Parkinson's Disease

Mild Cognitive Impairment and Dementia in Parkinson's Disease

Lead Guest Editor: Ji Hyun Ko
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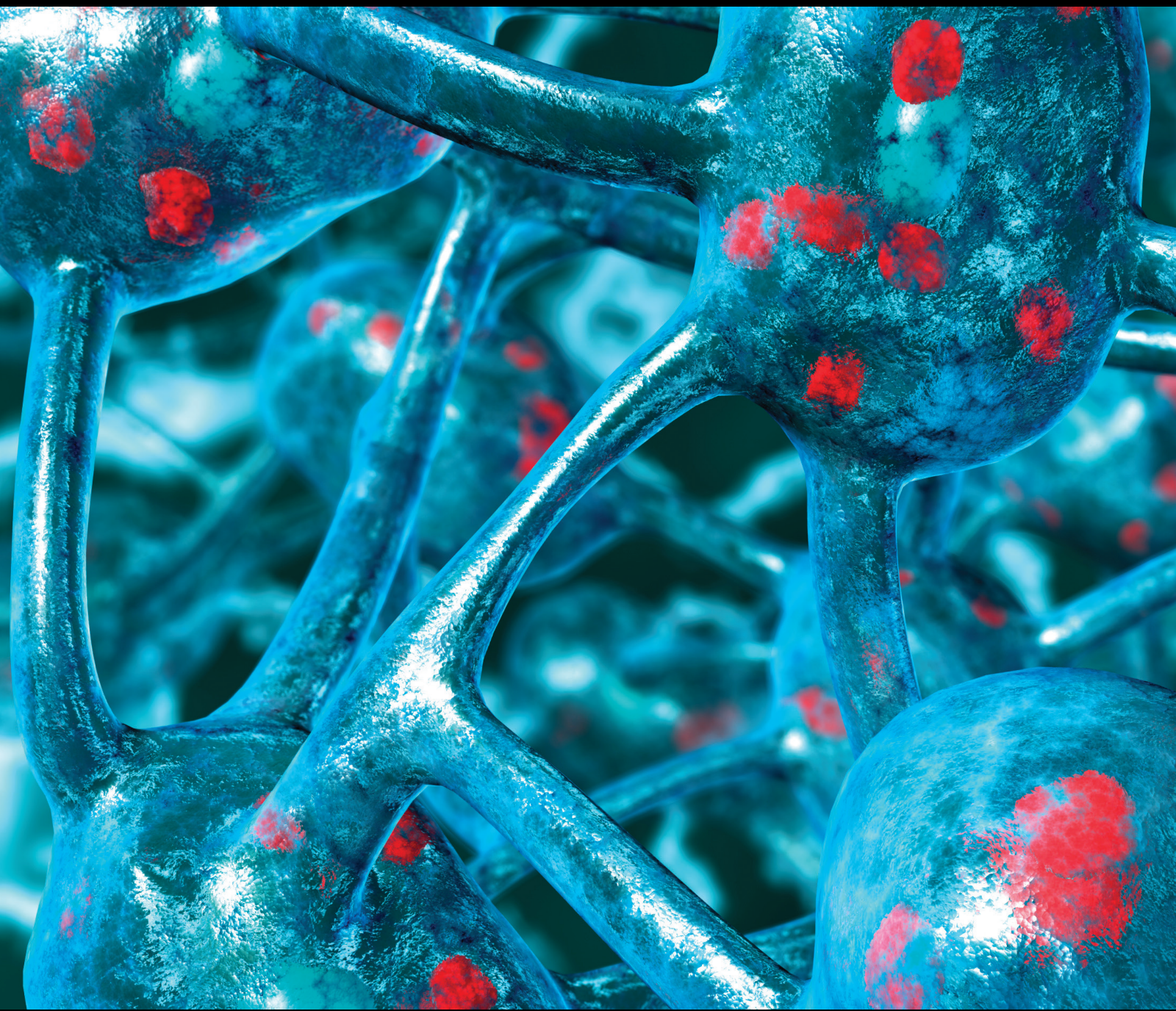

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Research Article

Validation of Revised Chinese Version of PD-CRS in Parkinson's Disease Patients

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Guest Editor: Ji Hyun Ko

There is a high prevalence of mild cognitive impairment (MCI) and dementia in Parkinson's disease (PD) patients, but a Chinese version of cognitive rating scale that is specific and sensitive to PD patients is still lacking. The aims of this study are to test the reliability and validity of a Chinese version of Parkinson's disease-cognitive rating scale (PD-CRS), establish cutoff scores for diagnosis of Parkinson's disease dementia (PDD) and PD with mild cognitive impairment (PD-MCI), explore cognitive profiles of PD-MCI and PDD, and find cognitive deficits suggesting a transition from PD-MCI to PDD. PD-CRS was revised based on the culture background of Chinese people. Ninety-two PD patients were recruited in three PD centers and were classified into PD with normal cognitive function (PD-NC), PD-MCI, and PDD subgroups according to the cognitive rating scale (CDR). Those PD patients underwent PD-CRS blind assessment by a separate neurologist. The PD-CRS showed a high internal consistency (Cronbach's Alpha = 0.840). Intraclass Correlation coefficient (ICC) of test-retest reliability reached 0.906 (95% CI 0.860–0.935, $p < 0.001$). ICC of inter-rater reliability was 0.899 (95% CI 0.848–0.933, $p < 0.001$). PD-CRS had fair concurrent validity with MDRS (ICC = 0.731, 95% CI 0.602–0.816). All the frontal-subcortical items showed significant decrease in PD-MCI compared with the PD-NC group ($p \leq 0.001$), but the instrument cortical items did not (confrontation naming $p = 0.717$, copying a clock $p = 0.620$). All the frontal-subcortical and instrumental-cortical functions showed significant decline in PDD compared with the PD-NC group ($p \leq 0.001$). The cutoff value for diagnosis of PD-MCI is 80.5 with the sensitivity of 75.7% and the specificity of 75.0%, and for diagnosis of PDD is 73.5 with the sensitivity of 89.2% and the specificity of 98.9%. Revised Chinese version of PD-CRS is a reliable, acceptable, valid, and useful neuropsychological battery for assessing cognition in PD patients.

1. Introduction

Cognitive impairment is common in Parkinson's disease (PD), even in its early stages. Mild cognitive impairment (MCI) may be identified in approximately 25% of newly diagnosed patients [1], and those PD patients are at a higher risk of developing dementia compared with normal cognition PD patients [2–4]. Parkinson's disease dementia (PDD) has a cumulative prevalence up to 75–90% of those with a disease duration of 10 years or more [5]. Cognitive impairment in PD patients includes attention deficits, executive dysfunction, visuospatial defects, free-recall memory

problems, confrontation naming difficulties, as well as encoding deficits [6–8].

Diagnosis of PDD largely relies on neuropsychological measurements and evaluation. Four neuropsychological evaluation tools have been designed specifically for PD patients so far. Minimental Parkinson (MMP) and Parkinson Neuropsychometric Dementia Assessment (PANDA) are short screen tests for cognitive impairment in PD patients, but lack extensive clinimetric evaluation [9–11]. Scale for Outcomes of Parkinson's Disease-Cognition (SCOPA-COG) is a reliable and valid instrument for assessing "frontal-subcortical" function, but the "instrumental-cortical" function is missing [12], which has been identified in approximately 15–20% of PD patients [6]. Parkinson's disease-cognitive rating scale (PD-CRS), designed by Dr. Kulisevsky, is a comprehensive, reliable, and valid instrument for assessing both "frontal-subcortical" functions (sustained attention, working memory, alternating and action verbal fluencies, clock drawing, and immediate and delayed free-recall verbal memory) and "instrumental-cortical" functions (confrontation naming, copying a clock) [13–15]. China has over 2 million PD patients, but cognitive impairment is substantially underestimated because of the lack of a Chinese version neuropsychological evaluation tool specific for PD patients. The aims of the present study are to test the reliability and validity of the Chinese version PD-CRS; establish cutoff scores for diagnosis of PDD and PD-MCI; explore cognitive profiles of PD-MCI and PDD; and find cognitive deficits suggesting a transition from PD-MCI to PDD.

2. Materials and Methods

2.1. Revised Chinese Version of PD-CRS. China has different culture and language systems from western countries. Therefore, three steps were executed to make ensure that the PD-CRS was adapted to Chinese people. First, the English version of PD-CRS was translated to a provisional Chinese version and was examined in a consensus meeting. Second, the provisional Chinese version of PD-CRS was administered to 15 Chinese healthy volunteers with age ranging from 60–85 and with 6 or more years of education. The preliminary test showed that senior Chinese people were not familiar with some of the pictures in the picture naming section, such as "jingle bell," "guitar," "berry," and "stool." The Spring Festival is the traditional festival in China, which is similar to the Christmas day in the West. It is a tradition to hang lanterns at the Spring Festival which is akin to hanging jingle bells on Christmas day. Thus, using "lantern" instead of "jingle bell" kept the difficulty level of naming. We made four modifications in the confrontation naming part: "lantern" replaced "jingle bell," "erhu" replaced "guitar," "strawberry" replaced "berry," and "chair" replaced "stool." All experts approved of these modifications in the picture-naming section in the consensus meeting. We also found that most of these senior Chinese people did not know English letters. We made the following changes to the "sustained attention," "working memory," and "alternating verbal fluency," with the help from Dr. Kulisevsky, the author of PD-CRS. The original instructions in the "sustained attention" section are to read an ascending series of letters and numbers to the subject, asking the subject to say how many letters are there in the series. In the revised Chinese version, the instructions are to read an ascending series of numbers to the subject, asking the subject to say how many odd numbers are there in the series. Thus, in both the original and revised instruction, the subjects need to memorize what they heard and be able to operate classification at the same time. The original instructions in the "working memory" section is to read aloud a randomized list of numbers and letters ranging in length from 2 to 6 letters and numbers. After each series, the subject is asked to repeat the numbers first, and then the letters. In the revised Chinese version, the instructions are to read aloud a randomized list of numbers in length from 2–6 numbers. After each series, the subject is asked to repeat the numbers backward. The revised method is similar to the backward digit span test and tests the subject's working memory. The original instructions in the "alternating verbal fluency" section asks the subject to generate as many different words as possible by alternating between words beginning with the letter "S" and articles of clothing for a 60-second duration. In the revised Chinese version, the instructions are to ask the subject to make as many different phrases as possible by alternating between providing words starting with the written form of Chinese character "发" pronounced as "fa" and articles of clothing for a 60-second duration. Third, after all modifications were completed, the newly revised Chinese version of PD-CRS was finally approved in a consensus meeting. The new version was then retested in 15 Chinese healthy volunteers. All the participants and examiners had good understanding and comprehensibility of the instructions. The revised Chinese version of PD-CRS was attached as supplementary material.

