Sex Differences in Cognitive Decline of De Novo Parkinson's Disease Patients: A Longitudinal Study

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SEX DIFFERENCES IN COGNITIVE DECLINE OF PD PATIENTS

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Abstract

Parkinson's disease (PD) is one of the most common progressive neurodegenerative disorders affecting elderly people. Cognitive impairment is an evident non-motor symptom (NMS) of PD and is often already present at early stages of the disease. Despite research on cognitive functioning of PD men and PD women, little is known about sex differences in cognitive decline of de novo PD patients and PD patients, therefore, replication of earlier studies is needed. The goal of this study is to gain a better understanding of sex differences in cognitive decline of de novo PD patients. Therefore, we compared cognitive functioning between de novo PD men and women and Healthy Control (HC) men and women. In addition, we looked at cognitive decline over time in PD patients, comparing men and women. Cognitive functioning of PD patients (n = 93, 73.1% male) was compared to HC participants (n = 126, 49.2% male). An extensive neuropsychological test battery was conducted in which all cognitive domains were included. Results show that de novo PD patients performed worse on all cognitive domains than HCs. Similar to sex differences found in HCs, within de novo PD patients, men have worse cognitive functioning on all cognitive domains compared to women. In early PD, in contrast to HCs, visuospatial functioning in men seems to be worse than women. It can be concluded that there are no sex differences in cognitive decline in de novo PD patients over a timeframe of three years. Future research could include an extended period of time and could take level of education into account as a variable to determine cognitive decline between men and women with de novo PD.

Keywords: de novo PD, cognitive decline, neuropsychological tests, sex differences

Sex Differences in Cognitive Decline of De Novo Parkinson's Disease Patients

Parkinson's disease (PD) is one of the most common progressive neurodegenerative disorders affecting elderly people (Bamford & Henderson, 2021). A key feature in the pathology of PD is described as the loss of dopaminergic neurons in the substantia nigra (Balestrino & Schapira, 2019). The disease is characterized by motor symptoms and non-motor symptoms (NMS). Common motor symptoms in PD include bradykinesia, resting tremor, rigidity, and postural instability (Cerri et al., 2019; Meoni et al., 2020; Sousa-Fraguas et al., 2022). In the past decades, increasingly more studies focused on NMS within PD. NMS include, among others, depression, cognitive dysfunction, autonomic dysfunction, sleep disorders and hyposmia (Poewe, 2008; Boccalini et al., 2022). Cognitive impairment is one of the most evident NMS of PD and is often already present at early stages of the disease (Kehagia et al., 2010). NMS might predate the onset of motor symptoms and, as the disease progresses, the NMS become more prevailing in PD patients (Rodriguez-Blazquez et al., 2020). Amidst patients, cognitive impairment is of heterogeneous nature (Jellinger, 2022). A wide range of cognitive dysfunctions are present in patients with PD, ranging from mild cognitive impairment (PD-MCI) to dementia (PDD). And all PD patients have subjective cognitive decline (SCD) (Aarsland et al., 2021; Jellinger, 2022). Moreover, cognitive impairment differs among PD patients and may affect memory, attention, executive functioning, visuospatial functioning, and/or language abilities (Kehagia et al., 2010). A growing interest in possible risk factors for PD have been present in the research field over the past decades. Findings of Cereda et al. (2016) stated that, next to age and disease duration, male sex is also a risk factor for dementia in PD.

Gender differences

The fact that male sex is a risk factor for dementia in PD is also shown through the heterogeneous clinical picture of the prevalence and incidence of PD (Meoni et al., 2020). More men than women are diagnosed with PD (Meoni et al., 2020). More specifically, Moisan et al. (2016) found that the male-female ratio of PD is around 1.50 for prevalence and incidence and increases with age. This finding is consistent with previous meta- analytic studies (Wooten et al., 2004; Taylor et al., 2007). Furthermore, men usually have an earlier onset of the disease, they have more severe motor symptoms, their progression of motor symptoms is more severe, and cognitive decline is more frequently observed in comparison to women with PD (Meoni et al., 2020). It is hypothesized that the differences between the two genders can be explained by the neuroprotective effect of oestrogens in women (Meoni et al., 2020). As proposed by Haaxma et al. (2006) higher levels of oestrogens in women result in higher striatal dopamine levels. Which explains the fact that women have a lower incidence and higher age of onset of PD (Haaxma et al., 2006). Another explaining factor for the differences in incidence and prevalence of PD between men and women is that women usually have less exposure to occupational toxins and have a smaller prevalence of head trauma than men (Savica et al., 2013).

