The sex's role on the neurocognitive function in patients with Parkinson's Disease

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Abstract

This study aimed to elucidate the role of sex in neurocognitive function in patients with Parkinson's disease (PD). Ninety-four idiopathic PD and 167 healthy elderly as normal controls (NCs) were recruited and underwent comprehensive neuropsychological assessments. The sex difference were found in NCs but not in PD. In male, PD patients had worse performance on the Digit symbol substitution (DSS) ($p < 0.001$) and the Symbol Searching (SS) ($p < 0.001$) than NCs. In female, PD patients had the worse score on the category score of the Modified Wisconsin Card Sorting Test ($p < 0.001$), the SS ($p < 0.001$), and the pentagon copying ($p < 0.001$) than NCs. After controlling age and years of education, Hoehn and Yahr Stage can predict the performance of the Color Trail Test part A ($\beta A = 0.241$, $pA = 0.036$), the Stroop Word-Color Test ($\beta = -0.245$, $p = 0.036$), and the DSS ($\beta = -0.258$, $p = 0.035$) in male PD patients. Sex differences were found in NCs but not in PD. The mental flexibility and visuospatial function are susceptible to female in the PD course. Male PD patients' working memory and processing speed can be predicted by the disease severity.

1. Introduction

Parkinson's Disease (PD) is the second most common neurodegenerative disease. The prevalence of PD increases with age and is generally more prevalent among males [1,2]. PD's pathological hallmark is the aggregation of Lewy bodies and degeneration of dopaminergic neurons. The nigrostriatal pathway's involvement reduces the striatum's dopamine levels and causes a variety of motor and non-motor symptoms (NMS) in patients[3]. Neurocognitive dysfunction is closely related to other NMS and causes impairment in the quality of life of PD patients. Since full-blown dementia is the final stage of neurocognitive impairment, the detrimental impacts will eventually develop, including impairment in the self-care functions, the burden of caregivers, as well as the surging cost for health care [4,5]. According to previous studies' findings, the domains of neurocognitive deficits involved include executive function, attention, processing speed, visuospatial ability, memory, and language [4,6–8].

In the healthy aging population, sex differences in neurocognitive function have been reported. Evidence revealed that females performed better than males in verbal-related tests [9], and males performed better than females in visual-spatial tests [10]. In the population of PD patients, some studies suggested that no sex difference in patients' general neurocognitive function [11–13]. Nevertheless, not all studies lent support for the lack of sex differences. Some studies reported that male patients have more subjective complaints [14], lower global cognitive function in the early stage [15–17], more mild cognitive impairment [4,18,19], and the development of mild cognitive impairment is more rapid in males than females [4,19]. On the contrary, some studies suggested that female PD patients have poor general cognitive function [20].

Previous investigations provided some evidence to show that the domains involved in the neuropsychological deficits of PD may be sex-specific. Male patients present with better visuospatial ability [11,12,16,21], but the results of other domains are not consistent across different studies. Female patients show better verbal memory [12,21], but other studies argue that there is no significant difference among memory-related assessments [11,16]. The same inconsistency can be found in processing speed, and some studies revealed that females have better processing speed than males; other studies show no significant difference of sex [12]. Furthermore, some results revealed no significant difference in attention[11,13]. Among all the executive functions that are frequently impaired in PD patients, males perform worse on verbal fluency [13,16,17,21,22], while another study showed no significant difference [12]. In addition, some studies suggested that female PD patients have poor executive [11,23], and visuospatial-function [11,12,16,21]. On the inhibition ability, males perform worse than females[13]. However, there are also studies showing no significant sex difference on the high-level executive function [16,21].

The diverging results in the previous studies may be secondary to the application of brief screening tests, such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment, or self-reported questionnaires, to measure neurocognitive function, and these results cannot represent the detailed or comprehensive neurocognitive function. Besides, lack of healthy controls and focus on the early-stage patients might create a grey zone of clarifying whether performance differences originate from sex or disease. Moreover, the clinical characteristics (e.g., onset age, disease duration, the severity of the disease, and LED) were found to be related to the neurocognitive function[4,18] and can provide advice on clinical treatment in PD patients. Few studies elucidated different sex separately and did not cover the comprehensive neurocognitive domain, so it is challenging to clarify the relationship between sex, clinical characteristics, and neurocognitive function.

Thus, we aimed to elucidate the impact of disease and sex on neurocognitive function. We overcome the limitation of previous studies, including the lack of a control group, only focus on the early-stage patients, and only use a screening test to elucidate disease and sex's impact on various neurocognitive domains. In addition, we further explore the relationship between neurocognitive function and clinical

characteristics, including the age of onset, disease duration, levodopa equivalent dose (LED), and Hoehn and Yahr Staging Scale (H&Y stage) of patients of each sex.

2. Materials And Methods

2.1. Participants

A total of 94 PD patients and 167 healthy participants as NCs were recruited. All patients were diagnosed with PD according to the United Kingdom PD Society Brain Bank clinical diagnostic criteria, whose motor symptom onset after 50 years of age. The NCs were recruited from communities. All participants' exclusion criteria were as followed: with atypical features of parkinsonism, history of brain operations, severe systemic diseases, psychiatric diseases (e.g., depression and schizophrenia), or illiteracy. Informed consent was obtained from all participants following the ethical standards laid down in the 1964 Declaration of Helsinki, and the Institutional Review Boards (IRBs) of National Cheng Kung University Hospital confirmed the study protocols.

