As

PD progresses, it appears that individuals with PD-SCD^{+} may experience more pronounced cognitive decline compared to those with PD-SCD^{-}. Semantic fluency seems to play an important role in assessing cognitive function in PD and might serving as a potential indicator of cognitive decline in individuals with PD. Evidence suggests that rehabilitation training could be a beneficial intervention for individuals diagnosed with PD, as it appears to improve various cognitive domains and may lead to meaningful enhancements in language skills. These findings underscore the potential value of proactive screening and intervention for this patient group.

Abbreviations

PD, Parkinson's disease; SCD, subjective cognitive decline; MCI, mild cognitive impairment; PDD, Parkinson's disease dementia; PD-MCI, mild cognitive impairment in Parkinson's disease; DTI, diffusion tensor imaging; SCD-I, Subject Cognitive Decline Initiative; WMHs, white matter hyperintensities; HAMD, Hamilton Depression Scale; C-MMSE, Chinese Mini-Mental State Examination; BJ-MoCA, the Beijing version of the Montreal Cognitive Assessment; CDT, clock-drawing task; UPDRS, Unified Parkinson's Disease Rating Scale; VIF, variance inflation factor; OR, odds ratio; K-MMSE, the Korean version of Mini-Mental State Examination.

Ethics Approval and Informed Consent

We received approval from the ethics committee of First Affiliated Hospital of Harbin Medical University for our study (V1.0,2019.02.01) and obtained written informed consent from all study participants (V1.0,2019.06.01).

Consent for Publication

Written informed consent for publication was obtained from all participants.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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