Cognitive functioning

With regard to cognition, several studies have shown that cognitive functioning of patients with PD involves a gender difference. Men with PD have a higher risk of developing cognitive impairment than women with PD (Cholerton et al., 2018; Meoni et al., 2020). Additionally, in men with PD, compared to women with PD, there is an increased rate of progressing to PD-MCI and progression to dementia (Cholerton et al., 2018; Meoni et al., 2020). However, these studies did not include a healthy control group. Therefore, it cannot be determined whether the influence of gender on the progression of cognitive functioning in PD

is a process of normal aging. In normal aging it was shown that gender is of influence on cognitive functioning over the course of life. Where women perform better on verbal learning and memory, whilst men perform better on visuospatial tasks (Munro et al., 2012; Brunet, Caldwell & Miller, 2018; Bayram et al., 2019). In advanced PD, men have worse performance than advanced PD women on memory (Reekes et al., 2020), verbal fluency (Reekes et al., 2020), processing speed (Reekes et al., 2020) and inhibition (Curtis et al., 2019; Reekes et al., 2020). Whilst, women with advanced PD present with worse performance in visuospatial functioning than men with advanced PD (Reekes et al., 2020). Non-demented PD patients, compared to age-matched HCs, showed deficits of moderate effect in frontal executive, verbal memory, and visuospatial functioning (Curtis et al., 2019). In relation to HCs, non-demented PD men had worse performance in frontal executive functioning than non-demented PD women. Non-demented PD men and women were similarly impaired in verbal memory and visuospatial abilities, compared to HCs (Curtis et al., 2019). Less is known about the early phase of PD and whether the sex differences mentioned above can also be found in this disease stage. A recent longitudinal study of four years found that sex differences at baseline in de novo PD patients were limited to verbal memory and visuospatial functioning, where women had better verbal memory and men had better visuospatial functioning (Bayram et al., 2019). Liu et al. (2015) found that, in de novo PD patients, men performed worse on global cognition (Liu et al., 2015; Oltra et al., 2022), memory (Liu et al., 2015), processing speed (Oltra et al., 2022), semantic verbal fluency (Oltra et al., 2022), verbal recall as well as delayed verbal recall (Oltra et al., 2022) than women. While men perform better on visuospatial functioning than women (Liu et al., 2015). Similar differences in cognitive functioning between men and women were found in the general population. There was found that men perform worse on psychomotor speed (Munro et al., 2012), and verbal learning and memory than women (Bayram et al., 2019; Brunet, Caldwell & Miller, 2018; Munro et al.,

2012), while women perform worse on visuospatial functioning (Bayram et al., 2019; Munro et al., 2012). On the other hand, Reekes et al. (2020) found no difference in verbal fluency, inhibition, and processing speed between men and women of the general population. Overall, studies have found different findings, but similar results in all studies were found regarding the differences in performance of cognitive functioning between (de novo) PD men and (de novo) PD women.

Cognitive decline

Despite research on cognitive functioning of PD men and PD women, little is known about sex differences in cognitive decline of PD patients, and studies present with contradicting results. Cholerton et al. (2018) found that male PD patients present with faster cognitive decline than female PD patients, as male PD patients progressed more rapidly from having no cognitive impairment to PD-MCI or PDD than female PD patients. Cereda et al. (2016) found that within the group of PD men, compared to the group of PD women, higher rates of dementia were present. Therefore, the study of Cereda et al. (2016) indicates the same sex difference in PD progression as the study of Cholerton et al. (2018). On the other hand, Altmann et al. (2022) looked at the rate of progression of PD and did not find sex differences of the rate of cognitive decline between PD men and PD women. Bayram et al. (2019) studied the rate of cognitive decline between de novo PD men and de novo PD women and also did not find sex differences in cognitive decline. As a result of these conflicting results, replication is needed.

In this study, the main objective is to assess sex differences in cognitive decline of treatment naïve, de novo PD patients. In addition, differences in cognitive decline over the course of three years of de novo PD men and the novo PD women will be assessed.
With the current study, a better understanding of differences in cognitive decline between men and women with de novo PD over a period of three years can be established. When this

difference is identified, the outcome of this study can be seen as a next step towards personalized treatment in de novo PD patients.

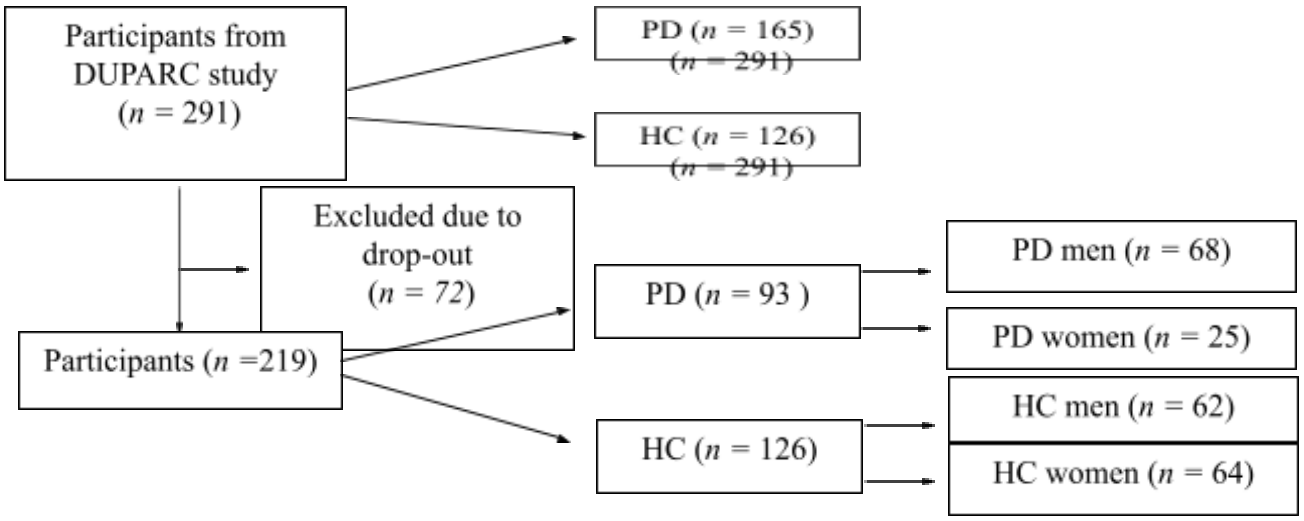
According to previous mentioned findings we expect that de novo PD men will perform worse than de novo PD women on memory, attention and processing speed and executive functioning (Liu et al., 2015; Oltra et al., 2022). We expect that de novo PD women will perform worse than de novo PD men on visuospatial functioning (Liu et al., 2015). Moreover, the expectation is that de novo PD men will show a faster decline in cognitive functioning than de novo PD women (Cholerton et al., 2018).