2.2 Assessment

2.2.1 Demographic and Clinical Characteristics.

We collected the age and years of education of PD patients and NCs, age of onset, disease duration, the Hoehn and Yahr Staging Scale, and the levodopa equivalent dose of PD patients.

2.2.2. Neuropsychological Assessment

We evaluated six neurocognitive domains, including executive function, memory, processing speed, visuospatial ability, attention, and language. The detailed neuropsychological assessment in each domain was list in Table 1.

Table 1
The neuropsychological tests used in the current study.

Domain	Neuropsychological tests
Executive Function	Modified Wisconsin Card Sorting Test (M-WCST): the number of categories achieved, and perseverative errors
	Stroop Word-Color Test (SWCT): color-word score
	Category Fluency (fruit, fish, and vegetable)
	Color Trails Test (CTT)-part B
	Similarities[a]
	Matrix reasoning[a]
Attention	Attention Test···
	Digit Span[a]
Processing Speed	SWCT: word score and color score
	CTT-part A
	Digit Symbol Substitution[a]
	Symbol Searching[a]
Visuospatial ability	Pentagon copy···
	Block design[a]
Memory	Logical Memory (LM)[b]
	Visual Reproduction (VR)[b]
Language···	Naming
	Repetition
	Verbal comprehension

[a]Subtest of Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)

[b]Subtest of Wechsler Memory Scale-Third Edition (WMS-III)

···Subtest of Mini-Mental State Examination (MMSE)

2.3. Statistical Analysis

All variables were tested for normal distribution using the Kolmogorov-Smirnov test. The study groups were compared using the t-test and the Mann–Whitney U test for continuous variables and the Chi-square test or Fisher-Freeman-Halton exact test[24] for categorical variables.

We performed three types of comparison to explore the role of disease or gender in neurocognitive function. First, comparing the neurocognitive performance among PD patients and NCs. Second, we compared sex differences in neurocognitive function among patients with PD and healthy controls. Third, the participants' sex-stratified analysis was used to further assess the neurocognitive function among PD patients and NCs in males and females. Moreover, we performed a further regression analysis of the relationship between clinical characteristics (e.g., age of onset, disease duration, LED, and H&Y stage) and neurocognitive function in male and female patients with PD, respectively.

All statistical analyses were conducted using IBM SPSS Statistics 22 (SAS Institute Inc., Cary, NC). Significance tests were 2-tailed, with a $p < 0.05$. To decrease the likelihood of a Type II error, a Bonferroni correction for multiple comparisons was applied, resulting in the adoption of 0.002 (i.e., 0.05/25) as the cut-off for a statistical significance.

3. Results

The comparisons between the study groups are shown in Table 2. We found that PD patients had worse performance on the category score of Modified Wisconsin Card Sorting Test (M-WCST, $p < 0.001$), the total score of Category Fluency ($p < 0.001$), the word score of Stroop Word-Color Test (SWCT) ($p < 0.001$), the scaled score of Digit Symbol Substitution (DSS, $p < 0.001$), the scales score of Symbol Searching (SS, $p < 0.001$), the pentagon copying($p < 0.001$), the scales score of Block Design (BD, $p = 0.002$), and the raw score of Logical Memory (LM, $p = 0.002$) than NCs.

Table 2
the demographic data and neurocognitive function in study groups

	PD (n = 94)	NC (n = 167)	*p* value
	Mean(SD)	Mean(SD)	
age, y	63.96(6.17)	64.88(8.54)	0.320[c]
Education, y	12.10(4.05)	11.94(3.60)	0.393[c]
Executive function			
M-WCST-C	4.38(2.04)	5.56(1.65)	< 0.001[c]*
M-WCST-P	5.77(8.49)	3.42(4.80)	0.024[c]
SWCT-color word score	29.12(11.69)	32.50(10.99)	0.041[c]
Category Fluency	34.04(8.26)	38.73(8.83)	< 0.001[c]*
CTT-B	136.15(90.66)	108.21(37.71)	0.013[c]
Similarities	10.66(2.89)	11.78(2.69)	0.002[c]
Matrix Reasoning	10.86(2.96)	11.85(2.89)	0.009[c]
Attention			
Attention test…	7.28(1.15)	7.61(0.73)	0.028[c]
Digit Span	11.45(2.62)	12.01(2.77)	0.181[c]
Processing speed			
SWCT-word score	75.13(20.07)	84.31(17.89)	< 0.001[b]*
SWCT-color score	57.66(265.969)	62.86(14.02)	0.007[b]
CTT-A	69.14(38.74)	52.23(19.06)	< 0.001[c]*
Digit Symbol Substitution	10.16(2.35)	12.10(2.38)	< 0.001[c]*
Symbol Searching	10.35(2.65)	12.31(2.32)	< 0.001[c]*
Visuospatial ability			
Pentagon copy…	12/82	3/164	< 0.001[a]*
Block Design	9.93(2.67)	10.94(2.75)	0.002[c]*
Memory			
LM-I(r.s.)	30.03(13.49)	35.46(11.51)	0.002[c]*
LM-II(r.s.)	17.43(10.65)	21.84(9.25)	0.001[b]*
LM-recognition(r.s.)	22.64(4.35)	24.49(3.75)	0.001[c]*
VR-I(r.s.)	67.05(19.99)	74.67(14.22)	0.005[c]
VR-II(r.s.)	44.99(23.44)	52.36(21.45)	0.019[c]
VR-recognition(r.s.)	41.16(4.13)	42.24(3.90)	0.027[c]
Language…			
Naming	0/94	0/167	-