2.2. Subjects. A cohort of 92 PD patients were recruited from 3 centers, including the Neurology Department of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine; Neurology Department of Nanjing Brain Hospital affiliated to Nanjing Medical University; and Neurology Department of the First Affiliated Hospital of China Medical University. The inclusion criteria for the enrollment were diagnosis of idiopathic PD according to the UK Brain Bank, ages of 60–85 years, and 6 or more years of education. The exclusion criteria were other neurological diseases, such as stroke, epilepsy, tumor, brain trauma (history and cranial MRI), and abnormalities on brain CT or MRI in the past 12 months; nutritional and metabolic abnormalities (folic acid or vitamin B12 or vitamin B1 deficiency); psychiatric problems for which who now or used to have psychiatric medicine dependence; serious sleep disorder; history of surgery under general anesthesia within the last year; evidence of physical illness; hearing or vision loss; and severe cardiac or respiratory disorders. This study protocol was approved by the Ethics Committee of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine. Written informed

Table 1: Demographic and clinical characteristics between PD-NC, PD-MCI, and PDD groups.

	PD-NC	PD-MCI	PDD	p
N	37	44	11	—
Age	68.08 ± 6.202	69.82 ± 6.366	71.27 ± 4.563	0.237[a]
Male (%)	25 (67.6%)	34 (77.3%)	7 (63.6%)	0.511[b]
Education (year)	12.35 ± 2.879	11.63 ± 3.441	10.73 ± 2.284	0.225[c]
Disease duration (year)	5.32 ± 5.716	5.18 ± 3.598	7.82 ± 3.401	0.033[c]
H–Y staging	1.70 ± 0.6714	1.90 ± 0.6522	2.45 ± 0.650	0.009[c]
Smoke (−)	34 (91.9%)	38 (86.4%)	10 (90.9%)	0.712[b]
Alcohol (−)	34 (91.9%)	39 (88.6%)	9 (81.8%)	0.656[b]
Diabetes (−)	32 (86.5%)	39 (88.6%)	9 (81.8%)	0.838[b]
Hypertension (−)	27 (73.0%)	29 (65.9%)	7 (63.6%)	0.739[b]
Coronary heart disease (−)	31 (83.8%)	36 (81.8%)	11 (100%)	0.139[b]
Cerebrovascular disease (−)	33 (89.2%)	39 (88.6%)	10 (90.0%)	0.976[b]
Levodopa (+)	25 (67.6%)	36% (81.8%)	10 (90.0%)	0.151[b]
Dopamine agonists (+)	22 (59.5%)	20 (45.5%)	5 (45.5%)	0.418[b]
COMT inhibitor (+)	3 (8.1%)	10 (22.7%)	0 (0%)	0.061[b]
MAO-B inhibitor (+)	13 (35.1%)	8 (18.2%)	1 (9.1%)	0.090[b]
Anticholinergic (+)	0 (0%)	2 (4.5%)	1 (9.1%)	0.177[b]
Amantadine (+)	3 (8.1%)	7 (15.9%)	2 (18.2%)	0.488[b]
LEDD (mg/d)	323.97 ± 249.571	430.73 ± 287.325	540.91 ± 301.719	0.038[a]
UPDRS-III	12.89 ± 8.906	20.48 ± 13.473	26.00 ± 11.773	0.001[c]
BDI	5.68 ± 4.295	11.45 ± 8.019	16.45 ± 10.727	<0.001[c]
MDRS	138.16 ± 6.265	131.43 ± 9.260	114.27 ± 15.755	<0.001[c]

[a]One-way analysis of variance (ANOVA); [b]Chi-square test; [c]Kruskal–Wallis test. PD: Parkinson's disease; PD-NC: PD patients with normal cognition; PD-MCI: PD patients with mild cognitive impairment; PDD: PD patients with dementia; H–Y staging: Hoehn and Yahr staging; COMT inhibitor: catechol O-methyltransferase inhibitor; MAO-B inhibitor: monoamine oxidase-B inhibitor; LEDD: levodopa equivalent daily dose; UPDRS-III: the Unified Parkinson's Disease Rating Scale part III; BDI: Beck Depression Inventory; MDRS: Mattis Dementia Rating Scale.

consent was obtained from all participants in the study as well.

2.3. Assessments. For baseline, the collection of demographic and clinical data included age, gender, education, disease duration, past disease history (diabetes, hypertension, coronary heart disease, and cerebrovascular disease), current medications converted to levodopa equivalent daily dose (LEDD), history of smoking or alcohol consumption, the Unified Parkinson's Disease Rating Scale part III (UPDRS-III), Beck Depression Inventory (BDI), and PD-CRS. For the second visit, the same neurologist evaluated the same patient with PD-CRS after 2 weeks. For the third visit, another neurologist evaluated the same patient with PD-CRS, Mattis Dementia Rating Scale (MDRS) and Clinical Dementia Rating (CDR) in an interval of 6 ± 2 weeks from the second visit. Based on CDR, the PD patients were divided into PD-NC, PD-MCI, and PDD subgroups; CDR = 0 in the PD-NC group, CDR = 0.5 in the PD-MCI group, and CDR ≥1 in the PDD group.

2.4. Statistical Analysis. All continuous demographic and clinical data were presented as mean ± SD and compared by Analysis Of Variance (ANOVA) or Kruskal–Wallis test. All categorical variables were presented as numbers and estimated by Chi-squared test. Normality of distribution was evaluated by Kolmogorov–Smirnov (K–S) test initially. Test-retest reliability and inter-rater reliability were assessed by intraclass correlation coefficients (ICCs). The ICC is equal to the degree of individual variation divided by the total variability, so the value is between 0 and 1. Landis and Koch recommend ICC should be more than 0.80; 0.61–0.80 classified as good; 0.41–0.60 as fair, 0.11–0.40 as low, and 0.1 or less as no consistency. Internal consistency reliability was evaluated by the Cronbach's alpha coefficient (≥0.80 was considered acceptable) and the corrected item-total correlation (≥0.40 was considered acceptable). Acceptability rating was determined as acceptable for each PD-CRS item if there was <5% of missing data rates and <15% of the floor/ceiling effects (floor: the proportion of patients with the minimum possible score; ceiling: the proportion of patients with the maximum possible score). Receiver operator characteristic (ROC) curves were generated to identify the discriminative power of PD-CRS for diagnosing PD-MCI and PDD. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratios (LR+), and negative likelihood ratios (LR−) were calculated. The appropriate cutoff point was chosen according to the maximum combined sensitivity and specificity. All tests were two-sided, and the results were considered statistically significant at $p < 0.05$. Statistical analysis was performed using SPSS 20.0.

3. Results

3.1. Demographic and Clinical Data. The demographic and clinical data were presented in Table 1. Of the 92 PD patients, 37 were classified into the PD-NC group, 44 into the PD-MCI group, and 11 into the PDD group. The distributions of age, gender, education, history of smoking,

Table 2: Reliability and internal consistency for both total and individual item scores of PD-CRS.

Subscale	Test-retest reliability		Inter-rater reliability		Internal consistency	
	ICC (95% CI)	p	ICC (95% CI)	p	Corrected item – total correlation	Cronbach's alpha if the item is deleted
Immediate free-recall verbal memory	0.817 (0.747–0.867)	<0.001	0.692 (0.580–0.782)	<0.001	0.705	0.830
Confrontation naming	0.717 (0.554–0.844)	<0.001	0.709 (0.562–0.807)	<0.001	0.452	0.837
Sustained attention	0.810 (0.743–0.867)	<0.001	0.775 (0.667–0.857)	<0.001	0.704	0.829
Working memory	0.706 (0.571–0.808)	<0.001	0.650 (0.521–0.759)	<0.001	0.602	0.835
Clock drawing	0.728 (0.506–0.851)	<0.001	0.675 (0.449–0.822)	<0.001	0.629	0.834
Copying a clock	0.814 (0.423–0.925)	<0.001	0.826 (0.429–0.922)	<0.001	0.566	0.838
Delayed free-recall verbal memory	0.825 (0.743–0.894)	<0.001	0.748 (0.614–0.845)	<0.001	0.665	0.829
Alternating verbal fluencies	0.727 (0.608–0.815)	<0.001	0.592 (0.471–0.693)	<0.001	0.730	0.822
Action verbal fluencies	0.691 (0.562–0.796)	<0.001	0.720 (0.596–0.821)	<0.001	0.711	0.821
Frontal-subcortical functions	0.911 (0.865–0.939)	<0.001	0.893 (0.841–0.929)	<0.001	0.977	0.787
Instrumental-cortical functions	0.780 (0.632–0.870)	<0.001	0.789 (0.655–0.872)	<0.001	0.645	0.829
PD-CRS	0.906 (0.860–0.935)	<0.001	0.899 (0.848–0.933)	<0.001	Cronbach's alpha = 0.840	

PD-CRS: Parkinson's disease-cognitive rating scale; ICC: intraclass correlation coefficients; CI: confidence interval.

alcohol consumption, diabetes, hypertension, coronary heart disease, and cerebrovascular disease were similar between the groups ($p > 0.05$). There were significant differences in disease duration, H–Y staging, LEDD, UPDRS-III, BDI, and MDRS scores among the three groups ($p < 0.05$). PDD patients have longer disease duration, higher scores of UPDRS-III and BDI, and lower scores of MDRS.

3.2. Reliability. Cronbach's alpha was used to measure internal consistency of the PD-CRS scale. The PD-CRS showed a high internal consistency among all items in this scale (Cronbach's Alpha = 0.840). Correction item – total correlation ranged from 0.452 (confrontation naming) to 0.730 (alternating verbal fluencies) (Table 2). No item improved Cronbach's alpha (0.840) if removed. As for the test-retest reliability, the intraclass correlation coefficient (ICC) for each item score of the PD-CRS is presented in Table 2. ICC of the total score of PD-CRS reached 0.906 (95% CI 0.860–0.935, $p < 0.001$), which indicated high test-retest reliability. ICC of each item ranged from 0.691 to 0.825 ($p < 0.001$). For inter-rater reliability (Table 2), the ICC of the total PD-CRS score was 0.899 (95% CI 0.848–0.933, $p < 0.001$), and the ICC of each item ranged from 0.592 to 0.826 ($p < 0.001$). These results indicated that the revised Chinese version of PD-CRS has good internal consistency, test-retest reliability, and inter-rater reliability according to the criteria mentioned in Section 2.4.