Method

Participants

This study is part of the DUtch PARkinson Cohort (DUPARC) study (Boertien et al., 2020). Therefore, the baseline data and follow-up data used in this study are from the dataset of the DUPARC study. Participants gave written informed consent before participation with the study (Boertien et al., 2020). The de novo PD patients were treatment naïve at baseline and were recruited through a network of PD treating neurologists in the northern part of the Netherlands (Parkinson Platform Northern Netherlands, PPNN). The healthy controls were recruited with the use of purposive sampling. Inclusion criteria for the de novo PD participants were a PD diagnosis within three months before participation with the study and that they were Dutch. PD diagnosis was confirmed with 18F-FDOPA PET imaging. Exclusion criteria for the de novo PD participants were that they did not complete the follow up neuropsychological assessment. Inclusion criteria for the healthy controls were that they fell within the age range of the PD participants. Exclusion criteria for the healthy controls were having a diagnosis affecting cognition. The flow diagram of sample selection can be found in figure 1.

Figure 1
Flow diagram of sample selection.



Materials

Memory

The imprinting and recall scores of Rey Auditory Verbal Learning Test (Rey AVLT) were used to determine verbal memory functioning (Schmidt, 1996). The test consists of five trials in which fifteen words were read out loud by a computer to the participants. After each trial, participants had to state all recalled words. Twenty minutes later, participants were asked to state all words they recalled from earlier. There were no time restrictions. During the five trials, a total maximum score of 75 could be obtained. The maximum score of recall was fifteen. A higher score indicates a better performance (Schmidt, 1996). The total amount of words imprinted after five trials was used to determine the imprinting scores of the participants. The total amount of words recalled after twenty minutes were used to determine verbal memory functioning of the participants.

Attention and processing speed

The Trail Making Test: part A was used to determine processing speed (Partington & Leiter, 1949). The test consists of 25 circles with numbers in it. Participants had to connect the numbers in ascending order as fast as possible. The faster the participant connected all the

numbers, the better the performance. A maximum score of 360 seconds was set (Overton et al., 2018). A higher score indicated a worse performance. The total amount of time used to connect all the numbers was used to determine processing speed of the participants.

The Stroop Color-Word Test (SCWT): part one was used to determine attention and processing speed (Stroop, 1935). The test consisted of a hundred names of colours. The participants had to read the names of colours printed in black ink on the card as fast as possible. The faster the participant read the whole card, the better the performance (Scarpina & Tagini, 2017). This means that a higher score indicates a worse performance. The total amount of time used to complete the card was used to determine attention and processing speed of the participants.

Executive Functioning

The Trail Making Test: part B was used to determine executive functioning (Partington & Leiter, 1949). The test consists of 25 circles with numbers and letters in it. Participants had to connect the numbers and letters alternately and in ascending order as fast as possible. The faster the participant completed the task, the better the performance. A maximum score of 360 seconds was set (Overton et al., 2018). A higher score indicates a worse performance. The total amount of time used to connect all the numbers was used to determine executive functioning of the participants.

The SCWT: part three was used to determine executive functioning (Stroop, 1935). The test consists of a hundred names of colours. The participants had to name the colour in which the names of colours were printed as fast as possible. The faster the participant completed the task, the better the performance (Scarpina & Tagini, 2017). This means that a higher score indicates a worse performance. The total amount of time used to complete the card was used to determine executive functioning of the participants.

Visuospatial Functioning

The Benton Judgment of Line Orientation (JOLO) test was used to determine visuospatial ability (Benton et al., 1994). The JOLO test consists of five practice items and thirty test items. The participants had to indicate which lines of the multiple-choice response card had the same orientation as two stimulus lines. The stimuli appeared in the upper part of a spiral-bound book and the response card appeared in the lower part of the book. There were no time restrictions. Participants verbally told their chosen responses to the examiner. For each correct item one point was given. A maximum score of thirty could be obtained (Benton et al., 1994). A higher score indicates a better performance. The number of correct items was used to determine visuospatial functioning of the participants.