	PD (n = 94)	NC (n = 167)	*p* value
Repetition	1/93	4/163	0.657[a]
Verbal comprehension	2/92	3/164	> 0.999[a]

[a]Fisher Exact Test; [b]*t* test; [c]Mann-Whitney U test; *p < 0.002(Bonferroni correction for multiple comparisons)

¨Subtest of Mini-Mental State Examination (MMSE)Abbreviations: please see Table 1 and SD, standard deviation; r.s., raw score; LM-I, immediate memory of the logical memory; LM-II, delayed memory of the logical memory; VR-I, immediate memory of the visual reproduction; VR-II, delayed memory of the logical memory; M-WCST-C and M-WCST-P indicate the achieved categories and perseverative, respectively.

The comparisons between sexes in each study group and the participants' sex-stratified analysis are shown in Table 3. In the NCs group, years of education in male NCs are longer than in female NCs. After adjusting for years of education as covariates, female NCs had a higher total score of Category Fluency ($p < 0.001$), the word and the color score of SWCT ($p < 0.001$), the raw score of LM immediate recall ($p = 0.001$) and delayed recall ($p = 0.002$). However, there was no significant difference between males and females in the PD group. In male participants, male PD patients had worse performance on Color Trail Test (CTT) part A ($p < 0.001$) and DSS ($p < 0.001$), which are used to assess processing speed, than male NCs. On the other hand, female PD patients had the worse score on the category score of M-WCST ($p < 0.001$), DSS ($p < 0.001$), and the pentagon copying ($p < 0.001$) than female NCs.

Table 3
Gender-stratified analysis of the neurocognitive tests in PD and NCs.

	male NCs(n = 53)	female NCs(n = 114)	male PD(n = 60)	female PD(n = 34)	p^w value	p^x value	p^y value	p^z value
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)				
age, y	66.59(8.92)	64.09(8.28)	64.45(5.62)	63.09(7.04)	0.077[c]	0.307[b]	0.098[c]	0.760[c]
education, y	12.91(3.31)	11.49(3.65)	12.38(4.06)	11.59(4.05)	0.012[c]*	0.254[c]	0.920[c]	0.514[c]
onset age, y	-	-	60.15(5.86)	59.09(6.78)	-	0.429[b]	-	-
Disease duration, y	-	-	4.47(2.76)	4.19(3.79)	-	0.249[c]	-	-
LED	-	-	557.53(265.38)	463.92(277.75)	-	0.085[c]	-	-
H&Y stage	-	-	1.50(0.893)	1.26(1.05)	-	0.329[b]	-	-
Executive function								
M-WCST-C	5.47(1.69)	5.60(1.63)	4.47(2.054)	4.24(2.05)	0.310[e]	0.585[c]	0.009[c]	< 0.001[c]*
M-WCST-P	3.81(6.09)	3.24(4.08)	5.43(8.073)	6.35(9.29)	0.226[e]	0.539[c]	0.398[c]	0.022[c]
SWCT-color word score	30.66(11.55)	33.36(10.66)	28.33(11.12)	30.50(12.71)	0.006[e]	0.391[b]	0.278[b]	0.350[c]
Category Fluency	34.53(7.71)	40.68(8.66)	32.48(7.46)	36.79(8.97)	< 0.001[d]*	0.005[c]	0.218[c]	0.024[b]
CTT-B	108.44(36.78)	108.10(38.30)	139.40(102.79)	130.42(64.93)	0.383[e]	0.890[c]	0.082[c]	0.127[c]
Similarities	12.00(3.03)	11.68(2.52)	10.73(2.85)	10.53(2.99)	0.296[e]	0.949[c]	0.024[c]	0.043[c]
Matrix Reasoning	12.26(2.71)	11.66(2.95)	10.95(3.07)	10.71(2.79)	0.799[e]	0.692[c]	0.023[c]	0.081[c]
Attention								
Attention test…	7.57(0.82)	7.63(0.68)	7.30(1.18)	7.24(1.10)	0.615[e]	0.588[c]	0.278[c]	0.046[c]
Digit Span	11.81(2.99)	12.10(2.72)	11.10(2.72)	12.06(2.36)	0.056[e]	0.088[b]	0.250[c]	1.000[c]
Processing speed								
SWCT-word score	76.51(16.24)	87.94(17.52)	71.23(19.164)	82.00(20.06)	< 0.001[d]*	0.012[b]	0.120[b]	0.127[c]
SWCT-color score	58.68(14.31)	64.81(13.51)	54.467(14.38)	63.29(18.12)	< 0.001[d]*	0.011[b]	0.122[b]	0.599[b]
CTT-A	52.54(21.14)	52.09(18.10)	70.07(40.46)	67.50(36.04)	0.556[e]	0.726[c]	< 0.001[c]*	0.003[c]
DSS	11.93(2.49)	12.18(2.34)	9.88(2.30)	10.65(2.40)	0.029[e]	0.137[c]	< 0.001[c]*	< 0.001[c]*
Symbol Searching	12.76(2.49)	12.09(2.21)	10.50(2.60)	10.09(2.75)	0.615[e]	0.276[c]	0.009[c]	0.045
Visuospatial ability								
Pentagon copy…	1/52	2/112	4/56	8/26	> 0.999[a]	0.026[a]	0.369[a]	< 0.001[a]*

