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Differences in Cognitive Decline in Probable Brain-First and Body-First Parkinson's Disease

N.C. Buist

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s3390365
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Department of Psychology
University of Groningen
Examiner: prof. dr. J. M. Spikman
Daily supervisor: A.C. Slomp, dr. S. van der Zee

Abstract

Parkinson's Disease (PD) is a progressive neurodegenerative disorder, and many patients experience non-motor symptoms such as cognitive impairments. Given the heterogeneity between patients, assessing biomarkers to predict better PD progression is essential. A recent theory on the connection between the location of the first pathological synuclein and the asymmetrical distribution of the dopaminergic deficiency of the disease is known as the α-Synuclein Origin and Connectome (SOC) model. According to this model, subtypes with a more symmetric distribution at the *de novo* stage experience a higher burden of PD and deteriorate faster than the asymmetrical subgroup. When the origin of PD is understood, a better prognosis can be made for further development and appropriate therapy. 102 newly diagnosed and treatment-naïve PD patients were included and underwent an extensive neuropsychological assessment. Cognitive differences were tested between symmetrical and asymmetrical subtypes, as differentiated by FDOPA-PET imaging. The symmetrical subgroup performed worse on the cognitive screening and the domains of attention and processing speed, executive functioning, language, and memory. After adjusting for age, these effects were only present to a limited extent. The symmetrical group showed only a faster decline in executive functioning. In conclusion, limited evidence supports a higher burden in body-first types, as described in the SOC model, and no evidence supports faster deterioration in this type. Further investigation is necessary, and the inclusion of follow-up data over more than three years is recommended.

Keywords: asymmetry index, dopaminergic deficiency, cognitive decline, Parkinson's Disease, α-Synuclein Origin and Connectome model.

Differences in Cognitive Decline in Probable Brain-First and Body-First Parkinson's Disease

Parkinson's Disease (PD) is a well-known progressive neurodegenerative disorder characterized by various symptoms. The clinical diagnosis of PD is constructed on the appearance of motor symptoms, for example, bradykinesia, postural imbalance, rigidity, and resting tremor (Hawkes et al., 2007; Reichmann, 2010). However, before the onset of motor symptoms, a long prodromal phase occurs, characterized by non-motor symptoms (NMS), such as constipation, fatigue, olfactory dysfunction, and sleep disorders (Hawkes, 2007; Reichmann, 2010). Other common NMS are nonuniversal cognitive impairments, which can be visible in multiple cognitive domains and significantly impact the quality of life (Kalia & Lang, 2015; Lawson et al., 2014).

Due to the considerable clinical heterogeneity of PD, the manifestation of motor and non-motor symptoms varies in individuals, including differences in cognitive decline (von Coelln & Shulman, 2016). Research suggests particularly the domains of executive functioning, memory, and processing speed are being affected (Altmann et al., 2022; Yang et al., 2022). Careful and accurate assessment of symptoms and the discovery of biomarkers are essential, if not necessary, to classify PD subtypes, which may be able to predict the progression of further deterioration better (Aarsland et al., 2021).

Dopaminergic neurodegeneration in the substantia nigra describes the pathological process that underlies PD (Aarsland et al., 2021; Halliday et al., 2014). The aberrant deposition of the misfolded protein α-synuclein results in clumps, also known as Lewy bodies, that deteriorate the synapses of dopamine-producing neurons (Aarsland et al., 2021; Goedert, 2001; Venda et al., 2010). Lewy bodies are found in the brain, the spinal cord, and the peripheral nervous system (Kalia & Lang, 2015). The dopaminergic neuronal loss in the substantia nigra is correlated with motor dysfunctions in PD, especially bradykinesia and

rigidity, and neuronal loss is found in many other brain regions (Kalia & Lang, 2015).