Social Cognition

The Ekman 60 Faces Test as part of the Facial Expression of Emotion – Stimuli and Test (FEEST) was used to determine social cognition (Young, Perett, Calder, Sprengelmeyer, & Ekman, 2002). The Ekman 60 Faces Test consists of sixty black and white photographs of ten different male and female individuals. Each photograph randomly displayed an individual expressing one of the six emotions: anger, disgust, fear, happiness, sadness, and surprise. Participants had to label which emotion matched the picture. Each emotion was displayed ten times. A maximum score of sixty could be obtained overall and a maximum score of ten could be obtained of each emotion. A higher score indicated a better performance (Young, Perett, Calder, Sprengelmeyer, & Ekman, 2002). The number of correct items were used to determine social cognition of the participants.

Procedure

At baseline and at three years follow-up, PD patients visited the UMCG two times for a neuropsychological, clinical, and motor function assessment. The HC group were seen once in the UMCG or at home. They underwent the same neuropsychological assessment as the PD patients. The study has been approved by the medical Ethics Review Board of the University

Medical Centre of Groningen (MEtc UMCG). All participants gave written informed consent before participation (Boertien et al., 2020). The study was performed in accordance with the declaration of Helsinki.

Statistical Analyses

Before the analysis, the data was checked for outliers. The data has been analysed with the use of SPSS version 28 (IBM Corp., 2022). All statistical tests were two-tailed, and a *P* – value of 0.05 or lower was classified as statistically significant.

First, the demographics of the male and female PD group and the male and female HC group were checked for similarities in age and education level with the use ANOVA. The assumption of normality was checked for the demographics and the baseline and follow-up neuropsychological test scores of all groups, using normality plots. The baseline data of all groups of the Rey Auditory Verbal Learning Test and the FEEST were normally distributed. Therefore, a parametric test has been used to perform the analysis. A one-way ANOVA test was used to compare the raw scores on the Rey Auditory Verbal Learning Test and the FEEST between the male and female PD group and the male and female HC group at baseline. *P*-scores lower than 0.05 were considered as significant. Effect sizes were classified according to guidelines of Cohen's Partial Eta Squared (0.01 = small, 0.06 = medium, 0.14 = large; Cohen, 1973). The data of the other tests were not normally distributed at baseline. Therefore, non-parametric tests were used to perform the analysis. With the use of the Kruskal Wallis test, raw scores on the Trail Making test, Stroop Color-Word test, and JOLO were compared between the male and female PD group and the male and female HC group at baseline. *P*-scores below 0.05 were considered as significant. Effect sizes were classified according to guidelines of Kelly's Epsilon Squared (0.01 = small, 0.06 = medium, 0.14 = large; Kelly, 1935).

To look at the cognitive decline of male and female PD patients, a repeated measures ANOVA was performed to compare raw scores on the neuropsychological tests at baseline with the raw scores on the neuropsychological tests at three-year follow-up. Because the assumption of sphericity was not met, a Greenhouse-Geisser correction was used to determine whether the difference in scores were statistically significant or not. *P* – scores lower than 0.05 were considered as statistically significant. Effect sizes were classified according to guidelines of Cohen's Partial Eta Squared (0.01 = small, 0.06 = medium, 0.14 = large; Cohen, 1973). To correct for multiple comparisons the Bonferroni correction was used as a post-hoc test. *P*- scores of comparisons lower than 0.05 were considered as statistically significant.

Hypotheses

Question 1: Is there a difference in cognitive performance over time between male and female PD patients? We expected that, over a period of three years' time, de novo PD men would show a steeper decline in cognitive functioning in all cognitive domains than de novo PD women.

*Hypothesis 1.*H0: De novo PD men show the same decline in cognitive functioning in all cognitive domains as de novo PD women. Ha: Decline in cognitive functioning differs between de novo PD men and de novo PD women on all cognitive domains.

Question 2: Is there a difference in cognitive functioning between de novo PD patients and healthy controls? The expectation was that the de novo PD patients performed worse on all cognitive domains than the HCs.

Hypothesis 2. H0: De novo PD patients perform the same on memory, attention, processing speed, executive functioning, visuospatial functioning, and social cognition as the HC group. Ha: The performance on memory, attention, processing speed, executive functioning, visuospatial functioning, and social cognition differs between the de novo PD patients and the HC group.

Question 3: Is there a sex difference in cognitive functioning between de novo PD men and de novo PD women and is the same difference observed in the HC group? And in which cognitive domains is this difference shown? Based on previous literature, we expected that there will be a sex difference in cognitive functioning between de novo PD men and de novo PD women. Another expectation is that de novo PD men would perform worse on memory, attention, processing speed, executive functioning and social cognition than de novo PD women. It was also expected that de novo PD women would perform worse on visuospatial functioning than de novo PD men. We expected that the same sex differences in cognitive functioning would be observed in the HC group

Hypothesis 3a. H0: De novo PD men perform the same on memory, attention, processing speed, executive functioning, and social cognition as de novo PD women and the HC men perform the same on memory, attention, processing speed, executive functioning, and social cognition as HC women. Ha: The performance of de novo PD men on memory, attention, processing speed, executive functioning and social cognition differs from the performance of de novo PD women. And there is a difference in performance of HC men and HC women on memory, attention, processing speed, executive functioning and social cognition.

Hypothesis 3b. H0: De novo PD women perform the same on visuospatial functioning as de novo PD men and HC women perform the same on visuospatial functioning as HC men. Ha: The performance of de novo PD women differs from de novo PD men on visuospatial functioning. And the performance of HC women differs from HC men on visuospatial functioning.