	male NCs(n = 53)	female NCs(n = 114)	male PD(n = 60)	female PD(n = 34)	p^w value	p^x value	p^y value	p^z value
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)				
Block Design	11.57(2.74)	10.65(2.72)	9.87(2.94)	10.03(2.14)	0.187[e]	0.934[c]	0.003[c]	0.086[c]
Memory								
LM-I(r.s.)	33.13(13.07)	36.54(10.60)	27.97(13.58)	33.68(12.73)	0.001[e]*	0.037[c]	0.060[c]	0.317[c]
LM-II(r.s.)	20.00(10.08)	22.70(8.76)	15.78(10.59)	20.32(10.26)	0.002[e]*	0.041[c]	0.043[c]	0.357[c]
LM-recognition(r.s.)	24.04(4.00)	24.70(3.61)	22.08(4.48)	23.62(3.97)	0.039[e]	0.128[c]	0.015[c]	0.163[c]
VR-I(r.s.)	74.83(16.38)	74.59(13.18)	66.15(21.31)	68.65(17.62)	0.672[e]	0.587[c]	0.029[c]	0.138[c]
VR-II(r.s.)	50.57(24.94)	53.19(19.68)	43.62(24.36)	47.41(21.87)	0.084[e]	0.376[c]	0.131[c]	0.248[c]
VR-recognition(r.s.)	42.34(4.17)	42.19(3.79)	41.15(4.20)	41.18(4.07)	0.591[e]	0.991[c]	0.094[c]	0.179[c]
Language[···]								
Naming	0/53	0/114	0/60	0/34	-	-	-	-
Repetition	2/51	2/112	0/60	1/33	0.592[a]	0.362[a]	0.218[a]	> 0.999[a]
Verbal comprehension	2/51	1/113	1/59	1/33	0.237[a]	> 0.999[a]	0.599[a]	0.408[a]

[a]Fisher Exact Test; [b]*t* test;[c]Mann-Whitney U test; [d]ANCOVA(adjusted for years of education as covariates); [e]rank analysis of covariance (adjusted for years of education as covariates); [···]Subtest of Mini-Mental State Examination (MMSE); *p < 0.002(Bonferroni correction for multiple comparisons)

Abbreviations: please see Table 1&2; SD, standard deviation; LED, levodopa equivalent dose; H&Y stage, Hoehn and Yahr Staging Scale; DSS, Digit symbol substitution; r.s., raw score; LM-I, immediate memory of the logical memory; LM-II, delayed memory of the logical memory; VR-I, immediate memory of the visual reproduction; VR-II, delayed memory of the logical memory; M-WCST-C and M-WCST-P indicate the achieved categories and perseverative, respectively.

[w]Comparisons between male NCs and female NCs; [x]Comparisons between male PD and female PD; [y]Comparisons between male NCs and male PD; [z]Comparisons between female NCs and female PD.

The correlation between clinical characteristic and neurocognitive function are shown in Tables 4 & 5. The result of the regression showed (Table 6), after controlling the age, years of education, H&Y Stage could predict the performance of working memory (CTT part B, β_B = 0.222, p_B= 0.046), and processing speed (CTT part A, β_A = 0.241, p_A = 0.036; the color score of the SWCT, β = -0.245, p = 0.036; DSS, β = -0.258, p = 0.035) in male PD patients. However, in female PD patients, the regression result did not show any clinical characteristics that could predict the neurocognitive function's performance.

Table 4
Correlations between the clinical characteristics and the neurocognitive performances in male PD