3.3. Acceptability. Ceiling effect (>15% of the respondents with the highest possible score) and floor effect (>15% of the respondents with the lowest possible score) were analyzed. Nonfloor effects were observed for the total, subcortical, and cortical scores of the PD-CRS when analyzed in all PD patients, specifically PD-NC and PD-MCI subgroup (Table 3, Supplementary Tables 1 and 2). But in the PDD subgroup, items of immediate free-recall verbal memory, confrontation naming, sustained attention, working memory, alternating verbal fluencies, and delayed free-recall verbal memory showed floor effects (Supplementary Table 3), indicating that those cognitive functions were severely and commonly impaired in PDD patients. The ceiling effect was observed in confrontation naming (15.2%), clock drawing (32.6%), and copying a clock (72.8%) (Table 3) when analyzed in whole PD patients, and more items (confrontation naming 21.6%, sustained attention 21.6%, clock drawing 54.1% and copying a clock 86.5%) showed ceiling effects in the PD-NC subgroup (Supplementary Table 1), whereas only copying a clock showed the ceiling effect (20.5%) in the PD-MCI subgroup (Supplementary Table 2), indicating that the ceiling effects were mainly due to the PD-NC group.

3.4. Concurrent and Discriminative Validity. Concurrent validity was analyzed in total PD-CRS scores with MDRS scores, as well as subscales of PD-CRS with corresponding parts of MDRS (Table 4). PD-CRS showed fair concurrent validity with the MDRS scores (ICC = 0.731, 95% CI

Table 3: Acceptability of PD-CRS.

Item	Mean ± SD	Min-max	Skewness	Kurtosis	Floor effect (%)	Ceiling effect (%)
Immediate free-recall verbal memory	7.32 ± 2.693	0–12	−0.154	−0.653	1.1	6.5
Confrontation naming	17.02 ± 2.580	10–20	−1.131	0.840	4.3	15.2
Sustained attention	5.90 ± 2.894	0–10	−0.357	−0.822	4.3	10.8
Working memory	5.34 ± 2.190	0–10	0.481	−0.177	1.1	5.4
Clock drawing	8.00 ± 2.335	0–10	−1.467	1.812	1.1	32.6
Copying a clock	9.34 ± 1.639	0–10	−4.018	18.591	1.1	72.8
Delayed free-recall verbal memory	5.72 ± 3.068	0–12	−0.124	−0.829	6.5	1.1
Alternating verbal fluencies	7.50 ± 4.040	0–16	−0.191	−0.438	6.5	2.2
Action verbal fluencies	9.18 ± 4.501	0–24	0.417	0.300	2.2	1.1
Frontal-subcortical functions	48.96 ± 15.777	11–82	−0.382	−0.357	2.2	1.1
Instrumental-cortical functions	26.36 ± 3.274	15–30	−1.441	2.082	1.1	13.0
PD-CRS total score	75.32 ± 17.818	30–109	−0.533	−0.092	1.1	1.1

PD-CRS: Parkinson's disease-cognitive rating scale; SD: standard deviation.

Table 4: Validity of PD-CRS.

	MDRS		
	ICC	95% CI	p
PD-CRS total score	0.731	[0.602, 0.816]	<0.001
Working memory vs. MDRS (A)	0.408	[0.223, 0.577]	<0.001
Alternating verbal fluencies vs. MDRS (E)	0.470	[0.261, 0.625]	<0.001
Delayed free-recall verbal memory vs. MDRS (AF + AG)	0.638	[0.503, 0.749]	<0.001

PD-CRS: Parkinson's disease-cognitive rating scale; MDRS: Mattis Dementia Rating Scale; ICC: intraclass correlation coefficients; CI: confidence interval.

Table 5: Comparisons of PD-CRS between PD-NC, PD-MCI, and PDD groups.

	PD-NC	PD-MCI	PDD	p	PD-NC vs. PD-MCI[c]	PD-NC vs. PDD[c]	PD-MCI vs. PDD[c]
Immediate free-recall verbal memory	8.81 ± 2.132	6.70 ± 2.681	4.73 ± 1.191	<0.001[a]	<0.001	<0.001	0.014
Confrontation naming	17.57 ± 2.523	17.09 ± 2.351	14.91 ± 2.809	0.008[b]	0.717	0.006	0.051
Sustained attention	7.46 ± 2.116	5.32 ± 2.785	3.00 ± 2.646	<0.001[a]	<0.001	<0.001	0.008
Working memory	6.46 ± 2.445	4.82 ± 1.618	3.64 ± 1.362	<0.001[b]	0.012	0.001	0.168
Clock drawing	9.05 ± 1.311	7.82 ± 2.026	5.18 ± 3.573	<0.001[b]	0.007	<0.001	0.143
Copying a clock	9.84 ± 0.442	9.57 ± 0.818	6.73 ± 3.495	<0.001[b]	0.620	<0.001	<0.001
Delayed free-recall verbal memory	7.43 ± 2.714	5.11 ± 2.572	2.36 ± 2.420	<0.001[a]	<0.001	<0.001	0.002
Alternating verbal fluencies	9.70 ± 3.566	6.64 ± 3.577	3.55 ± 3.045	<0.001[b]	0.004	<0.001	0.069
Action verbal fluencies	10.97 ± 4.213	8.77 ± 4.220	4.82 ± 3.219	<0.001[a]	0.019	<0.001	0.005
Frontal-subcortical functions	59.89 ± 10.448	45.18 ± 12.901	27.27 ± 11.577	<0.001[a]	<0.001	<0.001	<0.001
Instrumental-cortical functions	27.41 ± 2.682	26.66 ± 2.272	21.64 ± 4.523	<0.001[b]	0.203	<0.001	0.004
PD-CRS total score	87.30 ± 11.244	71.84 ± 14.144	48.91 ± 14.916	<0.001[a]	<0.001	<0.001	<0.001

PD-CRS: Parkinson's disease-cognitive rating scale; PD: Parkinson's disease; PD-NC: PD patients with normal cognition; PD-MCI: PD patients with mild cognitive impairment; PDD: PD patients with dementia. [a]One-way analysis of variance (ANOVA); [b]Kruskal–Wallis test; [c]Bonferroni test.

0.602–0.816). The concurrent validity of PD-CRS-working memory with the digit span forward and backward subtest (A) of MDRS (ICC = 0.408, 95% CI 0.223–0.577); alternating verbal fluencies with initiation-preservation subscale (E) of MDRS (ICC = 0.470, 95% CI 0.261–0.625); and delayed free-recall verbal memory with free memory (AF + AG) of MDRS (ICC = 0.638, 95% CI 0.503–0.749) are shown in Table 4. These results show that the concurrent validity of subscales of PD-CRS with corresponding parts of MDRS only reach the fair scope of ICC (0.41–0.60) according to the criteria recommended by Landis and Koch. We think it is due to the different difficulty degrees of these two scales. For example, the working memory subscale of PD-CRS is a randomized list of numbers in length from 2–6 numbers and asking the subject to repeat the numbers backward. In digit span test of MDRS, it is a randomized list of numbers in length 2–4.

For discriminative validity, significant differences were observed in total PD-CRS, frontal-subcortical functions, and instrumental-cortical functions, and each PD-CRS item scores among PD-NC, PD-MCI, and PDD groups ($p < 0.001$) (Table 5). PD-MCI and PDD patients perform differently when compared with PD-NC patients. The frontal-subcortical items showed a significant decrease in the PD-MCI subgroup compared with the PD-NC subgroup ($p < 0.05$), but the instrument cortical items did not (confrontation naming $p = 0.717$ and copying a clock $p = 0.620$), which means that the cortical functions are relatively intact in PD-MCI patients (instrumental-cortical functions,

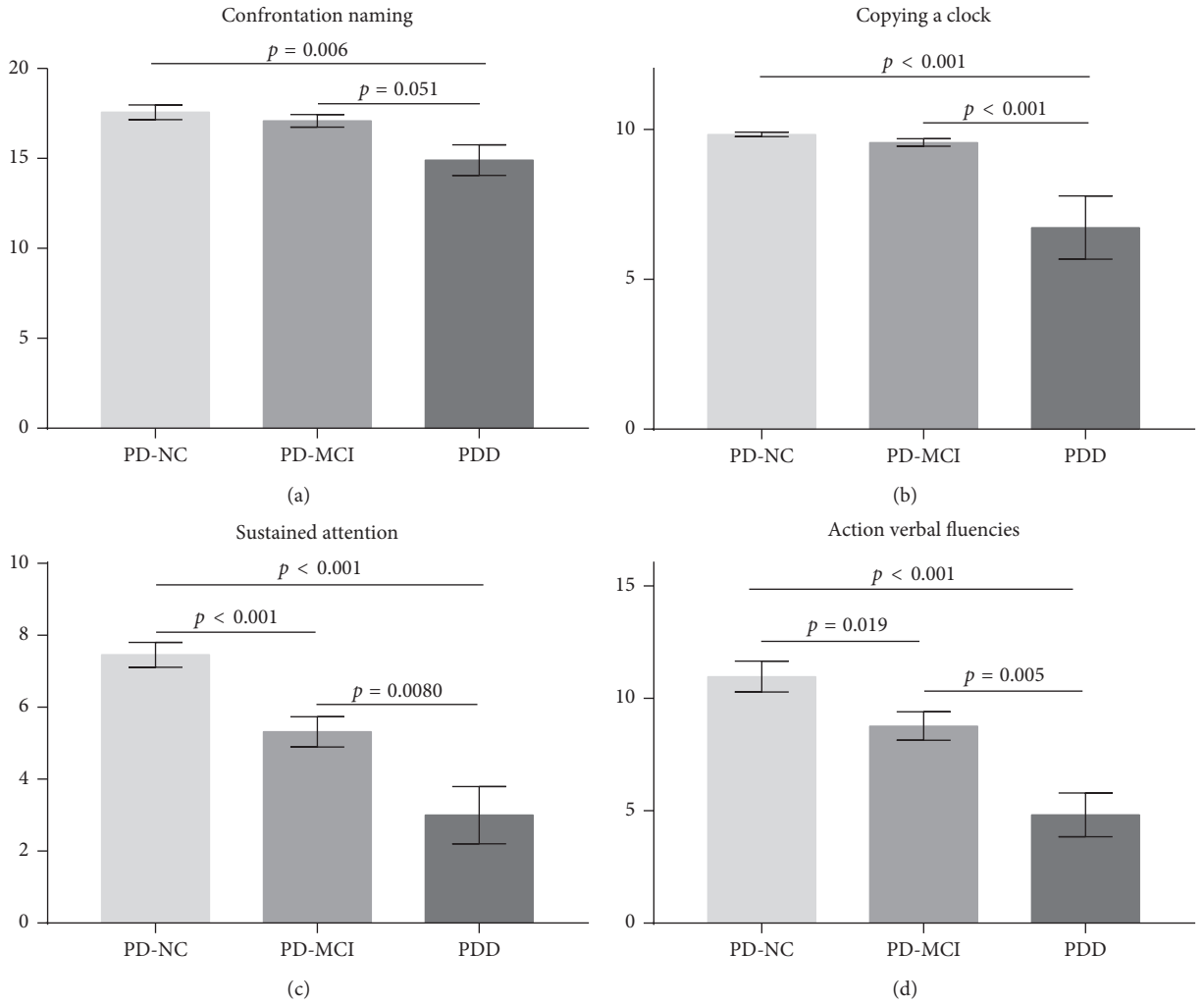

Figure 1: Comparative progression of impairment of "frontal-subcortical functions" and "instrumental-cortical functions" in PD-NC, PD-MCI, and PDD subgroups (mean ± SE). Cortical functions (confrontation naming and copying a clock) are relatively normal in PD-MCI, but had abrupt decline in the PDD group (a and b). Sustained attention and action verbal fluencies were used as examples to show marked decline of subcortical functions in both PD-MCI and PDD (c and d).