Results

Demographic characteristics, Clinical features, and other assessment scores

Baseline comparisons

In total, 93 de novo PD patients (73.1% male) and 126 age-matched healthy controls (49.2 % male) were included in this study. The demographics of the participants are shown in table 1. A difference of level of education was found. A post-hoc test revealed that PD women had a significantly higher level of education than HC men (p = 0.016). No further differences were found between the four groups.

Table 1

Means (SD) and statistical comparisons of baseline measures

					Statistical comparisons			
	PD (*n* = 93)		HC (*n* = 126)		Gender		Study group	
	Men (*n* = 68)	Women (*n* = 25)	Men (*n* = 62)	Women (*n* = 64)	F	*p*	F	*p*
Age M (SD)	64.40 (8.69)	61.48 (8.37)	64.63 (8.93)	63.34 (7.91)	2.100	0.15	0.988	0.40
Level of education M (SD)	5.4 (1.2)	4.8 (1.2)	5.53 (0.99)	5.40 (1.05)	5.088	0.03*	3.084	0.03*
UPDRS III total	31.12 (10.23)	22.92 (7.51)	-	-	13.36	< 0.001*	-	-
UPDRS Hoehn and Yahr	1.91 (0.64)	1.52 (0.51)	-	-	7.57	0.01*	-	-

Note. N = sample size, PD = Parkinson's Disease, HC = healthy controls, M = mean, SD = standard deviation.

*Statistical significance

Cognition

Baseline comparisons PD group and HC group

Comparisons raw scores Neuropsychological Tests. The means, standard deviations, effect sizes, and statistical comparisons of raw test scores of the different neuropsychological tests at baseline are displayed in table 2. PD men performed significantly worse than PD women on the RAVLT: imprinting and recall, the FEEST, the TMT: part A and B, and on the

SCWT: part I and III. No significant difference in scoring between PD men and PD women was found on the JOLO test. There is a large effect size of the difference in scoring of the RAVLT: imprinting and recall, the TMT: part A and B, and on the SCWT: part I and III. A medium effect size was found within the FEEST. Within the HC group, HC women performed significantly better than HC men on the RAVLT: imprinting and recall, TMT part A and B, and the SCWT: part I and III. There is a small effect size within the difference of scoring on these tests. No significant difference in scoring between HC men and women has been found in the FEEST, the JOLO test. The PD group scores significantly lower than the HC group on the RAVLT: imprinting and recall, the FEEST, the JOLO test, the TMT: part A and B, and the SCWT: part I and III.

Table 2

Means (SD), effect sizes and statistical comparisons of baseline scores of the Neuropsychological Tests

	PD (*n* = 93)		HC (*n* = 126)		Statistical comparisons		
	Men	Women	Men	Women	Diagnostic group	Main gender-effect PD group	Main gender-effect HC group
Rey Auditory Verbal Learning Test: imprinting	35.01 (9.64)	46.96 (7.03)	38.71 (9.56)	46.31 (9.74)	F(1, 217) = 7,263, p = 0.008*, partial η^2 = 0.018	F(1, 91) = 32.462, p < 0.001*, partial η^2 = 0.263	F (3,211)= 2.413, p = 0.122, partial η^2 = 0.000
Rey Auditory Verbal Learning Test: recall	6.87 (2.73)	10.17 (2.48)	7.90 (2.83)	9.75 (3.30)	*H* = 35.232[a], p < 0.001* ϵ2 = 0.117	*H* = 22.610[a,b], p < 0.001* ϵ2 = 0.235	*H* = 10.039[a,b], p = 0.002*, ϵ2 = 0.001
Facial expressions of emotion: Stimuli and tests	43.81 (0.69)	46.96(6.79)	46.47 (6.98)	48.20 (4.95)	F(1, 213) = 10.289, p = 0.002*, partial η^2 = 0.031	F(1, 90) = 4.865, p = 0.030*, partial η^2 = 0.051	F(3,211) = 0.711, p = 0.400, partial η^2 = 0.000
Judgement of Line Orientation Test	24.68 (3.63)	25.54 (3.80)	26.34 (3.62)	24.31 (3.83)	*H* = 13.264[a], p = 0.004* ϵ2 = 0.117	*H* = 1.047[a,b], p = 0.306 ϵ2 = 0.237	*H* = 11.391[q,b], p < 0.001*, ϵ2 = 0.001