male PD	onset age		Disease duration		LED		Stages	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
executive function								
M-WCST-C	-0.143	0.275	0.003	0.980	-0.122	0.353	-0.222	0.088
M-WCST-P	0.293	0.023*	-0.155	0.238	0.065	0.622	0.188	0.150
SWCT-color word score	-0.224	0.085	-0.120	0.361	-0.197	0.131	-0.116	0.377
Category Fluency	-0.042	0.753	-0.024	-0.855	-0.166	0.205	-0.151	0.248
CTT-B	0.466	< 0.001**	0.115	0.383	0.003	0.980	0.294	0.023*
Similarities	0.166	0.206	-0.104	0.428	-0.196	0.133	0.073	0.577
Matrix Reasoning	0.010	0.942	-0.010	0.941	-0.024	0.856	0.096	0.466
Attention								
Attention test…	-0.224	0.085	-0.080	0.541	0.123	0.348	-0.144	0.271
Digit Span	-0.110	0.402	-0.013	0.922	-0.208	0.112	0.070	0.596
Processing speed								
SWCT-word score	-0.257	0.047*	-0.071	0.590	-0.156	0.235	-0.154	0.241
SWCT-color score	-0.257	0.048*	-0.160	0.222	-0.145	0.267	-0.269	0.037*
CTT-A	0.446	< 0.001**	0.014	0.913	0.087	0.507	0.292	0.024*
Digit Symbol Substitution	-0.089	0.498	0.043	0.745	-0.235	0.071	-0.235	0.070
Symbol Searching	-0.147	0.264	0.054	0.684	-0.214	0.100	0.000	> 0.999
Visuospatial ability								
Pentagon copy…	-0.177	0.756	0.119	0.366	-0.005	0.969	0.075	0.566
Block Design	-0.206	0.114	-0.058	0.658	-0.144	0.271	0.032	0.806
Memory								
LM-I(r.s.)	-0.103	0.435	-0.230	0.077	-0.075	0.567	-0.144	-0.272
LM-II(r.s.)	-0.163	0.215	-0.216	0.098	-0.110	0.401	-0.160	0.221
LM-recognition(r.s.)	-0.232	0.075	-0.018	0.889	-0.061	0.644	-0.040	0.760
VR-I(r.s.)	-0.409	0.001**	-0.0110	-0.939	-0.045	0.730	-0.100	0.446
VR-II(r.s.)	-0.347	0.007**	-0.224	0.086	-0.160	0.223	-0.113	0.391
VR-recognition(r.s.)	-0.285	0.027*	-0.045	0.729	-0.046	0.729	-0.174	0.183
Language…								
Naming	-	-	-	-	-	-	-	-
Repetition	-	-	-	-	-	-	-	-
Verbal comprehension	-0.377	0.003**	0.070	0.596	0.053	0.686	0.074	0.577
Abbreviations: please see Table 1, 2, and 3.								

Table 5
Correlations between the clinical characteristics and the neurocognitive performances in female PD

female PD	onset age		Disease duration		LED		Stages	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Executive function								
M-WCST-C	-0.566	< 0.001**	− .254	0.146	-0.236	0.178	-0.156	0.377
M-WCST-P	0.303	0.082	0.472	0.005**	0.428	0.011*	0.287	0.100
SWCT-color word score	-0.338	0.051	-0.276	0.114	-0.312	0.072	-0.237	0.178
Category Fluency	-0.370	0.031*	-0.429	0.011*	-0.335	0.053	-0.296	0.090
CTT-B	0.406	0.017*	0.207	0.240	0.146	0.410	0.155	0.383
Similarities	-0.008	0.963	0.226	0.199	0.171	0.333	0.348	0.044*
Matrix Reasoning	-0.053	0.766	0.383	0.026*	0.276	0.114	0.099	0.576
Attention								
Attention test…	-0.238	0.175	-0.062	0.728	-0.163	0.356	-0.029	0.870
Digit Span	0.026	0.883	-0.016	0.930	-0.017	0.923	0.335	0.053
Processing speed								
SWCT-word score	-0.517	0.002**	-0.251	0.152	-0.226	0.152	-0.080	0.652
SWCT-color score	-0.405	0.018*	-0.231	0.188	-0.231	-0.188	-0.160	0.367
CTT-A	0.427	0.012*	0.094	0.596	0.094	0.596	0.121	0.497
Digit Symbol Substitution	-0.104	0.557	0.021	0.906	0.021	0.906	0.062	0.727
Symbol Searching	-0.165	0.351	0.020	0.910	0.020	0.910	0.013	0.943
Visuospatial ability								
Pentagon copy…	0.018	0.921	-0.065	0.717	0.002	0.992	0.008	0.965
Block Design	-0.055	0.759	0.188	0.286	0.154	0.384	0.091	0.610
Memory								
LM-I(r.s.)	-0.358	0.037*	-0.039	0.828	0.051	0.774	0.239	0.173
LM-II(r.s.)	-0.432	0.011*	0.097	0.584	0.081	0.649	0.199	0.259
LM-recognition(r.s.)	-0.445	0.008**	0.024	0.892	0.049	0.782	-0.127	0.473
VR-I(r.s.)	-0.331	0.056	-0.116	0.512	-0.034	0.850	-0.047	0.792
VR-II(r.s.)	-0.367	0.033*	-0.224	0.203	0.023	0.899	-0.092	0.606
VR-recognition(r.s.)	-0.555	0.001**	-0.050	0.777	-0.076	0.671	-0.025	0.887
Language…								
Naming	-	-	-	-	-	-	-	-
Repetition	0.002	0.990	0.149	0.401	0.169	0.343	-0.123	0.487
Verbal comprehension	-0.154	0.384	0.056	0.755	-0.023	0.897	0.044	0.803
Abbreviations: please see Table 1, 2, 3, and 4.								