The α-Synuclein Origin site and Connectome model (the SOC model) aims to explain the heterogeneity of PD and provides information about where the pathology of α-synuclein begins (Borghammer, 2021). According to this model, the anatomical location of the first pathogenic α-synuclein varies among patients, and the neural connectome, or the neural network, plays an essential role in the distribution of this pathological protein through the nervous system (Borghammer, 2021). Based on the origin site of the pathology, two subtypes are hypothesized where PD develops initially, that is, the body-first and the brain-first subtype (Knudsen et al., 2021). This recent hypothesis proposes that α-synuclein aggregation can start either in the central nervous system (CNS) or in the peripheral autonomic nervous system (PANS), leading to respectively probable brain-first and body-first subtypes of PD, and research supports this dissociation (Borghammer, 2021; Horsager et al., 2020).

Subsequently, the idea emerged that the brain-first subtype of PD has a short prodromal phase due to early involvement of the substantia nigra (Borghammer et al., 2022; Horsager et al., 2020; Knudsen et al., 2021). The earliest α-synuclein pathology seemingly arises in the limbic structures or the olfactory bulb, spreading rapidly to closely connected ipsilateral brain structures (Borghammer, 2021). In contrast, the body-first subtype has a long prodromal duration (Borghammer et al., 2022). The α-synuclein pathology arises in the enteric nervous system (ENS), or the digestive nervous system, and spreads bilaterally through the brainstem while having more time for widespread distribution in the nervous system (Borghammer, 2021; Horsager et al., 2020; Knudsen et al., 2021).

It is proposed that the dopaminergic deficiency of the brain-first type is more asymmetrical pronounced, and the pathology of the body-first type has a more prominent symmetric distribution, especially in *de novo* or early stages, before the confounding effect of the medication can occur (Borghammer, 2021). In addition, the burden of Lewy pathology is

higher in *de novo* patients of the body-first type. These patients are more at risk for accelerated progression of the disease (Borghammer et al., 2022).

REM-sleep Behavior Disorder (RBD) has been recognized as a vital marker for the body-first subtype (Knudsen et al., 2021). RBD displays a more symmetrical striatal degeneration and therefore supports the idea of body-first PD distributing more symmetric at the *de novo* stage (Knudsen et al., 2021). Additionally, the average time between the onset of RBD and the early development of PD is 12 to 14 years, suggesting a long prodromal phase (Postuma et al., 2015). Besides this, research has discovered that PD with RBD is associated with poorer cognitive functioning in the domains of attention, executive functioning, memory, and visuospatial functioning in contrast to PD without RBD (Jozwiak et al., 2017). Further, considering markers for the body-first subtype, such as RBD or constipation, research suggested that this subtype is more closely related to faster cognitive decline (Borghammer, 2021; Kong et al., 2020).

Although it is difficult to say where the α-synuclein pathology starts precisely, according to the SOC model, it might be possible to use the asymmetrical and symmetrical distribution of dopaminergic deficiencies as a suitable proxy, for respectively the brain-first and body-first subtypes of PD (Boertien et al., in preparation; Knudsen et al., 2021). Moreover, the SOC model indicates faster disease progression and accelerated cognitive decline in the symmetrical subtype of PD (Borghammer, 2021).

To determine asymmetry, striatal dopaminergic innervation can be assessed. The presynaptic dopaminergic deficiency can be quantified with 3,4-dihydroxy-6-18F-fluoro-1-phenylalanine (^{18}F-FDOPA) PET imaging. The putamen is a sensitive measure, as it is affected by nigrostriatal degeneration in the early stages of PD (Knudsen et al., 2021). Consequently, the FDOPA PET scan can be used to distinguish between asymmetrical and symmetrical distribution in PD patients.

A recent study offers some preliminary evidence, as the symmetrical PD group achieved lower scores with nominal statistical significance for the Montreal Cognitive Assessment (MoCA) compared to the asymmetrical group. However, after FDR correction, no significance is detected (Boertien et al., in preparation). However, this may suggest a possible disparity in cognition between the symmetrical and asymmetrical distribution of PD, and more research is needed to reveal a differential cognitive decline.