Trail Making Test: part A	45.43(21.81)	34.17(10.47)	37.53(16.69)	31.57 (9.97)	$H = 19.353^{a}$, $p < 0.001$* $\epsilon 2 = 0.117$	$H = 5.319^{a,b}$, $p = 0.021$* $\epsilon 2 = 0.235$	$H = 4.199^{1,b}$, $p = 0.040$* $\epsilon 2 = 0.002$
Trail Making Test: part B	115.35(69.94)	76.33(30.43)	84.81(37.03)	70.61(24.73)	$H = 21.978^{a}$, $p < 0.001$* $\epsilon 2 = 0.117$	$H = 8.180^{a,b}$, $p = 0.004$* $\epsilon 2 = 0.235$	$H = 5.471^{a,b}$, $p = 0.019$* $\epsilon 2 = 0.002$
Stroop Color - Word Test: Part I	56.62(16.17)	46.42 (7.30)	49.44 (8.22)	45.66 (7.07)	$H = 28.592^{a}$, $p < 0.001$* $\epsilon 2 = 0.117$	$H = 11.033^{a,b}$, $p < 0.001$* $\epsilon 2 = 0.235$	$H = 6.490^{a,b}$, $p = 0.011$* $\epsilon 2 = 0.001$
Stroop Color - Word Test: Part III	119.68(38.41)	89.21(17.92)	104.49(31.00)	92.70(24.15)	$H = 31.532^{a}$, $p < 0.001$* $\epsilon 2 = 0.117$	$H = 16.280^{a,b}$, $p < 0.001$* $\epsilon 2 = 0.235$	$H = 7.740^{a,b}$, $p = 0.005$ $\epsilon 2 = 0.001$

Note. Variables are stated as mean (SD), *N* = sample size, PD = Parkinson's Disease, HC = healthy controls, SD = standard deviation.
* Statistical significance

Longitudinal comparisons PD men and PD women

The changes in scores of several neuropsychological tests at baseline and at follow-up of PD men and PD women were analysed.

Neuropsychological tests. The mean raw scores at baseline and at follow-up on all neuropsychological tests used, are displayed in table 4. There were no significant interaction effects between gender and time within any of these tests. The RAVLT: imprinting and recall, the JOLO test, the TMT: part B, and the SCWT: part I and III showed a decrease of performance over time within the PD patient group. The decrease of the RAVLT: imprinting, the JOLO test, and the TMT: part B was of medium size. The decrease of the RAVLT: recall, and the SCWT: part I and III were of small size. The performance on the FEEST, and the TMT: part A did not differ over time. PD men performed worse on the RAVLT: imprinting and recall, the FEEST, TMT: part B, and the SCWT: part I and III than PD women. The difference in performance was of large size of the RAVLT: imprinting and recall. The difference in performance in the FEEST, the TMT: part B, and the SCWT: part I and III was of medium size. No difference in performance between PD men and PD women was found on

the JOLO test, and the TMT: part A. Post hoc comparisons indicated that the scores of PD men and PD women on the RAVLT: imprinting ($p = 0.002$), the JOLO test ($p = 0.009$) the TMT: part B ($p = 0.006$), and the SCWT: part I ($p = 0.039$) and III ($p = 0.047$) were significantly different from each other over a period of three-years' time. The scores of PD men on the FEEST ($p = 0.611$), the RAVLT: recall ($p = 0.085$), and the TMT: part A ($p = 0.185$) were not significantly different from each other over a period of three-years' time.

Table 4

Descriptive statistics and changes over time of PD men and PD women

	Baseline PD (n = 93)		Follow-up PD (n = 93)		Change between baseline and follow-up		
	Men	Women	Men	Women	Gender	Time	Interaction gender and time
Rey Auditory Verbal Learning Test: imprinting	35.01 (9.64)	47.00 (6.88)	32.54 (10.76)	44.92 (10.19)	$F = 31.096$, $p < 0.001$*, $\eta_p^2 = 0.255$	$F = 9.885$, $p = 0.002$*, $\eta_p^2 = 0.098$	$F = 0.073$, $p = 0.788$, $\eta_p^2 = 0.001$
Rey Auditory Verbal Learning Test: recall	6.87 (2.73)	10.28 (2.49)	6.26 (3.16)	10.04 (2.78)	$F = 32.885$, $p < 0.001$*, $\eta_p^2 = 0.265$	$F = 3.040$, $p = 0.085$, $\eta_p^2 = 0.032$	$F = 0.564$, $p = 0.455$, $\eta_p^2 = 0.006$
FEEST, M (SD)	43.76 (5.75)	46.96 (6.79)	43.13 (6.86)	48.17 (5.54)	$F = 8.823$, $p = 0.004$*, $\eta_p^2 = 0.090$	$F = 0.260$, $p = 0.611$, $\eta_p^2 = 0.003$	$F = 2.589$, $p = 0.111$, $\eta_p^2 = 0.028$
JOLO, M (SD)	24.68 (3.63)	25.44 (3.75)	23.99 (4.43)	23.92 (4.14)	$F = 0.170$, $p = 0.681$, $\eta_p^2 = 0.002$	$F = 7.193$, $p = 0.009$*, $\eta_p^2 = 0.073$	$F = 1.011$, $p = 0.317$, $\eta_p^2 = 0.011$
TMT: part A,	45.43(21.81)	34.28(10.27)	52.22(34.41)	33.96(10.07)	$F = 7.439$, $p = 0.185$, $\eta_p^2 = 0.019$	$F = 1.788$ $p = 0.008$*, $\eta_p^2 = 0.076$	$F = 2.159$, $p = 0.145$, $\eta_p^2 = 0.023$
TMT: part B,	104.20(50.73)	76.12(29.81)	130.48(89.51)	91.12(72.14)	$F = 5.507$, $p = 0.021$*, $\eta_p^2 = 0.060$	$F = 7.981$, $p = 0.006$*, $\eta_p^2 = 0.084$	$F = 0.596$, $p = 0.442$, $\eta_p^2 = 0.007$
Stroop Color-Word Test: part I, M (SD)	56.62(16.17)	46.68 (7.27)	59.49(20.77)	48.92 (7.626)	$F = 7.923$, $p = 0.006$*, $\eta_p^2 = 0.080$	$F = 4.381$, $p = 0.039$*, $\eta_p^2 = 0.046$	$F = 0.066$, $p = 0.798$, $\eta_p^2 = 0.001$
Stroop Color-Word Test: part III, M (SD)	119.68(38.41)	88.88(17.62)	132.72(68.97)	122.63(62.49)	$F = 10.700$, $p = 0.002$*, $\eta_p^2 = 0.105$	$F = 4.047$, $p = 0.047$*, $\eta_p^2 = 0.043$	$F = 0.488$, $p = 0.487$, $\eta_p^2 = 0.005$