Table 6
Multiple linear regression analyses in male PD with various tests

male PD	Color Trails Test-part B			Stroop Word-Color Test - color score			Color Trails Test-part A			Digit symbol substitution		
	ΔR^2	β Value	p-Value	ΔR^2	β Value	p-Value	ΔR^2	β Value	p-Value	ΔR^2	β Value	p-Value
Model 1	0.306			0.231			0.226			0.162		
Age, y		0.554	< 0.001		-0.364	0.003		0.826	< 0.001		-0.076	0.535
Education, y		-0.054.	0.629		0.336	0.005		-0.192.	0.100		0.400	0.002
Model 2	0.048			0.058			0.057			0.065		
Age, y		0.522	< 0.001		-0.329	0.006		0.442	< 0.001		-0.039	0.745
Education, y		-0.067	0.537		0.351	0.003		-0.206	0.070		0.415	0.001
Stages		0.222	0.046		-0.245	0.036		0.241	0.036		-0.258	0.035
	Total R^2 **= 0.354** p **= < 0.001**			**Total** R^2 **= 0.289** p **= < 0.001**			**Total** R^2 **= 0.283** p **= < 0.001**			**Total** R^2 **= 0.227** p **= 0.002**		

4. Discussion

In the current study, we explored how the disease or sex influences PD patients' neurocognitive function. We found that the PD patients' language and attention function were similar to healthy aging; however, the PD patients have poor performance in executive function, processing speed, visuospatial, and memory function than healthy aging. These findings were partially compatible with previous researches. Previous studies showed that PD patients started to develop neurocognitive deficits even in early-stage [4,5,7,8], while the language function is relatively preserved [6–8]. In the present study, we did not find a significant difference between patients and healthy aging in the attention function, these findings are inconsistent with previous studies [7,8,25]. This discrepancy may arise from the nature of attention and the tasks applied for the assessment of attention. We used the tools (i.e., information registration, serial seven, and digit span) to measure simple attention function rather than complex attention function in the present study. The researcher suggested that PD patients have impaired complex attention, but their simple attention is relatively preserved[26,27]. Previous studies revealed that the vital determinants of neurocognitive dysfunction depend on reducing the supervisory attentional system[28]. If the task demands are under the capacity of patients' attentional resources, the patient may have similar attention performance to healthy aging. Once the task's attention demands overwhelm the patient's attentional resources, it will require both internal cues and mental operation[29]. PD patients may not perform as well as their age-matched counterparts.

In this study, we compared the neurocognitive function of both sexes in two study groups (i.e., healthy aging and PD group) to understand the impact of sex on neurocognitive function. Our findings are compatible with previous research results [9,10,30] in the healthy aging population. We found that female healthy aging's verbal fluency, processing speed, and verbal memory were better than male healthy aging's performance. Besides, no significant difference was found in executive function, attention function, and language between the healthy aging populations. Nevertheless, several studies found that males have generally superior visuospatial ability than females[9,10], but we did not have the same finding. The inconsistent results may be due to the tests (i.e., copy pentagon of MMSE and block design) we applied in this study. The copy pentagon of MMSE may make the ceiling effect on participant elderly; thus, it decreased the detecting susceptibility of neurocognitive function [31]. The Block Design task contains visuospatial perception and construction abilities; besides, it is a time-limited test. Thus, we could hardly be sure whether males perform better than female ones due to the processing speed counts.

Numbers of studies suggested that sex has an impact on neurocognitive function in the PD population. The female PD patients perform better than male ones on verbal fluency[13,16,17,22], verbal memory[12,21], and processing speed[13,15,16]. Besides, male PD patients perform better than female ones on visuospatial ability[16,21–23]. In the current study, our male and female PD patients showed no difference in each

neurocognitive domain. The patients' heterogeneity may explain the discrepancy. Most PD patients recruited in the prior studies had shorter disease duration[12,13,16,17,21,22] or have intact mentality ability[13], and we recruited patients at all stages. Estrogen may have a protective ability and consequently reduce PD risk for females[32,33]. The estrogen's protection was found in the early disease stage but not in the later stage[34]. Evidence showed that estrogen could prevent striatum degeneration[35] but unable to protect the damaged striatum[36]. It is believed that estrogen may impact neurocognitive function[37,38]. Previous investigations have shown that the estrogen's protective ability on neurodegeneration might be related to the health of neurons it acts on[2]. That is, when the brain enters the disease state, the estrogen's protective effect may become weak or absent. Female PD patients have higher dopamine concentration than male, and thus clinical characteristics are more benign in females than males in the early disease stage[1,2,39]; however, once the dopamine depletion threshold in the striatum is exceeded, the protection will no longer last and the difference between sex in the neurocognitive dysfunction will not be found[34].

We found the gender difference in neurocognitive function in a healthy aging population (i.e., executive function, processing speed, and memory), but not within the PD group. The female healthy aging group has better verbal fluency, memory, and processing speed than the male healthy aging group, but such sex difference is not observed in the PD group. The estrogen's protection decrease may explain this once the individual reaches the disease stage [2]. We further applied sex-stratified analysis to explore the impact of the disease on various sex's neurocognitive function. It is not surprising that PD patients' processing speed is worse than healthy aging in both sex groups; besides, in the female population, we found that PD patients' visuospatial ability is worse than healthy aging. These findings are consistent with the previous study [40]. However, we further found that our female PD patients performed worse in the executive function (i.e., cognitive flexibility) than the female healthy aging group. Previous study didn't show a consistent result, whose participants were younger and in the early disease stage [40]. Our sample may be more representative because we recruited PD patients from all the stages within the disease course and severity. Our findings suggested that the impairment in the cognitive flexibility component of executive function and visuospatial ability is more pronounced in the female PD and has a higher risk of being damaged. This may result from the loss of estrogen's protection.