$p = 0.203$), but the subcortical functions are impaired (frontal-subcortical functions, $p < 0.001$). All the frontal-subcortical and instrumental-cortical functions showed significant decline in the PDD subgroup compared with the PD-NC subgroup, which indicates that PDD patients had global cognitive impairment. PDD patients had lowered scores in cortical functions than PD-MCI patients (instrumental-cortical functions 21.64 ± 4.523 vs. 26.66 ± 2.272, $p = 0.004$; confrontation naming 14.91 ± 2.809 vs. 17.09 ± 2.351, $p = 0.051$; copying a clock 6.73 ± 3.495 vs. 9.57 ± 0.818, $p < 0.001$), but there was no significant difference between PD-MCI and PDD in some of the subcortical functions, such as working memory ($p = 0.168$), clock drawing ($p = 0.143$), and alternating verbal fluencies ($p = 0.069$).

Comparative progression of impairment of "frontal-subcortical functions" and "instrumental-cortical functions" showed that those cortical functions (confrontation naming, copying a clock) are relatively normal in PD-MCI, but had abrupt decline in the PDD group (Figures 1(a) 1(b)). Subcortical functions had marked decline in both PD-MCI and PDD. Sustained attention and action verbal fluencies were listed as examples (Figures 1(c) and 1(d)). These results indicated that PD-MCI patients and PDD patients have different cognitive impairment profiles and patterns. The worse performance in cortical functions of PDD patients than PD-MCI patients showed a pattern of cognitive impairment transition from PD-MCI to PDD.

3.5. Discriminative Power of PD-CRS for Diagnosing PD-MCI and PDD. ROC curve indicated that a PD-CRS total score of 80.5 raised the maximum cutoff accuracy for detecting PD-MCI (AUC: 0.803, 95% CI: 0.709–0.898, $p < 0.001$, sensitivity 75.7%, specificity 75.0%, PPV 75.2%, and NPV 75.5%) (Figure 2, Table 6). The PD-CRS total score of 73.5 is the maximum accuracy cutoff for detecting PDD (AUC: 0.984, 95% CI: 0.957–1.000, $p < 0.001$, sensitivity 89.2%, specificity 98.9%, PPV 98.8%, and NPV 90.1%) (Figure 2, Table 6).

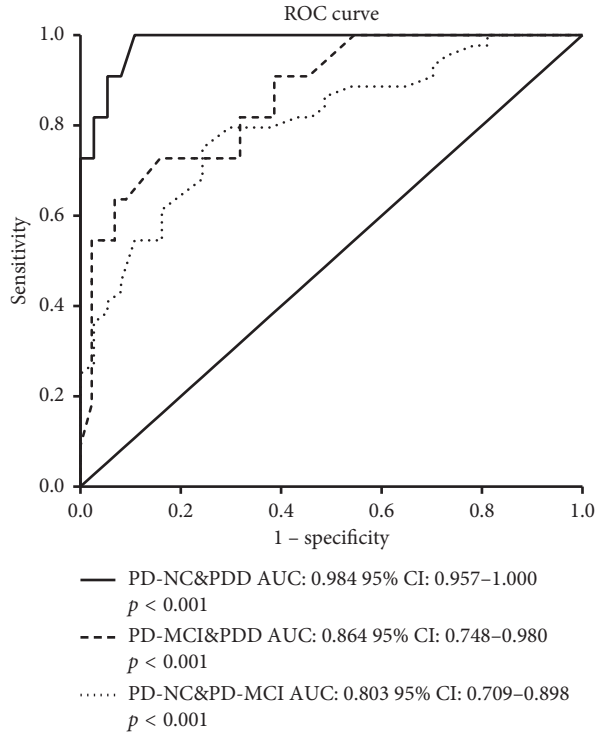

Figure 2: Discriminative power of PD-CRS for diagnosing PD-MCI and PDD. AUC for differentiating PD-MCI is 0.803, 95% CI: 0.709–0.898, $p < 0.001$. AUC for detecting PDD is 0.984, 95% CI: 0.957–1.000, $p < 0.001$.

Table 6: Accuracy measures of PD-CRS.

Scale version	Cutoff	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	LR (+)	LR (−)
PD-NC/PD-MCI (AUC 0.803)	78.5	78.4	65.9	69.7	75.3	2.29	0.33
	80.5	**75.7**	**75.0**	**75.2**	**75.5**	**3.03**	**0.32**
	81.5	73.0	77.3	76.3	74.1	3.22	0.35
PD-MCI/PDD (AUC 0.864)	54.5	90.9	63.6	71.4	87.5	2.49	0.14
	57.5	**84.1**	**72.7**	**75.5**	**82.1**	**3.08**	**0.22**
	58.5	77.3	72.7	73.9	76.2	2.83	0.31
PD-NC/PDD (AUC 0.984)	69.0	94.6	90.9	91.2	94.4	10.39	0.06
	73.5	**89.2**	**98.9**	**98.8**	**90.1**	**81.09**	**0.11**
	75.0	86.5	99.6	99.5	88.1	216.25	0.14

PD-CRS: Parkinson's disease-cognitive rating scale; SD: standard deviation; PD: Parkinson's disease; PD-NC: PD patients with normal cognition; PD-MCI: PD patients with mild cognitive impairment; PDD: PD patients with dementia; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR−: negative likelihood ratio.

4. Discussion

This Chinese version of PD-CRS was revised based on the culture background of Chinese people. Our results showed that the revised Chinese version of PD-CRS is a reliable, acceptable, valid, and useful neuropsychological battery that could accurately diagnose PDD as proven in previous reports [13, 14]. The PD-CRS showed a high internal consistency, test-retest reliability, and inter-rater reliability. The Chinese version of PD-CRS showed fair concurrent validity with the Chinese version of MDRS. No floor effects were observed in the total score of PD-CRS and individual items in whole PD patients, PD-NC, and PD-MCI subgroups; but items of immediate free-recall verbal memory, confrontation naming, sustained attention, working memory, alternating verbal fluencies, and delayed free-recall verbal memory showed floor effects in the PDD group, indicating that PDD patients were commonly and severely impaired in these functions. Ceiling scores were found in confrontation naming, clock drawing, and copying a clock in PD patients analyzed as a whole, but the ceiling scores were mainly distributed among PD-NC patients, and those items were still able to discriminate cognitive impairments in PD-MCI and PDD patients.

There is a spectrum of cognitive dysfunction, ranging from MCI to dementia in PD patients [16]. Executive dysfunction, impaired verbal fluency, visuospatial deficits, as well as encoding memory dysfunction are cognitive profiles

of PD-MCI [6–8]. At later stages, both subcortical and cortical functions might be impaired [17]. PD-MCI subjects differed from PD-NC patients in all frontal-subcortical items, whereas the two instrumental-cortical functions items were relatively intact in PD-MCI patients, but were selectively impaired in PDD patients. These results showed different cognitive impairment patterns between PD-MCI and PDD patients. The cutoff value for diagnosis of PD-MCI is 80.5 with the sensitivity of 75.7% and the specificity of 75.0%. PD-MCI subjects are at a higher risk to develop dementia compared with normal cognition PD patients; thus, the discriminant ability to diagnose PD-MCI by the PD-CRS suggests that this scale may be a good instrument for screening purposes. PD-CRS could accurately diagnose PDD, and the cutoff value for diagnosis of PDD is 73.5 with the sensitivity of 89.2% and the specificity of 98.9%. PDD patients showed a significant difference with PD-NC in all subcortical and cortical items, indicating PDD patients had global cognitive impairments.

There were two limitations in the present study. First, we have small sample of PDD patients which might cause bias to some results, such as the high level of floor effects in PDD subgroups. Second, PD patients with high BDI scores which might act as a confounding factor for cognitive function test were not excluded. There were 7 out of 44 PD-MCI patients (15.91%) and 4 out of 11 PDD patients (36.36%) who had BDI scores ≥20. The cognitive function was analyzed between BDI <20 and BDI ≥20 in PD-MCI and PDD subgroups separately. The results showed that PD-CRS total score and each item score have no significant difference between BDI <20 and BDI ≥20 scores in both PD-MCI and PDD subgroups (Supplementary Tables 4 and 5). A link between mood symptoms and cognitive impairment in PD has been found, but studies have been inconsistent regarding the relationship between mood symptoms and cognitive function. Ng et al. did not find significant correlation between early depression and cognitive function in both baseline and follow-up tests [18]. Jones et al. reported that depressive symptoms may be a harbinger for future cognitive decline among PD patients [19]. Petkus et al. found that poorer cognitive performance, across all cognitive domains, was a risk factor for increased symptoms of anxiety and depression [20]. In the present study, although we did not find significant difference of cognitive function between different BDI scores subgroups, it would be better to match BDI scores between subgroups to exclude the potential effects of depression on cognitive test.

5. Conclusion

Overall, our results showed that the Chinese version of PD-CRS is an applicable and valid tool for assessing cognition in PD patients. It is sensitive in detecting the cognitive impairment transition from predominantly subcortical impairments in PD-MCI patients to global cognitive decline in PDD patients.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure

Yuyan Tan, Weiguo Liu, and Juanjuan Du are the co-first authors.

Conflicts of Interest

The authors have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Supplementary Table 1: acceptability of PD-CRS in NC; Supplementary Table 2: acceptability of PD-CRS in PD-MCI; Supplementary Table 3: acceptability of PD-CRS in PDD; Supplementary Table 4: cognitive function comparison between BDI <20 and ≥ 20 in PD-MCI; Supplementary Table 5: cognitive function comparison between BDI <20 and ≥ 20 in PDD. (*Supplementary Materials*)

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Research Article

Atomoxetine Does Not Improve Complex Attention in Idiopathic Parkinson's Disease Patients with Cognitive Deficits: A Meta-Analysis

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Objectives. To evaluate the effects of atomoxetine on complex attention and other neurocognitive domains in idiopathic Parkinson's disease (PD). *Methods*. Interventional trials reporting changes in complex attention and other neurocognitive functions (Diagnostic and Statistical Manual of Mental Disorders-5) following administration of atomoxetine for at least 8 weeks in adults with idiopathic PD were included. Effect sizes (Cohen's *d*), the standardized mean difference in the scores of each cognitive domain, were compared using a random-effects model (MetaXL version 5.3). *Results*. Three studies were included in the final analysis. For a change in complex attention in PD with mild cognitive impairment (MCI), the estimated effect size was small and nonsignificant (0.16 (95% CI: −0.09, 0.42), $n = 42$). For changes in executive function, perceptual-motor function, language, social cognition, and learning and memory, the estimated effect sizes were small and medium, but nonsignificant. A deteriorative trend in executive function was observed after atomoxetine treatment in PD with MCI. For a change in global cognitive function in PD without MCI, the estimated effect size was large and significant. *Conclusion*. In idiopathic PD with MCI, atomoxetine does not improve complex attention. Also, a deteriorative trend in the executive function was noted.