Note. Variables are stated as mean (SD), N = sample size, PD = Parkinson's Disease, HC = healthy controls, SD = standard deviation.
* Statistical significance

Discussion

The goal of this study was to gain a better understanding of sex differences in cognitive decline of de novo PD patients to use as a next step towards personalized treatment. To gain better insight, this study looked at cognitive functioning at baseline of male and female de novo PD patients with the use of several neuropsychological tests. These neuropsychological tests measured cognitive functioning of verbal memory, visuospatial functioning, executive functioning, attention, processing speed, and social cognition. The test scores were compared to those of male and female HCs. In addition, sex differences in cognitive decline over time were assessed by comparing the changes over three years' time.

There are three key findings of the present research. First, the results showed that the PD group performed worse than the HC group on all neuropsychological tests at baseline. Second, results showed that PD women performed better than PD men on all tests. These sex differences in cognitive functioning were also found within the HC group, except for the sex differences found in visuospatial functioning. Third, no difference in cognitive functioning over time was shown in PD men compared to PD women.

Cognitive functioning

Firstly, we assessed the difference in cognitive functioning between de novo PD patients and healthy controls. Results of the present study provide supporting evidence for the expectation that the de novo PD patients perform worse on all cognitive domains than the HCs. Our findings strongly imply that verbal memory, social cognition, visuospatial functioning, attention, processing speed, and executive functioning is worse in de novo PD patients than in HCs. Which suggests that cognitive functioning in de novo PD patients show deficits in comparison to normal aging people.

Sex differences

Second, we assessed the sex differences in cognitive functioning between de novo PD men and women, and whether the same differences were observed in the HC group. The expectation that de novo PD men would perform worse on memory, attention, processing speed, executive functioning, and social cognition than de novo PD women is supported by the present study. Results of the present study show that de novo PD men performed significantly worse than de novo PD women on memory, social cognition, processing speed, and executive functioning.

As the results of the present study are in line with earlier findings, our study highlights that de novo PD men show deficits on verbal memory, social cognition, executive functioning, processing speed, and attention compared to de novo PD women. The same sex differences have been found in the HC group. This indicates that sex differences in de novo PD patients are identical to sex differences found in the general population.

With regard to visuospatial functioning, the present study does not provide supporting evidence for the expectation that de novo PD women would perform worse on visuospatial functioning than de novo PD men. It has shown that there is no significant difference in performance between de novo PD men and women on visuospatial functioning, although de novo PD men perform worse than the novo PD women. Within the HC group, HC men perform better than HC women on visuospatial functioning, whereas de novo PD men perform worse than de novo PD women on visuospatial functioning. This indicates that visuospatial functioning of de novo PD men seems to be more impaired than visuospatial functioning of de novo PD women compared to visuospatial functioning of male and female HCs. Although, this difference in performance is not significant.

Past researchers have found that PD women perform significantly worse on visuospatial functioning than PD men (Bayram et al., 2019; Liu et al., 2015). The contradicting results on visuospatial functioning between the current study and previous

findings of HC men and women compared to de novo PD men and women may be explained by the way visuospatial functioning was measured in different studies. The present study used a 30-item test to measure visuospatial functioning, whereas the study of Bayram et al. (2019) used a 15-item test to measure visuospatial functioning. Therefore, a more extensive test, such as used in the present study, may be more valid to determine visuospatial functioning. Although, the studies of Woodward et al. (1996) and Woodward et al. (1998) determined that the shorter JOLO test does not renounce reliability or validity of the test. In another study of Munro et al. (2012) a 24-item test was used to measure visuoconstruction. As visuoconstruction is a part of visuospatial functioning and not visuospatial functioning as a whole, these functions cannot be directly compared to each other (Ruffalo, 2004). Therefore, the results of Munro et al. (2012) can be taken into account but cannot be directly linked to the results of the current study.

The outcomes of our study can be seen as more reliable than earlier studies, because the current study used a more comprehensive neuropsychological test battery to determine cognitive functioning in different domains of de novo PD patients than earlier studies. For instance, Liu et al. (2015) and Oltra et al. (2022) used the Montreal Cognitive Assessment (MoCa) to determine cognitive functioning of PD patients. And Bayram et al. (2019) used a less extensive test battery to determine cognitive functioning in de novo PD patients.