Previous studies showed that PD patients' clinical characteristics (e.g., onset age, disease duration, LED, and H&Y stage) are correlated to the neurocognitive function [4,18,22]. In the present study, we found a gender difference in the relationship between clinical characteristics and specific neurocognitive function. Moreover, the disease severity (H&Y stage) can predict male PD patients' mental shifting ability and processing speed; however, no clinical features were found to be predictive factors in the female PD group. Although female PD patients are a minority group, there is a lack of research on the groups, and future study is needed to investigate the factors that modulate the female PD patients' neurocognitive function.

The current study has some limitations. First, the lack of accurate biological markers as an estrogen level index limits our extrapolation of estrogen's neuroprotective effect on cognition in the female healthy aging group. Moreover, the mechanism of the protective effect of estrogen on cognitive function remains not entirely clear, and further studies are needed. Secondly, the heterogeneity of motor symptoms might be related to neurocognitive performance or cognitive decline speed, and male / female patients might have different motor symptoms. However, the topic is beyond the scope of the current study. Therefore, we suggest future studies to include motor symptom subtypes for the more accurate prediction of the neurocognitive function's performance in PD patients.

In brief, the sex difference in neurocognitive function was found in healthy aging but not in the PD population. No sex difference in neurocognitive function may be due to the estrogen's protective effect, which disappears after the central nervous system reaches the disease stage. After developing the manifestations of PD, the processing speed is the susceptible cognitive function domain, regardless of sex. The mental flexibility and visuospatial deterioration were the vulnerable functions in female PD patients. Although no sex difference was found in the patient group, the clinical characteristics have sex differences in predicting neurocognitive function. The female PD patients' neurocognitive function needs further study urgently.

Declarations

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Author contributions M.L. Chen and R.L. Yu conceived and designed the study; M.L. Chen, C.H. Tan, H.C. Su, P.S. Sung, Chung-Yao Chien and W.J. Hwang collected the data; M.L. Chen and R.L. Yu analyzed and/or interpreted the data; M.L. Chen, Chia-Yi Chien and R.L. Yu drafted the manuscript; R.L. Yu revised the manuscript critically for important intellectual content; All authors approved of the version of the manuscript to be published.

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Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Boards (IRBs) of National Cheng Kung University Hospital.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication All authors have seen and approved the manuscript in the form submitted to the journal. The authors declare that they have conformed to the highest standards of ethical conduct in the submission of accurate data and that they acknowledge the work of others when applicable.

References

1 Gillies, G. E., Pienaar, I. S., Vohra, S. & Qamhawi, Z. Sex differences in Parkinson's disease. *Frontiers in neuroendocrinology* **35**, 370-384 (2014).

2 Miller, I. N. & Cronin-Golomb, A. Gender differences in Parkinson's disease: clinical characteristics and cognition. *Movement disorders* **25**, 2695-2703 (2010).

3 Chaudhuri, K. R., Healy, D. G. & Schapira, A. H. Non-motor symptoms of Parkinson's disease: diagnosis and management. *The Lancet Neurology* **5**, 235-245 (2006).

4 Aarsland, D. *et al.* Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. *Neurology* **75**, 1062-1069 (2010).

5 Arie, L., Herman, T., Shema-Shiratzky, S., Giladi, N. & Hausdorff, J. Do cognition and other non-motor symptoms decline similarly among patients with Parkinson's disease motor subtypes? Findings from a 5-year prospective study. *Journal of neurology* **264**, 2149-2157 (2017).

6 Muslimović, D. *Cognitive sequelae of Parkinson's disease: nature, course, risk factors and functional impact*. (2009).

7 Muslimović, D., Post, B., Speelman, J. D. & Schmand, B. Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology* **65**, 1239-1245 (2005).

8 Yu, R.-L. *et al.* Neuropsychological profile in patients with early stage of Parkinson's disease in Taiwan. *Parkinsonism & related disorders* **18**, 1067-1072 (2012).

9 McCarrey, A. C., An, Y., Kitner-Triolo, M. H., Ferrucci, L. & Resnick, S. M. Sex differences in cognitive trajectories in clinically normal older adults. *Psychology and aging* **31**, 166 (2016).

10 Munro, C. A. *et al.* Sex differences in cognition in healthy elderly individuals. *Aging, Neuropsychology, and Cognition* **19**, 759-768 (2012).

11 Gao, L. *et al.* Sex differences in cognition among Chinese people with Parkinson's disease. *Journal of Clinical Neuroscience* **22**, 488-492 (2015).

12 Bayram, E., Banks, S. J., Shan, G., Kaplan, N. & Caldwell, J. Z. Sex Differences in Cognitive Changes in De Novo Parkinson's Disease. *Journal of the International Neuropsychological Society*, 1-9 (2019).

13 Reekes, T. H. *et al.* Sex specific cognitive differences in Parkinson disease. *npj Parkinson's Disease* **6**, 1-6 (2020).

