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 (βA = 0.241, pA = 0.036), the Stroop Word-Color Test (β = -0.245, p = 0.036), and the DSS (β = -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. 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. 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. According to previous studies' findings, the domains of neurocognitive deficits involved include executive function, attention, processing speed, visuospatial ability, memory, and language.

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, and males performed better than females in visual-spatial tests. In the population of PD patients, some studies suggested that no sex difference in patients' general neurocognitive function. Nevertheless, not all studies lent support for the lack of sex differences. Some studies reported that male patients have more subjective complaints, lower global cognitive function in the early stage, more mild cognitive impairment, and the development of mild cognitive impairment is more rapid in males than females. On the contrary, some studies suggested that female PD patients have poor general cognitive function.

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, but the results of other domains are not consistent across different studies. Female patients show better verbal memory, but other studies argue that there is no significant difference among memory-related assessments. 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. Furthermore, some results revealed no significant difference in attention. Among all the executive functions that are frequently impaired in PD patients, males perform worse on verbal fluency, while another study showed no significant difference. In addition, some studies suggested that female PD patients have poor executive, and visuospatial-function. On the inhibition ability, males perform worse than females. However, there are also studies showing no significant sex difference on the high-level executive function.

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 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<sup>a</sup>                                                                  |
|                         | Matrix reasoning<sup>a</sup>                                                              |
| Attention               | Attention Test                                                                            |
|                         | Digit Span<sup>a</sup>                                                                    |
| Processing Speed        | SWCT: word score and color score                                                          |
|                         | CTT-part A                                                                               |
|                         | Digit Symbol Substitution<sup>a</sup>                                                      |
|                         | Symbol Searching<sup>a</sup>                                                              |
| Visuospatial ability    | Pentagon copy<sup>−</sup>                                                                  |
|                         | Block design<sup>a</sup>                                                                   |
| Memory                  | Logical Memory (LM)<sup>b</sup>                                                            |
|                         | Visual Reproduction (VR)<sup>b</sup>                                                       |
| Language<sup>−</sup>     | Naming                                                                                   |
|                         | Repetition                                                                               |
|                         | Verbal comprehension                                                                      |