1. Introduction

Locus coeruleus (LC) is a small pontine nucleus of about 15,000 noradrenergic neurons innervating a large number of cortical and subcortical areas in the brain, for many of which, it is the only source of norepinephrine [1]. It serves as the major noradrenergic supply to the forebrain including the prefrontal cortex and is critically important for cognitive functions [2, 3]. Loss of LC neurons has been correlated with cognitive decline in different neurodegenerative diseases [4–6]. Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder, primarily characterized by bradykinesia, rigidity, and tremor [7]. It results from the degeneration of dopaminergic neurons in the substantia nigra caused by the accumulation of misfolded α-synuclein into Lewy neurites and Lewy bodies [7]. Interestingly, cognitive decline coarises with motor symptoms in idiopathic PD [8]. Several other clinical features throughout the different stages of idiopathic PD have been attributed to the central and peripheral norepinephrine imbalance [9]. Some of these features include autonomic and olfactory deficits, depression, and sleep disturbances along with emotional disorders [10].

Similar to other neurodegenerative diseases, loss of LC neurons has been found in idiopathic PD [11, 12]. Neuronal

loss in LC correlates not only with the stage of idiopathic PD pathology [13, 14] but also with the cognitive decline [15–17]. However, as compared to the other neurodegenerative diseases, neuronal loss in LC in idiopathic PD is more extensive resulting in a widespread degeneration of the noradrenergic axons arising from it. A decline in the noradrenergic function of LC can lead to a wide array of symptoms depending upon the projection target and its function, e.g., while there is an alteration in dopamine release from both the substantia nigra and the ventral tegmental area, the clinical manifestations could be completely different. The substantia nigra-related dopamine deficiency can lead to PD but that in the ventral tegmental area would affect attention. The attention-executive function-working memory system is likely to involve the prefrontal cortex, whereas semantic memory is largely dependent on the hippocampal circuitry [18, 19]. Evidence suggests that in idiopathic PD, α-synuclein accumulation in LC happens earlier than in substantia nigra [11, 20, 21]. This puts LC in a critical position in the early stages of idiopathic PD, making it a potential target for treatment [22].

Norepinephrine (NE) has an important role in attention. The prefrontal cortex and parietal cortex-mediated attention systems are under strict modulation of NE. The spiking pattern of LC determines arousal state and alertness, while the depletion of NE in the forebrain leads to a lack of attention and cognitive deficit [23]. Several treatment strategies have been tried to treat cognitive impairment involving the noradrenergic system in idiopathic PD. Adrenoceptor subtype-specific agonists and antagonists [24–27], norepinephrine precursors [28–30], and both selective and nonselective norepinephrine transporter (NET) inhibitors [31–34] have been used with varied results. Atomoxetine is a selective norepinephrine reuptake inhibitor working mainly on the norepinephrine transporters at the noradrenergic axon terminals throughout the brain [35]. It is approved by the United States Food and Drug Administration for the treatment of attention-deficit hyperactivity disorder (ADHD). Atomoxetine has minimal effects on other neuromodulator receptors [36], thus qualifying as a perfect candidate for teasing out norepinephrine-specific effects in ameliorating mild cognitive impairment (MCI) in idiopathic PD. As noradrenergic axons extensively and variably innervate several areas of the brain, systemic administration of any drug manipulating it will have a mixed effect on the functions depending on the dose and area of the brain involved in that particular function [37]. This can explain why different neurocognitive functions exhibit variable effects following the administration of the same norepinephrine-modulating drug [32, 38]. The picture gets more complicated in a disease state like idiopathic PD, where more than one neuromodulatory system is affected and mutual meta-modulatory effect on one system or another cannot be ruled out [9, 39].

The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) outlines six key neurocognitive domains, namely, executive function, perceptual-motor function, language, learning and memory, social cognition, and complex attention [19]. Neurocognitive deficit in one domain or the other should be ascribed to different brain regions and circuitries. It is to be mentioned that complex attention holds particular importance in idiopathic PD. Attention is the behavioral and cognitive process of selectively concentrating on a discrete aspect of information, whether deemed subjective or objective while ignoring other perceivable information. As per DSM-5, complex attention involves sustained attention, divided attention, selective attention, and information processing speed. Interestingly, the concentration of norepinephrine metabolite in the cerebrospinal fluid correlates well with attention and reaction time-dependent scores in idiopathic PD patients [27]. This leads to a possibility that atomoxetine may compensate for the noradrenergic deficits and improve complex attention in idiopathic PD patients.

In parallel, from a clinical point of view, it is important to understand the differential effects of noradrenergic modulation by atomoxetine on different neurocognitive domains. Multiple trials have demonstrated the beneficial effects of atomoxetine on cognitive functions, including attention, in adults with ADHD [40]. However, it is not very clear whether these beneficial effects can be extrapolated to a neurodegenerative disorder, such as idiopathic PD. Hence, this meta-analysis was conducted to evaluate the effects of atomoxetine on complex attention and other neurocognitive domains in idiopathic PD.

2. Materials and Methods

2.1. Study Design. The study protocol can be accessed in PROSPERO (CRD42018106560). Completed and published interventional trials investigating the effects of atomoxetine on cognitive functions in idiopathic PD were included. The inclusion criteria were as follows: interventional studies that included patients of age ≥18 years of either gender, diagnosed with idiopathic PD, and patients who had received atomoxetine of any dose for at least 8 weeks, and any domain of cognitive function was reported using any scale irrespective of statistical significance. The exclusion criteria were initiation or change in dose of any confounding comedication after initiating treatment with atomoxetine. The primary outcome of the study was the change in clinical score in any individual domain of cognitive function (DSM-5) [19]. Other reported neuropsychiatric assessments apart from cognitive functions were excluded from the analysis.

2.2. Search Strategy. MEDLINE/PubMed, IndMED, and Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL) and Cochrane Methodology Register) were searched until 28 November 2019. The search terms used in various combinations were "atomoxetine," "cognition," "cognitive therapy," "cognitive function," "idiopathic Parkinson's disease," "iPD," "Parkinson's disease," "PD," "neurodegenerative disease," "mild cognitive impairment," and "MCI." These search terms were adapted for use with different bibliographic databases in combination with database-specific filters for studies, if available. The search strategy was used to obtain titles and abstracts of relevant

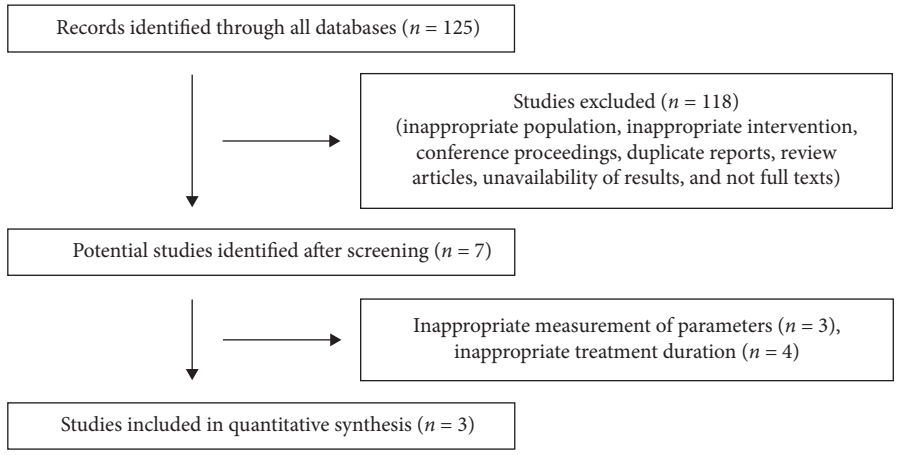

Figure 1: Study flowchart.

studies in the English language, and they were independently screened by two authors, who subsequently retrieved abstracts, and if necessary, the full text of articles to determine suitability. Disagreement resolution was done with a third author.

2.3. Data Extraction and Management. The data extraction was carried out independently by two authors using a preformatted data extraction spreadsheet. No assumptions or simplifications were made during data extraction. The included studies were assessed for risk of bias by two authors independently. Categorization of the individual study reported test scales of cognitive functions into each of the six DSM-5[19] delimited domains was performed by an experienced psychiatrist as reported in the literature [41–45]. In case of ambiguity regarding the fitness of a scale to any particular domain of cognitive function defined by DSM-5 [19], the corresponding data were excluded. The data obtained by using scales estimating the global cognitive function were analyzed separately. The direction of scoring in each scale was considered in the analysis. A random-effects model was used to ensure the robustness of the model across various population and susceptibility to outliers. Meta-analysis was performed wherever adequate data were available. Effect sizes (Cohen's d), the standardized mean difference in the scores of each cognitive domain, were compared in the patients using a random-effects model using MetaXL version 5.3 (© EpiGear International Pvt. Ltd.).

Attrition bias due to the amount, nature, or handling of incomplete outcome data was investigated. Attrition rate in terms of dropouts, loss to follow-up, and withdrawals were investigated. Issues of missing data and imputation methods were also critically appraised [46]. Heterogeneity was analyzed using $\chi 2$ test on $n - 1$ degrees of freedom, with an α error of 5% used for statistical significance and with an i^2 test [47, 48]. The i^2 values of 25%, 50%, and 75% corresponded to low, medium, and high levels of heterogeneity, respectively. Effect sizes of <0.2 were considered small, 0.2–0.8 were considered medium, and >0.8 were considered large [49].