So far, no extensive research has examined the cognitive decline in the symmetrical and asymmetrical subtypes of PD, as discussed above. With the Dutch Parkinson Cohort (DUPARC) study, newly diagnosed PD patients are extensively assessed, including several brain scans and an elaborative neuropsychological assessment examining all cognitive domains to discover and validate biomarkers for PD (Boertien et al., 2020). Patients are assessed at the time of diagnosis and at three-year follow-up, which allows investigation of the differences in cognitive functioning at the time of diagnosis and cognitive decline over time between PD patients with symmetrical versus asymmetrical dopaminergic deficiency. When the origin of the disease is understood, a better prognosis can be made about how the disease will develop and which treatment is most suitable for the individual patient.

This thesis will examine differences in cognitive functioning at the time of diagnosis between PD patients with symmetric and asymmetric dopaminergic deficiency as a proxy for respectively body-first and brain-first subtypes, using a comprehensive neuropsychological assessment covering all cognitive domains. Subsequently, this study will assess differences in cognitive decline between those subgroups over three years. This gave rise to the following research questions: Are PD patients with symmetrical versus asymmetrical dopaminergic deficiency significantly different in cognitive functioning at the time of diagnosis? Furthermore, can we detect significant differences in cognitive decline over three years in the PD subgroups?

Based on the theoretical review above, the expectation is to find a difference in cognitive functioning, with the symmetrical subgroup being more affected than the asymmetrical group. For this reason, the symmetrical group is expected to achieve lower results on the neuropsychological assessments. Not only in the cognitive screening and cognitive domains such as executive functioning and memory, these differences are expected to be found, but also in domains such as attention, processing speed, and visuospatial functioning. The assumption is that each group will reveal significant cognitive decline over three years, but the symmetrical group is expected to demonstrate faster deterioration.

Methods

Participants

In total, 102 PD patients (29% female) and 102 healthy controls (HC; 52% female) were included in this research. All the data originated from the DUPARC study, managed by the University Medical Center Groningen (UMCG). This study consisted of a convenience sample of *de novo* patients examined within three months after diagnosis. The patients voluntarily participated in a large-scale study on PD, recruited through the Parkinson Platform Northern Netherlands (PPNN; Boertien et al., 2020). At baseline, the patients were treatment naïve, and an extensive follow-up was performed after three years. In addition, a voluntary healthy control group was recruited through purposive sampling in the network of the researchers.

To allocate the PD patients to the symmetrical and asymmetrical groups, the striatal asymmetricity index (SAI) of the FDOPA PET striatal-to-occipital ratios (SOR) of the putamen was calculated for each patient at the time of baseline (Boertien et al., in preparation; Kaasinen, 2015). The patients with absolute values in the highest tercile were classified as PD-asymmetrical (PD-asym), and those in the lowest tercile were classified as PD-symmetrical (PD-sym; Boertien et al., in preparation).

$$SAI = | (right – left\ putamen\ SOR) / (right + left\ putamen\ SOR) |$$

The inclusion criteria for the PD groups at baseline were a PD diagnosis and a confirmed presynaptic dopaminergic deficiency according to the FDOPA PET scan. The exclusion criteria were the use of dopaminergic medication or incomplete data from the FDOPA PET scan (Boertien et al., 2020). Patients who fell in the middle tercile, as calculated with the SAI, were also excluded. The exclusion criteria for the control group were a history of a neurological disease, the suspicion of giving insufficient effort, or an obtained MoCA score lower than 25.

Materials

The dopaminergic brain images were constructed with the 18F-FDOPA PET scan for the current study. Education level was assessed according to the Dutch Verhage scale (Verhage, 1964). Researchers performed the neuropsychological assessment and motor assessment. All cognitive domains were included to measure baseline differences and evaluate cognitive decline over time. One or two cognitive tests represented each domain.

Neuropsychological Assessment

Cognitive Screening. The MoCA was included to describe clinical characteristics with cognitive screening (Nazreddine et al., 2005). The MoCA assesses different cognitive domains, and a maximum score of 30 can be achieved.

Premorbid Functioning. The Dutch adult reading test (NLV) was included to estimate premorbid intelligence (Schmand et al., 1991). The NLV consists of 50 words with irregular pronunciation, and participants are asked to pronounce these words correctly. A maximum score of 100 can be achieved, two points per correctly pronounced word. This corresponded with a premorbid IQ of > 120, and a higher score indicated better performance. Raw test scores and calculated IQ scores were used in the statistical analyses.