<sup>a</sup>Subtest of Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)  
<sup>b</sup>Subtest of Wechsler Memory Scale-Third Edition (WMS-III)  
<sup>−</sup>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<sup>24</sup> 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 |
|--------------------------------------|-------------|--------------|---------|
| age, y                               | 63.96(6.17) | 64.88(8.54)  | 0.320<sup>c</sup> |
| Education, y                         | 12.10(4.05) | 11.94(3.60)  | 0.393<sup>c</sup> |
| **Executive function**               |             |              |         |
| M-WCST-C                             | 4.38(2.04)  | 5.56(1.65)   | <0.001<sup>*</sup> |
| M-WCST-P                             | 5.77(8.49)  | 3.42(4.80)   | 0.024<sup>c</sup> |
| SWCT-color word score                | 29.12(11.69)| 32.50(10.99) | 0.041<sup>c</sup> |
| Category Fluency                     | 34.04(8.26) | 38.73(8.83)  | <0.001<sup>a</sup> |
| CTT-B                                | 136.15(90.66)| 108.21(37.71)| 0.013<sup>c</sup> |
| Similarities                         | 10.66(2.89) | 11.78(2.69)  | 0.002<sup>c</sup> |
| Matrix Reasoning                     | 10.86(2.96) | 11.85(2.89)  | 0.009<sup>c</sup> |
| **Attention**                        |             |              |         |
| Attention test<sup>-</sup>           | 7.28(1.15)  | 7.61(0.73)   | 0.028<sup>c</sup> |
| Digit Span                           | 11.45(2.62) | 12.01(2.77)  | 0.181<sup>c</sup> |
| **Processing speed**                 |             |              |         |
| SWCT-word score                      | 75.13(20.07)| 84.31(17.89) | <0.001<sup>b*</sup> |
| SWCT-color score                     | 57.66(265.969)| 62.86(14.02)| 0.007<sup>b</sup> |
| CTT-A                                | 69.14(38.74)| 52.23(19.06) | <0.001<sup>c</sup> |
| Digit Symbol Substitution            | 10.16(2.35) | 12.10(2.38)  | <0.001<sup>c</sup> |
| Symbol Searching                     | 10.35(2.65) | 12.31(2.32)  | <0.001<sup>c</sup> |
| **Visuospatial ability**            |             |              |         |
| Pentagon copy<sup>-</sup>            | 12/82       | 3/164        | <0.001<sup>a</sup> |
| Block Design                         | 9.93(2.67)  | 10.94(2.75)  | 0.002<sup>c</sup> |
| **Memory**                           |             |              |         |
| LM-I(r.s.)                           | 30.03(13.49)| 35.46(11.51) | 0.002<sup>c</sup> |
| LM-II(r.s.)                          | 17.43(10.65)| 21.84(9.25)  | 0.001<sup>b*</sup> |
| LM-recognition(r.s.)                 | 22.64(4.35) | 24.49(3.75)  | 0.001<sup>*</sup> |
| VR-I(r.s.)                           | 67.05(19.99)| 74.67(14.22) | 0.005<sup>c</sup> |
| VR-II(r.s.)                          | 44.99(23.44)| 52.36(21.45) | 0.019<sup>c</sup> |
| VR-recognition(r.s.)                 | 41.16(4.13) | 42.24(3.90)  | 0.027<sup>c</sup> |
| **Language**                         |             |              |         |
| Naming                               | 0/94        | 0/167        | -        |
|                  | PD (n = 94) | NC (n = 167) | p value |
|-----------------|-------------|--------------|---------|
| Repetition      | 1/93        | 4/163        | 0.657\(^a\) |
| Verbal compreheision | 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 value | p* value | p# value | p* value |
|--------------------------|------------------|---------------------|----------------|------------------|---------|----------|----------|----------|
| age, y                   | Mean(SD)         | Mean(SD)            | Mean(SD)       | Mean(SD)         |         |          |          |          |
| education, y             | 66.59(8.92)      | 64.09(8.28)         | 64.45(5.62)    | 63.09(7.04)      | 0.077<sup>c</sup> |          |          |          |
| onset age, y             | -                | -                   | 60.15(5.86)    | 59.09(6.78)      | -       | 0.429<sup>b</sup> | -         | -         |
| Disease duration, y      | -                | -                   | 4.47(2.76)     | 4.19(3.79)       | -       | 0.249<sup>c</sup> | -         | -         |
| LED                      | -                | -                   | 557.53(265.38) | 463.92(277.75)   | -       | 0.085<sup>c</sup> | -         | -         |
| H&Y stage                | -                | -                   | 1.50(0.893)    | 1.26(1.05)       | -       | 0.329<sup>b</sup> | -         | -         |
| **Executive function**   |                  |                     |                |                  |         |          |          |          |
| M-WCST-C                 | 5.47(1.69)       | 5.60(1.63)          | 4.47(2.054)    | 4.24(2.05)       | 0.310<sup>e</sup> | 0.585<sup>c</sup> | 0.009<sup>c</sup> | < 0.001<sup>c*</sup> |
| M-WCST-P                 | 3.81(6.09)       | 3.24(4.08)          | 5.43(8.073)    | 6.35(9.29)       | 0.226<sup>e</sup> | 0.539<sup>c</sup> | 0.398<sup>c</sup> | 0.022<sup>c</sup> |
| SWCT-color word score    | 30.66(11.55)     | 33.36(10.66)        | 28.33(11.12)   | 30.50(12.71)     | 0.006<sup>e</sup> | 0.391<sup>b</sup> | 0.278<sup>b</sup> | 0.350<sup>c</sup> |
| Category Fluency         | 34.53(7.71)      | 40.68(8.66)         | 32.48(7.46)    | 36.79(8.97)      | < 0.001<sup>d*</sup> | 0.005<sup>c</sup> | 0.218<sup>c</sup> | 0.024<sup>b</sup> |
| CTT-B                    | 108.44(36.78)    | 108.10(38.30)       | 139.40(102.79) | 130.42(64.93)    | 0.383<sup>e</sup> | 0.890<sup>c</sup> | 0.082<sup>c</sup> | 0.127<sup>c</sup> |
| Similarities             | 12.00(3.03)      | 11.68(2.52)         | 10.73(2.85)    | 10.53(2.99)      | 0.296<sup>e</sup> | 0.949<sup>c</sup> | 0.024<sup>c</sup> | 0.043<sup>c</sup> |
| Matrix Reasoning         | 12.26(2.71)      | 11.66(2.95)         | 10.95(3.07)    | 10.71(2.79)      | 0.799<sup>e</sup> | 0.692<sup>c</sup> | 0.023<sup>c</sup> | 0.081<sup>c</sup> |
| **Attention**            |                  |                     |                |                  |         |          |          |          |
| Attention test-          | 7.57(0.82)       | 7.63(0.68)          | 7.30(1.18)     | 7.24(1.10)       | 0.615<sup>e</sup> | 0.588<sup>c</sup> | 0.278<sup>c</sup> | 0.046<sup>c</sup> |
| Digit Span               | 11.81(2.99)      | 12.10(2.72)         | 11.10(2.72)    | 12.06(2.36)      | 0.056<sup>e</sup> | 0.088<sup>b</sup> | 0.250<sup>c</sup> | 1.000<sup>c</sup> |
| **Processing speed**     |                  |                     |                |                  |         |          |          |          |
| SWCT-word score          | 76.51(16.24)     | 87.94(17.52)        | 71.23(19.164)  | 82.00(20.06)     | < 0.001<sup>d*</sup> | 0.012<sup>b</sup> | 0.120<sup>b</sup> | 0.127<sup>c</sup> |
| SWCT-color score         | 58.68(14.31)     | 64.81(13.51)        | 54.467(14.38)  | 63.29(18.12)     | < 0.001<sup>d*</sup> | 0.011<sup>b</sup> | 0.122<sup>b</sup> | 0.599<sup>b</sup> |
| CTT-A                    | 52.54(21.14)     | 52.09(18.10)        | 70.07(40.46)   | 67.50(36.04)     | 0.556<sup>e</sup> | 0.726<sup>c</sup> | < 0.001<sup>c*</sup> | 0.003<sup>c</sup> |
| DSS                      | 11.93(2.49)      | 12.18(2.34)         | 9.88(2.30)     | 10.65(2.40)      | 0.029<sup>e</sup> | 0.137<sup>c</sup> | < 0.001<sup>c*</sup> | < 0.001<sup>c*</sup> |
| Symbol Searching         | 12.76(2.49)      | 12.09(2.21)         | 10.50(2.60)    | 10.09(2.75)      | 0.615<sup>e</sup> | 0.276<sup>c</sup> | 0.009<sup>c</sup> | 0.045<sup>c</sup> |
| **Visuospatial ability** |                  |                     |                |                  |         |          |          |          |
| Pentagon copy-           | 1/52             | 2/112               | 4/56           | 8/26             | > 0.999<sup>a</sup> | 0.026<sup>a</sup> | 0.369<sup>a</sup> | < 0.001<sup>a*</sup> |
|                          | 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 |
|--------------------------|------------------|----------------------|------------------|-------------------|-------------|-------------|-------------|-------------|
| Block Design             | 11.57 (2.74)     | 10.65 (2.72)         | 9.87 (2.94)      | 10.03 (2.14)      | 0.187       | 0.934       | 0.003       | 0.086       |
| Memory                   |                  |                      |                  |                   |             |             |             |             |
| LM-I (r.s.)              | 33.13 (13.07)    | 36.54 (10.60)        | 27.97 (13.58)    | 33.68 (12.73)     | 0.001       | 0.037       | 0.060       | 0.317       |
| LM-II (r.s.)             | 20.00 (10.08)    | 22.70 (8.76)         | 15.78 (10.59)    | 20.32 (10.26)     | 0.002       | 0.041       | 0.043       | 0.357       |
| LM-recognition (r.s.)    | 24.04 (4.00)     | 24.70 (3.61)         | 22.08 (4.48)     | 23.62 (3.97)      | 0.039       | 0.128       | 0.015       | 0.163       |
| VR-I (r.s.)              | 74.83 (16.38)    | 74.59 (13.18)        | 66.15 (21.31)    | 68.65 (17.62)     | 0.672       | 0.587       | 0.029       | 0.138       |
| VR-II (r.s.)             | 50.57 (24.94)    | 53.19 (19.68)        | 43.62 (24.36)    | 47.41 (21.87)     | 0.084       | 0.376       | 0.131       | 0.248       |
| VR-recognition (r.s.)    | 42.34 (4.17)     | 42.19 (3.79)         | 41.15 (4.20)     | 41.18 (4.07)      | 0.591       | 0.991       | 0.094       | 0.179       |
| Language                 |                  |                      |                  |                   |             |             |             |             |
| Naming                   | 0/53             | 0/114                | 0/60             | 0/34              | -           | -           | -           | -           |
| Repetition               | 2/51             | 2/112                | 0/60             | 1/33              | 0.592       | 0.362       | 0.218       | >0.999      |
| Verbal comprehension     | 2/51             | 1/113                | 1/59             | 1/33              | 0.237       | >0.999      | 0.599       | 0.408       |