3. Results

A total of 125 studies were screened, and three studies [32, 38, 50] were included in the final analyses (Figure 1). Out of these three studies, two were double-blind randomized control trials and one was an open-label single-arm trial. Two of these three studies were of moderate to high quality (Supplementary Figure 1). Two studies [32, 38, 50] included PD patients with MCI. The demographic details and cognitive measurements of the included studies are enumerated in Table 1. For a change in complex attention, the estimated effect size was small and nonsignificant (0.16 (95% CI: −0.09, 0.42) ($i^2 = 23\%$, $p = 0.21$), $n = 42$) (Figure 2). For a change in executive function, only one study [50] was included and the estimated effect size was medium but nonsignificant (−0.30 (95% CI: −0.62, 0.02), $n = 30$), although a trend of deterioration with atomoxetine was found (Supplementary Figure 2). For changes in perceptual-motor function (visuospatial perception), language (expressive language/confrontation naming), and social cognition (Neuropsychological Assessment Battery: Judgement), only one study [50] was included and the estimated effect sizes were small and medium, but nonsignificant (−0.06 (95% CI: −0.78, 0.65), $n = 30$; −0.12 (95% CI: −0.83, 0.60), $n = 30$; and 0.28 (95% CI: −0.44, 0.99), $n = 30$, respectively). For a change in learning and memory (Hopkins Verbal Learning Test-Revised Recognition Discrimination score), only one study [38] was included and the estimated effect size was small and nonsignificant (0.90 (95% CI: 0.06, 1.74), $n = 12$). For a change in global cognitive function (Mini-Mental State Examination (MMSE)) in PD without MCI, only one study [32] was included and the estimated effect size was large and significant (1.21 (95% CI: 0.64, 1.79), $n = 55$).

4. Discussion

We conducted this meta-analysis to evaluate the effects of atomoxetine on complex attention and other individual cognitive domains in idiopathic PD. We found that atomoxetine does not improve complex attention. It does not have a significant effect on other domains of cognitive

Table 1: Characteristics of the included studies.

Author, year (country)	Type of study	Demographic details			Comparator	Assessment of cognitive functions	
		Age (years) (mean ± SD)	Dose of atomoxetine (duration)	Concomitant medications		Cognitive domain (DSM-5)	Scale and subscale used
Hinson et al. 2016 (USA)	Double-blind randomized control trial	68 ± 8	40 mg/d (weeks 1-2); 80 mg/d (weeks 3–10); no dose adjustments	Memantine, anticholinergics, MAO inhibitors, neuroleptics, and acetylcholinesterase inhibitors excluded	Placebo	Complex attention	Paced Auditory Serial Addition Test
						Complex attention	Neuropsychological Assessment Battery: Part A and Part D
						Social cognition	Neuropsychological Assessment Battery: Judgement
						Executive function	Delis–Kaplan Executive Function System—Inhibition Time
						Executive function	Delis–Kaplan Executive Function System—Inhibition-Switching Time
						Executive function	Delis–Kaplan Executive Function System—Number-Letter Switching Time
						Executive function	Delis–Kaplan Executive Function System—Proverbs
						Executive function Language	Wechsler Adult Intelligence Scale: Digit Span Expressive Language/Confrontation Naming
						Perceptual-motor function	Visuospatial Perception
						Complex attention	Conners' Adult ADHD Rating Scale (Inattention)
						Complex attention	Conners' Adult ADHD Rating Scale (Hyperactivity)
						Complex attention	Conners' Adult ADHD Rating Scale (Impulsivity)
						Complex attention	Conners' Adult ADHD Rating Scale (Problems with self-concept)
						Complex attention	Conners' Adult ADHD Rating Scale (ADHD index)
Marsh et al. 2009 (USA)	Open-label single-arm trial	57.3 ± 7.2	25 mg/d (week 1), 50 mg/d (weeks 2–4), 75 mg/d (week 5), 100 mg/d (weeks 6–8); minimum 2.5 mg/d dose reductions for intolerance	Dopamine agonists, levodopa, apomorphine, COMT inhibitors, anticholinergics, selegiline, amantadine, antidepressants, atypical antipsychotics, benzodiazepine/ hypnotics allowed	Pretreatment vs. posttreatment	Learning and memory	Hopkins Verbal Learning Test-Revised Recognition Discrimination score
						Complex attention	Conners' Adult ADHD Rating Scale Long Form (Inattention/Memory)
						Complex attention	Conners' Adult ADHD Rating Scales Long Form (Hyperactivity)
						Complex attention	Conners' Adult ADHD Rating Scales Long Form (Impulsivity/Emotional Lability)
						Complex attention	Conners' Adult ADHD Rating Scales Long Form (Self-concept)
						Complex attention	Conners' Adult ADHD Rating Scales Long Form (Total ADHD Symptoms)
Weintraub et al. 2010 (USA)	Double-blind randomized control trial	64.3 ± 10.5	40 mg/d (weeks 1-2), 80 mg/d (weeks 3–8); 40 mg/d allowed if indicated	Antidepressants allowed; MAO inhibitors excluded	Placebo	Global cognitive function	Mini-Mental State Examination

ADHD: attention-deficit hyperactivity disorder; COMT: catechol-O-methyl transferase; DSM-5: Diagnostic and Statistical Manual of Mental Disorders-5; MAO: monoamine oxidase; NRI: norepinephrine reuptake inhibitor.

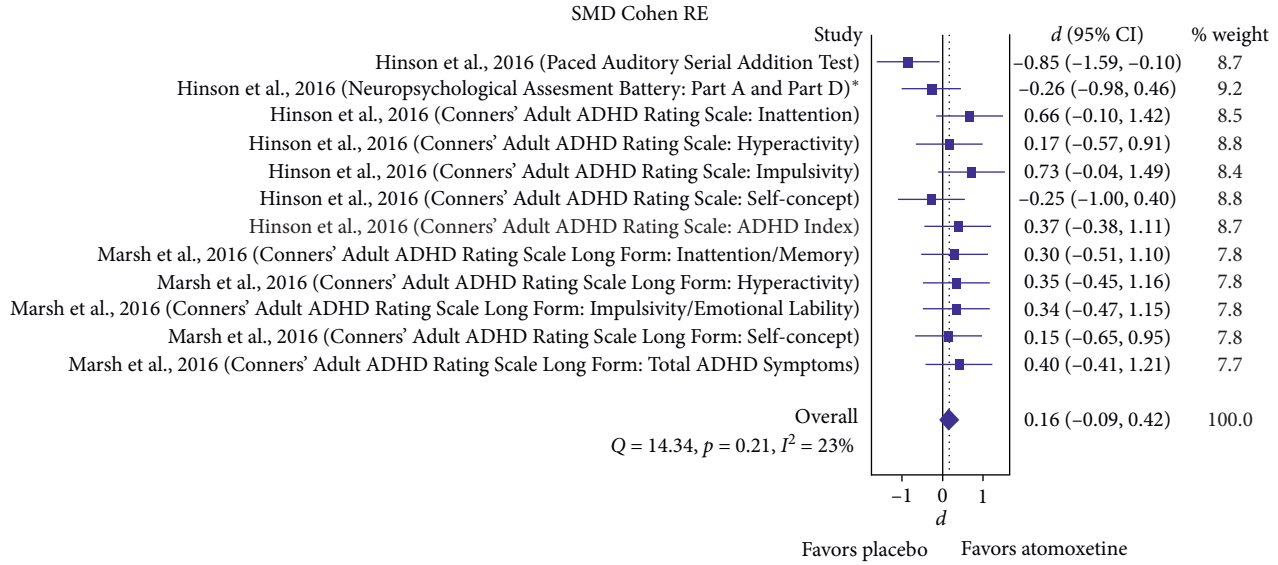

Figure 2: Forest plots showing the change in complex attention (DSM-5) (for Marsh et al. 2009 study, preatomoxetine data were compared to postatomoxetine data; for Hinson et al. 2016, postatomoxetine data were compared to placebo data) (ADHD: attention-deficit hyperactivity disorder). *The scores of Neuropsychological Assessment Battery (Part A and Part D) were combined.

function as well. Rather, a trend of deteriorating effect of atomoxetine was observed on executive function, although the results were not statistically significant. In the included studies, the patients received standard-of-care treatment, including dopaminergic drugs, and atomoxetine was used as an adjunctive agent.

A recently published systematic review [51] has efficiently summarized the effects of atomoxetine in idiopathic PD-related executive function. The authors have identified an improvement following atomoxetine administration. But such results need to be interpreted with caution. A majority (4 out of 7) of the included studies used a single dose of atomoxetine. In a chronic progressive neurodegenerative disorder, single-dose trials may lack relevance. In contrast, our study has included a minimum of 8 weeks' duration of atomoxetine administration, and further, we have evaluated the effects of atomoxetine on specific neurocognitive domains.

Although the main use and popularity of atomoxetine are generally attributed to the alleviation of ADHD, thereby rendering cognitive enhancement [52], it is understandable that the functions of atomoxetine are critically dependent on norepinephrine dynamics and noradrenergic receptor status, which can vary from disease to disease. The effects of atomoxetine on a specific disease depend on the affected brain area, its noradrenergic innervation, and the distribution of the adrenoceptors. Without these considerations, any generalization in terms of predicting the effects of atomoxetine across different diseases may go erroneous. Atomoxetine has been proven beneficial in ADHD; however, our results show that it does not improve complex attention in PD. Moreover, a trend of worsening executive function, which is also a prefrontal cortex- (PFC-) dependent function, was observed in PD patients receiving atomoxetine. This indicates that disease-specific noradrenergic pathophysiology will determine the outcome of atomoxetine treatment.

Atomoxetine prevents the reuptake of norepinephrine, thereby increasing its availability in the extracellular space for a long duration. PET studies suggest that NET deficiency occurs in PD [53] but not in ADHD [54]. Hence, in PD, atomoxetine has less amount of substrate to bind leading to a suboptimal availability of NE around the degenerating axons. In general, NE has a low affinity for $\alpha 1$ and a high affinity for $\alpha 2$ adrenoceptors. Thus, at a lower concentration of NE, $\alpha 2$ is preferentially more activated than $\alpha 1$[23]. Interestingly, the compensatory upregulation of $\alpha 1$ adrenoceptors and downregulation of $\alpha 2$ adrenoceptors have been reported in the brain in PD [55]. In general, $\alpha 1$ and $\alpha 2$ adrenoceptors have contrasting effects on PFC functioning. An increased $\alpha 1$ adrenoceptor stimulation is known to impair PFC functioning [23, 56, 57], whereas in contrast, increased $\alpha 2$ adrenoceptor functioning improves PFC function [23, 58]. Similarly, it has been reported that $\alpha 2$ antagonists can deteriorate the PFC function [59, 60]. Thus, in PD, even a suboptimal increase in the extracellular NE availability may render no effect or worsening effect due to a shifted receptor balance to increased $\alpha 1 : \alpha 2$ ratio. To the best of our knowledge, such a shift in the adrenoceptor ratio or noradrenergic degeneration has not been reported in ADHD. This explains why atomoxetine may remain ineffective in PD-MCI, but not in ADHD.