14 Lubomski, M., Rushworth, R. L., Lee, W., Bertram, K. L. & Williams, D. R. Sex differences in Parkinson's disease. *Journal of Clinical Neuroscience* **21**, 1503-1506 (2014).

15 Augustine, E. F. *et al.* Sex differences in clinical features of early, treated Parkinson's disease. *PloS one* **10**, e0133002 (2015).

16 Lin, S.-J., Baumeister, T. R., Garg, S. & McKeown, M. J. Cognitive profiles and hub vulnerability in Parkinson's disease. *Frontiers in neurology* **9**, 482 (2018).

17 Szewczyk-Krolikowski, K. *et al.* The influence of age and gender on motor and non-motor features of early Parkinson's disease: initial findings from the Oxford Parkinson Disease Center (OPDC) discovery cohort. *Parkinsonism & related disorders* **20**, 99-105 (2014).

18 Hughes, T. *et al.* A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. *Neurology* **54**, 1596-1603 (2000).

19 Cholerton, B. *et al.* Sex differences in progression to mild cognitive impairment and dementia in Parkinson's disease. *Parkinsonism & related disorders* **50**, 29-36 (2018).

20 Song, Y., Gu, Z., An, J., Chan, P. & Group, C. P. S. Gender differences on motor and non-motor symptoms of de novo patients with early Parkinson's disease. *Neurological Sciences* **35**, 1991-1996 (2014).

21 Liu, R. *et al.* Potential sex differences in nonmotor symptoms in early drug-naive Parkinson disease. *Neurology* **84**, 2107-2115 (2015).

22 Locascio, J. J., Corkin, S. & Growdon, J. H. Relation between clinical characteristics of Parkinson's disease and cognitive decline. *Journal of clinical and experimental neuropsychology* **25**, 94-109 (2003).

23 Riedel, O. *et al.* Cognitive impairment in 873 patients with idiopathic Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* **255**, 255-264 (2008).

24 Freeman, G. & Halton, J. H. Note on an exact treatment of contingency, goodness of fit and other problems of significance. *Biometrika* **38**, 141-149 (1951).

25 Goldman, J. G. *et al.* Cognitive impairment in Parkinson's disease: a report from a multidisciplinary symposium on unmet needs and future directions to maintain cognitive health. *npj Parkinson's Disease* **4**, 1-11 (2018).

26 Watson, G. S. & Leverenz, J. B. Profile of cognitive impairment in Parkinson's disease. *Brain Pathology* **20**, 640-645 (2010).

27 Hanna-Pladdy, B., Jones, K., Cabanban, R., Pahwa, R. & Lyons, K. E. Predictors of mild cognitive impairment in early-stage Parkinson's disease. *Dementia and geriatric cognitive disorders extra* **3**, 168-178 (2013).

28 Bouquet, C. A., Bonnaud, V. & Gil, R. Investigation of supervisory attentional system functions in patients with Parkinson's disease using the Hayling task. *Journal of Clinical and Experimental Neuropsychology* **25**, 751-760 (2003).

29 Brown, R. & Marsden, C. Internal versus external cues and the control of attention in Parkinson's disease. *Brain* **111**, 323-345 (1988).

30 De Frias, C. M., Nilsson, L. G. & Herlitz, A. Sex differences in cognition are stable over a 10-year period in adulthood and old age. *Aging, Neuropsychology, and Cognition* **13**, 574-587 (2006).

31 Spencer, R. J. *et al.* Psychometric limitations of the mini-mental state examination among nondemented older adults: an evaluation of neurocognitive and magnetic resonance imaging correlates. *Experimental aging research* **39**, 382-397 (2013).

32 Currie, L. J., Harrison, M. B., Trugman, J. M., Bennett, J. P. & Wooten, G. F. Postmenopausal estrogen use affects risk for Parkinson disease. *Archives of neurology* **61**, 886-888 (2004).

33 Marder, K. *et al.* Postmenopausal estrogen use and Parkinson's disease with and without dementia. *Neurology* **50**, 1141-1143 (1998).

34 Haaxma, C. A. *et al.* Gender differences in Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry* **78**, 819-824 (2007).

35 Dluzen, D. Estrogen decreases corpus striatal neurotoxicity in response to 6-hydroxydopamine. *Brain research* **767**, 340-344 (1997).

36 Gajjar, T., Anderson, L. & Dluzen, D. Acute effects of estrogen upon methamphetamine induced neurotoxicity of the nigrostriatal dopaminergic system. *Journal of neural transmission* **110**, 1215-1224 (2003).

37 Jacobs, D. M. *et al.* Cognitive function in nondemented older women who took estrogen after menopause. *Neurology* **50**, 368-373 (1998).

38 Yaffe, K., Sawaya, G., Lieberburg, I. & Grady, D. Estrogen therapy in postmenopausal women: effects on cognitive function and dementia. *Jama* **279**, 688-695 (1998).

39 Wooten, G., Currie, L., Bovbjerg, V., Lee, J. & Patrie, J. Are men at greater risk for Parkinson's disease than women? *Journal of Neurology, Neurosurgery & Psychiatry* **75**, 637-639 (2004).

40 Yang, K. *et al.* Cognitive characteristics in Chinese non-demented PD patients based on gender difference. *Translational neurodegeneration* **7**, 16 (2018).

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