*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; LM-recognition, immediate memory of the visual reproduction; VR-I, delayed memory of the logical memory; M-WCST-C and M-WCST-P indicate the achieved categories and perseverative, respectively.

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, $\beta_B = 0.222, P_B = 0.046$), and processing speed (CTT part A, $\beta_A = 0.241, P_A = 0.036$; the color score of the SWCT, $\beta = -0.245, p = 0.036$; DSS, $\beta = -0.258, p = 0.035$) 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.
| 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**         | -0.254 | 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.
better than female ones on visuospatial ability
better than male ones on verbal fluency
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, 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, while the language function is relatively preserved. 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. 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. Previous studies revealed that the vital determinants of neurocognitive dysfunction depend on reducing the supervisory attentional system. 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 to measure simple attention function instead of complex attention function in the present study.

In this 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. In the current study, our male and female PD patients showed no difference in each performance on simple attention function. However, our male PD patients showed significantly poorer performance on complex attention function than female PD patients. This difference may be due to the nature of the task applied for the assessment of attention.

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 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, 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. 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, verbal memory, and processing speed. Besides, male PD patients perform better than female ones on visuospatial ability. In the current study, our male and female PD patients showed no difference in each execution function.
neurocognitive domain. The patients’ heterogeneity may explain the discrepancy. Most PD patients recruited in the prior studies had shorter disease duration\textsuperscript{12,13,16,17,21,22} or have intact mentality ability\textsuperscript{19}, and we recruited patients at all stages. Estrogen may have a protective ability and consequently reduce PD risk for females\textsuperscript{32,33}. The estrogen's protection was found in the early disease stage but not in the later stage\textsuperscript{34}. Evidence showed that estrogen could prevent striatum degeneration\textsuperscript{35} but unable to protect the damaged striatum\textsuperscript{36}. It is believed that estrogen may impact neurocognitive function\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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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Consent to participate: Informed consent was obtained from all individual participants included in the study.

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