This may also explain why PD patients without MCI may have beneficial effects from atomoxetine. A smaller subset of PD patients does not develop MCI [61]. In the study by Weintraub et al. [32, 38, 50], the global cognitive function, as tested by MMSE, was significantly improved with a large effect size following atomoxetine treatment in PD patients without MCI. At the earliest stage of noradrenergic axon degeneration, there could still be sufficient NET left for atomoxetine to bind. Further, compensatory adrenoceptor upregulation and downregulation might not occur that

early. Thus, early intervention with atomoxetine can be beneficial in PD to prevent MCI and later dementia; however, this warrants further investigations. Besides, the fact that the frontal/executive function is not covered by MMSE emphasizes the variable role of noradrenergic intervention on the different cognitive functions [62, 63]. The inability of MMSE to sensitively identify MCI in PD should be given importance. Future studies in this field might be benefitted by using an alternative test, such as the Montreal Cognitive Assessment (MoCA), instead of MMSE [64].

Our study has certain limitations. We could retrieve only three studies fulfilling the eligibility criteria, and as a result, the sample size was relatively small. The study designs also varied. Next, we could not assess the effects of atomoxetine on each domain of cognitive function due to the lack of data. Further, all the three included studies did not uniformly report data on the specific cognitive domains, and for some of the outcomes, we could include only one study. The dose and duration of atomoxetine varied. The sensitivity of the outcome measures could also be affected by the patient heterogeneity at baseline and differences in the assessment scales. [65].

5. Conclusion

To the best of our knowledge, this is the first meta-analysis to demonstrate that in idiopathic PD with MCI, atomoxetine does not improve complex attention, contrary to the general notion in the field. Still, long-term randomized controlled trials in a large pool of patients are necessary to further elucidate the role of atomoxetine on cognitive functions in idiopathic PD.

Data Availability

All data are included in the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest associated with this article.

Authors' Contributions

AG and SD have contributed equally. AG has conceptualized the review; AG, SD, SS, and PK have drafted the study protocol; SD and AG were involved with literature search and study selection; SKB, SS, and PK were involved in disagreement resolution and finalization of the included studies; SD and AG have extracted data from the studies; SD performed the risk of bias analyses; SD has performed the analyses; AG, SD, SKB, KR, SS, PK, and NSN have interpreted the analyses; AG, SD, SKB, KR, and SS have drafted the review; SS, PK, and NSN have provided expert inputs and updated the final review.

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Supplementary Materials

Supplementary Figure 1: risk of bias summary: review authors' judgments about each risk of bias item for each included study. Supplementary Figure 2: forest plot showing the change in executive function (DSM-5). (*Supplementary Materials*)

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Research Article

Trait Impulsivity Is Independent of Mild Cognitive Impairment in a Parkinson's Disease Cohort

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Introduction. Patients with Parkinson's disease (PD) commonly experience cognitive deficits and some also develop impulse control disorders (ICDs); however, the relationship between impulsivity and cognitive dysfunction remains unclear. This study investigated whether trait impulsivity associates with mild cognitive impairment (MCI), or is altered in a PD patient cohort with MCI. *Methods*. A total of 302 patients with idiopathic PD were recruited sequentially from three Australian Movement Disorder clinics. Based on cognitive scores, participants were divided into two groups, one defined as having mild cognitive impairment (PD-MCI; $n = 113$) and the other with normal cognitive function (PD-C; $n = 189$). Trait impulsivity was evaluated using the Barrett Impulsiveness Scale 11 (BIS-11). Total impulsivity scores, as well as subscale scores, were compared between PD-C and PD-MCI groups. *Results*. The PD-MCI cohort had significantly lower scores in all cognitive domains, and mirrored expected clinical differences in medication, motor symptoms, and disease duration, when compared to the PD-C cohort. Self-reported impulsivity was not significantly different between groups, nor was there a difference within first-order subscale scores: attention ($p = 0.137$), cognitive instability ($p = 0.787$), self-control ($p = 0.503$), cognitive complexity ($p = 0.157$), motor impulsivity ($p = 0.559$), or perseverance ($p = 0.734$) between the PD-MCI and PD-C groups. *Conclusions*. These findings suggest that impulsive traits and behaviors are independent of changes in cognitive state and are not altered in PD patients with mild cognitive impairment.

1. Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder in which the cardinal motor symptoms are accompanied by a variety of nonmotor symptoms (NMS) including olfactory, autonomic, psychiatric, and cognitive dysfunction. Prodromal cognitive deficits are of particular interest, offering potential insight into disease progression and early diagnosis, as well as targets for disease-modifying therapies. Cross-sectional studies have observed that approximately 30% of people with PD (PwP) have dementia [1, 2]. Furthermore, a 20-year longitudinal Australian study revealed that over 80% of PwP develop increasing cognitive impairment as the disease progresses and eventually become demented [3].

There has also been increasing awareness of the occurrence of abnormal impulsive-compulsive behaviors in PD patients as the disease progresses, particularly those

treated with dopamine agonist drugs, which have been found to occur in as many as ~46% of patients followed over a 5-year period [4–6]. These have been collectively termed impulse control disorders (ICDs), include pathological gambling, shopping, eating, hoarding, and hypersexuality, as well as compulsive use of dopaminergic medications ("dopamine dysregulation syndrome") [7, 8], and are all regarded as compulsive reward-seeking forms of behavior. They confer heightened levels of distress for both patients and carers, as well as having serious implications for quality of life [9]. Heightened trait impulsivity is present in a subset of PD patients, particularly males [10], and is considered a risk factor for the development of ICDs.

The neural substrate of ICDs and increased impulsivity in PD is thought to involve dysregulation in mesolimbic and mesocortical networks, and changes in dopamine receptor (D2 and D3) binding in the ventral striatum [5, 11], but specific neuropathological correlates have not been identified. However, based on the disease staging studies by Braak et al., it might be envisaged that changes in impulsivity could correlate with Stage V, in which the Lewy pathology extends to the mesolimbic cortex, and could precede, or overlap with, the development of impaired cognition, as there is further extension to neocortical areas in Stage VI of the disease [12].

Although impulsivity and cognitive impairment frequently coexist in PD, it is unclear whether there are any interactive effects between them during the course of the disease. A link between impulsive traits and low cognitive scores has been observed in other cohorts, such as children with attention-deficit hyperactive disorder (ADHD) [13]. In addition, preliminary evidence suggests that, in PD, cognitive characteristics such as poor executive abilities, as well as poor action control and response inhibition, and certain personality traits such as negative affectivity and high premorbid levels of novelty seeking, may have impact on impulsivity and be risk factors for the development of ICDs [6, 11, 14]. However, relatively little is known about the link between cognitive abilities and behavioral changes in patients with PD, and there have been conflicting findings in the literature [15–17]. In particular, the relationship between subclinical impulsiveness and mild cognitive impairment (PD-MCI) in patients without a diagnosed ICD remains unclear, as previous studies have focused on cohorts with diagnosed behavioral disorders.

Accordingly, the aim of this cross-sectional study was to evaluate the relationship between MCI and subclinical impulsivity as measured using the Barratt Impulsiveness Scale 11 (BIS-11) in an Australian multicenter PD patient cohort. More specifically, we questioned whether in PD patients with MCI, there are changes in attentional and motor impulsiveness, and in measures of cognitive complexity and instability.

2. Methodology

2.1. Participants. A total of 302 patients were recruited sequentially into the Australian Parkinson's Disease Registry (APDR) from Movement Disorder Clinics at the Perron Institute in Perth, St. Vincent's Hospital in Melbourne, and Royal North Shore Hospital in Sydney. In all cases, the diagnosis of idiopathic PD was confirmed in accordance with the UK Brain Bank criteria prior to inclusion in the study. At the time of all assessments, patient response to medication was at optimum levels ("ON" period). Written informed consent was obtained from all participants, in accordance with the National Health and Medical Research Council guidelines. Patients who were unable to complete the cognitive and impulsivity protocols or had a diagnosed ICD were excluded from this study.

2.2. Demographic and Clinical Assessment. Patient demographic and clinical information was collected, including age, gender, date of diagnosis, motor symptom severity, smoking status, dopaminergic medications, and deep brain stimulation (DBS) history. For each patient, the total daily intake of all dopaminergic medications was converted to a levodopa equivalent dose (LED), as described elsewhere [18]. Part III of the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III) was employed to evaluate the severity of motor symptoms and was conducted by a clinician or trained research nurse. Lastly, patient quality of life data were collected using the self-assessed, 39-item Parkinson's Disease Questionnaire (PDQ-39) [19].

2.3. Assessment of Impulsivity. The Barratt Impulsiveness Scale 11 (BIS-11) is a self-report validated evaluation and assesses impulsivity as a multifaceted entity [20]. Second-order attentional impulsiveness is described as an inability to concentrate and can be categorised into first-order subscales for attention and cognitive instability. Motor impulsiveness is the tendency to act without thinking, with first-order motor and perseverance scales. Lastly, nonplanning impulsiveness is an inability to plan for the future, within which there are first-order subscales for cognitive complexity and self-control. The BIS-11 is entirely self-rated, with each item marked on a four-point scale, giving patients a score between 30 and 120. As the scoring scheme is reversed in some questions, each question was marked individually to ensure that higher BIS-11 scores gave a true indication of heightened impulsiveness.

2.4. Assessment of Global Cognition. Global cognition impairments were assessed using Addenbrooke's Cognitive Examination-Revised (ACE-R) [21], which has been used previously to determine cognitive impairment in PD patient cohorts [22, 23]. The ACE-R evaluated five prominent cognitive domains, with a maximum total score of 100 points: orientation and attention (18 points), memory (26 points), verbal fluency (14 points), language (26 points), and visuospatial (16 points) abilities. In all cognitive domains, lower scores represent poorer cognitive abilities. On the basis of the ACE-R scores, patients were allocated to either an MCI group (PD-MCI) or a cognitively normal group

(PD-C), according to a verified total ACE-R score cut-off of 88.5 (sensitivity 0.68 and specificity 0.91) [24].

2.5. Statistical Analysis. All data were analysed using IBM-SPSS (v. 25, IBM Corporation) and presented as mean ± standard deviation unless otherwise stated. For comparisons between PD-C and MCI groups, non-parametric Mann–Whitney U test was performed. Models were corrected for covariates that were demonstrated to significantly differ between PD-C and PD-MCI cohorts. A significant nominal p value of <0.05 was employed.

3. Results

3.1. Cognitive Characteristics of PD-C and PD-MCI Groups. The cohort was initially divided into two groups based on the presence or absence of mild cognitive impairments (PD-MCI and PD-C, respectively), as determined by ACE-R scores. ACE-R subdomains were compared between cognitive groups, revealing significant differences in each subdomain. Throughout attention and orientation ($p < 0.001$), memory ($p < 0.001$), fluency ($p < 0.001$), language ($p < 0.001$), and visuospatial ($p < 0.001$) domains, significant differences were present between the PD-C and PD-MCI subgroups (Table 1).