Attention and Processing Speed. The Trail Making Test (TMT-A) was used to appraise attention and processing speed (Reitan, 1956). The TMT-A is a visual task where the participant has to find digits and draw a line between them in ascending order. Furthermore, the Stroop Color Word Test (SCWT-I) was also applied to assess functions of attention and processing speed (Stroop, 1935). In the SCWT-I, a card is shown with rows of words printed in black expressing names of colors (blue, green, red, yellow), and the participant is asked to read it out loud (Hammes, 1971). For both tasks, the experimenter measured the time in sec it took to finish the task, and higher scores were indicated with poorer performance. A maximum score of 300 sec was adjusted for the TMT-A.

Executive Functioning. The inference version of the TMT (TMT-B) assessed executive functioning (Reitan, 1956). In this version of the TMT, digits and letters are depicted, and the participant is asked to draw a line while switching between the numbers and letters in ascending order. In addition, the inference version of the Stroop (SCWT-III) was included to determine executive functioning by suppressing a verbal response (Stroop, 1935). In the SCWT-III, rows with words of colors (blue, green, red, yellow) are depicted, however, this time, they are printed in different colors (blue, green, red, yellow), and the participant is asked to identify the color of the ink rather than the word itself (Hammes, 1971). Time in sec was measured for both tasks, and a higher score was indicated with poorer performance. For the TMT-B, a maximum score of 300 was specified.

Language. The semantic fluency task was assessed to measure language (Lezak et al., 2012). The participant is asked to generate as many words as possible in 60 sec within a specific category, in this case, animal names. No maximum score could be reached, and a higher score characterized better performance.

Memory. The Rey auditory verbal learning test (RAVLT) assessed immediate and delayed memory (Saan & Deelman, 1986). The RAVLT consists of 15 words that are read five times in spoken voice, and after each trial, the participant is asked to reproduce the words that are remembered, the immediate recall (IR). After 15-20 minutes, the participant is asked again to reproduce the words, the delayed recall (DR). The participant could obtain a maximum score of 75 for the IR and 15 for the DR; higher scores were referred to as better performance.

Social Cognition. The Ekman 60 faces test of the Facial Expression of Emotion: Stimuli and Tests (FEEST) was used to assess social cognition (Ekman & Friesen, 1976). Black and white photographs of different people expressing basic emotions are presented on a computer screen. The participant is asked to choose the emotion expressed in the picture, which can be

anger, disgust, fear, happiness, sadness, or surprise. The maximum score for the FEEST was 60, and a higher score indicated a better performance.

Visuospatial Functioning. The Judgement of Line Orientation (JOLO) was used to determine the visuospatial orientation (Benton et al., 1978). In a booklet, 11 lines are depicted at different angles, each with their corresponding number, and above that figure, two lines are depicted at specific angles. The participant is asked to correctly match the two lines with the corresponding numbers of the lines in the response-choice illustration without a time limit. A maximum score of 30 could be obtained, and a higher score illustrated better performance.

Motor Assessment

Motor severity and progression. The Movement Disorders Society Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS-III) was used to assess the severity and progression of motor functioning at baseline (Goetz et al., 2008). The MDS-UPDRS-III consists of 18 tasks with 33 items that can be scored from 0 to 4, with more severe motor functioning coinciding with a higher score. The Hoehn and Yahr scale describes PD progression in five stages, where a higher stage corresponds with a higher disability (Hoehn & Yahr, 1967).

Medication. The Levodopa Equivalence Daily Dose (LEDD-score) was used to calculate a standardized score to compare dose intensities of different dopaminergic medications used during follow-up (Tomlinson et al., 2010). Higher scores corresponded with higher doses.