In conclusion, compared to de novo PD men and women, similar sex differences have been found in the HCs regarding verbal memory, social cognition, processing speed, attention, and executive functioning. These findings are directly in line with earlier findings. A difference between HCs and de novo PD patients regarding sex differences have been found on visuospatial functioning. Which suggests that visuospatial functioning in de novo PD men seems to be more impaired than visuospatial functioning of de novo PD women. Moreover, there can be stated that visuospatial functioning is more degenerated in de novo PD men

compared to healthy men. There can be concluded that de novo PD men are generally more impaired in all cognitive domains than de novo PD women and HC men.

Cognitive decline

The last research question was: 'What are the sex differences in cognitive decline over a period of three years' time in de novo PD patients?'. The expectation that de novo PD men would show a steeper decline in cognitive functioning in all cognitive domains than de novo PD women over a period of three years' time was not supported by the results of the current study. No significant interaction effects between gender and time were found in any of the neuropsychological tests used in the current study. This shows that there are no sex differences in cognitive decline of de novo PD patients, although de novo PD men performed worse on all cognitive domains than de novo PD women. The results of the present study show a decrease in performance over time on verbal memory, visuospatial functioning, and executive functioning in all de novo PD patients. The performance did not differ over time with regard to social cognition and processing speed within the de novo PD patients.
These present results are consistent with Bayram et al.'s (2019) findings that there are no sex differences in cognitive decline of de novo PD patients. Although, the study of Bayram et al. (2019) used different neuropsychological tests to measure cognitive functioning of de novo PD patients over a four-year period of time than the neuropsychological tests used in the current study. The current study further supports the findings of Bayram et al. (2019) that there are no sex differences in cognitive decline of de novo PD patients.

Limitations

There are at least three potential limitations concerning the results of this study. A first potential limitation is the difference in sample size between the four groups. The de novo PD group consists of 68 men and 25 women, whereas the HC group consists of 62 men and 64 women. The number of PD women participating in this study is clearly of a smaller number

than the PD men and HC men and women participating in the study. This might have been of influence on the results of the current study. Meaning that the sample size of female PD patients could possibly be too small to reflect the female PD population and give a valid image of cognitive decline of these patients.

A second potential limitation is the possibility of random error during the collection of the data of the study. Different examiners were involved in administering the neuropsychological tests to the participants and calculating the scores of the participants on the tests. During this process, mistakes in the calculation of the scores could be made by the examiners and the observed and true scores of the participants can be different from each other. This means that it is a possibility that scores used in this study could possibly not represent the actual scores. This causes for the likelihood of an untrue representation of sex differences in cognitive decline of de novo PD patients.

A third potential limitation is that purposive sampling was used to recruit the healthy controls of the study. This may lead to an inaccurate representation of the general population in the study. For example, the healthy controls in the study are likely to have a higher level of education than the general population as university students recruited them.

Implications

Despite these limitations, these results have some potential implications. First of all, a better understanding of differences in cognitive decline between men and women with de novo PD over a period of three years has been established. No difference has been found between men and women with de novo PD in cognitive decline. Therefore, this study can attribute to the growing scientific knowledge about sex differences in cognitive decline in de novo PD patients and help other researchers to take the step towards better treatment of de novo PD patients. A second implication is that the current study has replicated and further explored previous, conflicting findings regarding sex differences in cognitive decline of de

novo PD patients. Therefore, this study enhanced knowledge about these differences in de novo PD patients and makes a stronger case for the fact that no sex differences have been found in cognitive decline of de novo PD patients. This is because the same results have been found in the study of Bayram et al. (2019). Another implication is that the present study examined PD patients who were newly diagnosed and drug naïve. This group of PD patients have not been extensively researched in the past, as most studies have focused on PD patients instead of de novo PD patients. Therefore, with the current study, more literature has come available about the early stage of PD patients. Consequently, a clearer picture about cognitive decline in de novo PD patients has become available.

Future research

In terms of future research, it would be useful to extend the current findings by looking at the sex differences in cognitive functioning of de novo PD patients over an extended period of time. This is because the current time period of three years did not show any sex differences in cognitive decline of de novo PD patients, while previous studies indeed found a faster cognitive progression of the disease in PD men than PD women within the same timeframe (Cholerton et al., 2018; Meoni et al., 2020). It would also be useful to include a larger sample size within the study. As a consequence, findings would become more generalizable to de novo PD patients. It would also be useful to look at the possible influence of cognitive reserve on cognitive decline in de novo PD patients. As PD women had a significantly higher level of education than HC men. Overall, PD women had a better performance than PD men on neuropsychological tests at baseline. A possibility is that cognitive reserve might be of influence on cognitive functioning in de novo PD patients.

Conclusion

In summary, results of the present study provide supporting evidence that de novo PD patients perform worse on all cognitive domains than HCs. Men have worse cognitive

functioning on all domains compared to women in both de novo PD patients as HCs. In early PD, in contrast to HCs, visuospatial functioning in men seems to be worse than women. With regard to cognitive decline, no sex differences were found in this study. The findings of the current study contribute to a growing body of evidence that there are no sex differences in cognitive decline of de novo PD patients over a period of three- or four-years' time. Future research could include an extended period of time and could take level of education into account as a variable to determine cognitive decline between men and women with de novo PD.

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