3.2. Cohort Demographics and Clinical Differences between PD-C and PD-MCI Cohorts. Table 2 summarizes clinical and demographic characteristics of the complete patient cohort ($n = 302$), the PD-MCI subgroup, and the PD-C subgroup. Patients in the PD-MCI group were more likely to be older (63.2 ± 9.48 vs. 66.4 ± 8.51, $p = 0.003$), have a longer disease duration (7.39 ± 5.09 vs. 9.75 ± 6.10, $p < 0.001$), be male (OR = 4.24, $p = 0.039$), to have more severe motor symptoms (17.7 ± 11.0 vs. 23.6 ± 15.4, $p = 0.002$), and a poorer quality of life (26.9 ± 18.8 vs. 40.9 ± 26.4, $p < 0.001$) than those in the PD-C cohort. In terms of therapeutic interventions, the PD-MCI group were more likely to be using DBS treatment (OR = 4.72, $p = 0.030$) and have a higher LED (765 ± 571 vs. 970 ± 620, $p < 0.001$) than those with normal cognitive function. As such, further analysis of the relationship between impulsivity scores and cognitive status included age at assessment, gender, disease duration, LED, and DBS as covariates.

3.3. Impulsivity Scores in PD-C and PD-MCI Groups. Total BIS-11 scores of all patients ranged from 30 to 102, with an interquartile range of 12 points. Patients with PD-MCI, compared to those who were PD-C, scored higher on total impulsivity measures and multiple subscales of impulsivity; however, no differences reached statistical significance (Table 3). BIS-11 subscales were only analysed in corrected comparisons where significance was seen in naïve pairwise comparison.

Specifically, individuals within the PD-MCI group had higher total BIS-11 scores, although not statistically significant (59.5 ± 8.77 vs. 60.2 ± 10.2, $p = 0.318$). Second-order attentional subscale findings reflected total BIS-11 scores, with differences between groups remaining minimal with no significance noted (15.3 ± 3.18 vs. 15.4 ± 3.80, $p = 0.704$). Within this attentional subscale, first-order attentional subscale scores also saw no significant differences ($p = 0.137$), whilst cognitive instability scores were significantly different ($p = 0.019$). However, in fully corrected models controlled for confounding factors, cognitive stability was no longer significant in effect ($p = 0.787$). Subsequent analysis of second-order nonplanning scores and motor scores indicated no differences in mean scores (23.8 ± 4.81 vs. 23.8 ± 5.67, $p = 0.175$; 21.0 ± 3.26 vs. 21.0 ± 2.90, $p = 0.737$), mirrored by insignificant differences in first-order subscales (Table 3).

4. Discussion

Cognitive dysfunction is an important nonmotor manifestation of PD, which increases in frequency and severity as the disease progresses, and can range from mild impairment in one or more cognitive domains, to outright dementia. People with PD are twice as likely to develop MCI and six times more likely to become demented when compared to age-matched controls [25]. Furthermore, the onset of PD-MCI has been recognized as a predictive factor for other debilitating symptoms such as sleep problems, depression, hallucinations, and ICDs [26]. It has been suggested that cognitive impairment may be involved in the development of ICDs [15, 16, 27], and it has been proposed that the two disorders may share a common underlying neurobiological substrate [8].

While it has previously been suggested that there may be a link between cognitive impairment and trait impulsivity, which is thought to underlie the development of ICDs, we were unable to demonstrate such an association in the present study using the ACE-R cognitive screening protocol. We did not find any significant differences in attentional, nonplanning, or motor impulsivity BIS-11 measures between a PD-MCI group and a cognitively normal PD group (PD-C), when controlling for other confounding factors. The findings of this study therefore suggest that the presence of PD-MCI in PwP does not align with higher levels of subclinical impulsivity, nor is there evidence for an inverse relationship between impaired cognition and impulsivity, or any indication of a change in any specific impulsivity traits in the cognitively impaired PD group. However, the study did not investigate the influence of domain-specific MCI, which may relate to impulsivity subscales.

Contention exists in the literature surrounding the relationship between cognition and ICDs, with some studies in PD cohorts with diagnosed ICDs reporting no differences in cognitive abilities and others reporting a better level of functioning in some tasks assessing cognition [17, 28]. Moreover, conflicting conclusions have been reached in regard to which specific cognitive functions relate to ICDs. In the current study, the PD-MCI group performed significantly lower in all cognitive domains, and it is possible that impairments in some of these domains could lead to

Table 1: Differences in ACE-R subdomain scores in the PD-C and PD-MCI groups.

	All subjects ($n = 302$)	PD-C ($n = 189$)	PD-MCI ($n = 113$)	Arm comparison
ACE-R total	88.02 (11.3)	94.4 (3.09)	77.4 (12.1)	$t = 14.6$ ($p < 0.001$)
Attention and orientation	17.3 (1.56)	17.9 (0.364)	16.4 (2.18)	$t = 10.4$ ($p < 0.001$)
Memory	21.8 (4.63)	24.3 (1.79)	17.6 (4.88)	$t = 12.3$ ($p < 0.001$)
Fluency	9.23 (3.71)	11.3 (2.28)	5.79 (3.04)	$t = 12.2$ ($p < 0.001$)
Language	24.8 (1.99)	25.4 (1.02)	23.9 (2.75)	$t = 5.85$ ($p < 0.001$)
Visuospatial	14.7 (2.44)	15.5 (1.00)	13.5 (3.42)	$t = 5.84$ ($p < 0.001$)

Table 2: Clinical and demographic characteristics of cohort, when grouped by cognitive status.

	All subjects ($n = 302$)	PD-C ($n = 189$)	PD-MCI ($n = 113$)	Arm comparison
Age of assessment (years)	64.4 (9.20)	63.2 (9.48)	66.4 (8.51)	$t = -2.95$ ($p = 0.003$)
Gender: male (%)	186 (61.6)	108 (57.1)	78 (69.0)	OR = 4.28 ($p = 0.039$)
Disease duration (years)	8.27 (5.60)	7.39 (5.09)	9.75 (6.10)	$t = -3.57$ ($p < 0.001$)
MDS-UPDRS III score	19.9 (13.1)	17.7 (11.0)	23.6 (15.4)	$t = -3.17$ ($p = 0.002$)
Total levodopa equivalent dosage (mg/day)	841 (597)	765 (571)	970 (620)	$t = -3.046$ ($p < 0.001$)
Deep brain stimulation treatment (%)	32 (11.0)	14 (4.8)	18 (15.9)	OR = 4.72 ($p = 0.030$)
Parkinson's Disease Questionnaire (PDQ-39)	32.5 (23.1)	26.9 (18.8)	40.9 (26.4)	$t = -4.785$ ($p < 0.001$)

Table 3: Total BIS-11 and first- and second-order scores in the overall cohort and PD-C and PD-MCI groups.

	All subjects ($n = 302$)	PD-C ($n = 189$)	PD-MCI ($n = 113$)	Naïve pairwise comparison	Covariate corrected comparison
BIS-11 total score	59.7 (9.33)	59.5 (8.77)	60.2 (10.2)	$p = 0.318$	NS
Second-order attentional	15.3 (3.42)	15.3 (3.18)	15.4 (3.80)	$p = 0.704$	NS
First-order attentional	10.1 (2.66)	9.96 (2.53)	10.4 (2.56)	$p = 0.137$	NS
First-order cognitive instability	5.21 (1.58)	5.34 (1.49)	4.98 (1.70)	$p = 0.019$	$p = 0.787$
Second-order nonplanning	23.4 (5.15)	23.8 (4.81)	23.8 (5.67)	$p = 0.175$	NS
First-order self-control	12.07 (3.56)	12.0 (3.29)	12.2 (3.73)	$p = 0.503$	NS
First-order cognitive complexity	11.3 (2.58)	11.1 (2.47)	11.57 (2.74)	$p = 0.157$	NS
Second-order motor	21.0 (3.51)	21.1 (3.26)	21.0 (2.90)	$p = 0.737$	NS
First-order motor	13.6 (2.98)	13.7 (2.77)	13.5 (3.33)	$p = 0.559$	NS
First-order perseverance	7.46 (1.71)	7.43 (1.63)	7.50 (1.85)	$p = 0.734$	NS

*NS = not significant.

higher impulsivity, whilst impairments in other domains could mitigate other aspects of trait impulsivity. The failure to find any such associations in this study may reflect limitations of the BIS-11 self-reporting scale, and further studies employing more sensitive instruments for trait impulsivity and more comprehensive cognitive testing protocols would therefore be worthwhile to explore this possibility further.

No study has yet demonstrated a relationship between impulsivity and cognition in a cohort of PwP, though an association has been established in other populations. The BIS-11 scale quantifies an individual's perception of various behaviors, thoughts, and actions that are associated with impulsivity [20]. It has been suggested that individuals with lower cognitive abilities may be less likely to comprehend the consequences of reporting their impulsive events, and are therefore more likely to disclose impulse-related behaviors and feelings, and to self-report high impulsivity. This phenomenon has been reported in prison inmates [29], and in children with learning difficulties [30] and ADHD [13]. Alternatively, many individuals with higher cognitive abilities are thought to under-report impulsive behaviors due to embarrassment, or because they are fearful of potential consequences in disclosing impulsive behaviors. The extent to which these potential limitations of the self-reported BIS-11 scale may apply to the PD patient cohort is uncertain, although it is possible that individuals who have MCI may be less able to objectively identify problematic behaviors, and that participants in a research study may have different attitudes to reporting impulsive traits.

5. Limitations

A number of other limitations warrant consideration when interpreting the findings of the present study. Firstly, the self-report nature of the BIS-11 assessment is likely to introduce a degree of variability and bias in responses. As patients may be reluctant to report impulsive tendencies, this may limit the reliability of the results of the study. While more objective behavioral measures to assess situational "state" impulsivity and to screen for specific personality traits were not employed in this study, it is important that these aspects be addressed in future studies. In regard to

cognition, the PD-C and PD-MCI groupings were established using predefined cut-off scores for global MCI, and the study did not investigate the influence of domain-specific MCI, which may relate to impulsivity subscales, or relation between executive function and nonplanning impulsivity. Furthermore, possible overlap exists between certain items in the BIS-11 and ACE-R scales: e.g., the "attentional impulsiveness" subscale in the BIS-11 and the "attention and orientation" domain in the ACE-R. Moreover, the cross-sectional nature of the study precludes any possible conclusions of a causal relationship, or lack thereof, between deficits in specific cognitive domains and impulsiveness.

6. Conclusion

The present results have established that subtle shifts in cognitive circuitry, as related to PD-MCI, do not necessarily associate with individual variability in trait impulsivity. Absence of any obvious relationship between the complex multidimensional constructs of impulsivity and cognition suggests that the underlying neurobiology may not relate, at least at a subclinical level. This prompts a need to reconsider the underpinnings of impulsivity in PD as a separate construct to cognition, in order to better characterize and treat symptoms experienced by patients.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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