Procedure

Patients visited the UMCG twice for an extensive investigation, each at baseline and follow-up, which amounts to four times. The patients were subjected to a comprehensive study procedure, to be precise, an extensive cognitive assessment, several imaging techniques, an ophthalmological assessment, and a clinical assessment. The healthy control group only attended the cognitive assessment to compare the cognitive performance of both PD groups to

healthy controls. Approvement of the Medical Ethics Board of the UMCG (MEtc UMCG) was required, and the details of the participants were treated with confidentiality. All patients and healthy controls confirmed the investigation with written informed consent. The research was performed in line with the Declaration of Helsinki.

Statistical analysis

The data was processed and analyzed using IBM SPSS Statistics 28. The first step in this process was describing the clinical characteristics and demographics of the three groups, PD-sym, PD-asym, and HC, using descriptive statistics. The data was checked for normality with the Shapiro-Wilk test and quantile-quantile (QQ) plots. In the case of the three groups, the data was compared using Analysis of Variance (ANOVA) when the data was normally distributed or the Kruskal-Wallis test when the data was not normally distributed. Regarding two group comparisons, chi-square tests were used when the data was normally distributed, and the Mann-Whitney U test was used as a nonparametric variant. Secondly, raw neuropsychological test scores of the three groups at baseline were compared using ANOVA or the Kruskal-Wallis test. A p-value of $\alpha < 0.05$ was considered statistically significant. In post hoc analyses, data was corrected with the Bonferroni adjustment for three comparisons ($\alpha / 3 < 0.0167$). Additionally, an Analysis of Covariance (ANCOVA) was performed with age as a covariate, and again Bonferroni was used in post hoc analyses. Finally, difference scores were computed to assess cognitive decline between the PD groups over three years. Test scores were converted to difference scores by subtracting the follow-up score from the baseline score (difference score = BL – FU). To compare the difference scores per test between the two groups, independent sample t-tests were used for parametric data and Mann-Whitney U tests for non-parametric data.

Results

Differences in cognitive functioning at the time of diagnosis

Demographic and clinical characteristics

Table 1 provides an overview of the demographic and clinical characteristics of the PD-sym (n = 51), PD-asym (n = 51), and HC (n = 102). Firstly, age significantly differs between groups, with PD-sym having a significantly higher age than PD-asym and HC. However, PD-asym and HC do not have significantly different ages. The level of education is not significantly different between PD-sym and PD-asym and between PD-sym and HC. However, the level of education significantly differs between PD-asym and HC, with PD-asym having lower education levels. Lastly, the PD-sym group scores significantly higher on the MDS-UPDRS III and Hoehn & Yahr scale than the PD-asym group, indicating more severe motor symptoms and higher motor disability in this group.

Table 1

Clinical characteristics and demographics at baseline

	PD-sym (*n* = 51)	**PD-asym (*n* = 51)**	**HC (*n* = 102)**	**Test statistic**	**p-value**	**Post-hoc Bonferroni**
Age Mean (*SD*)	67.98 (8.238)	63.02 (8.828)	63.05 (8.169)	$F = 6.689$	0.002*	Sym > asym = HC
Sex female *n* (%)	15 (29.4%)	15 (29.4%)	53 (52.0%)	$F = 5.588$	0.004*	Sym = asym < HC
Education Median [IQR]	5 [2]	5 [2]	6 [1]	$F = 4.453$	0.013*	Sym = asym; asym < HC; sym = HC
MDS-UPDRS III Mean (*SD*)	34.31 (12.857)	27.92 (10.421)		t (df) = 2.758 (100)	0.007*	
Hoehn & Yahr Median [IQR]	2 [0]	2 [1]		χ^2 (df) = 9.313 (3)	0.025*	

Note. * = significance level α = 0.05. Abbreviations: *SD*, standard deviation; *n*, sample size; IQR, interquartile range; *F*, ANOVA; *t*, independent sample t-test; *df*, degree of freedom, χ^2, Chi-square test.

Neuropsychological assessment

The following section provides the results of the differences between cognitive tests in the three groups, as illustrated in Table 2. Significant differences are observed between the clinical and control groups for several cognitive tests. The PD-sym group achieves significantly lower scores than the PD-asym group on the MoCA, the semantic fluency test, and the RAVLT IR and DR, indicating worse performance. In addition, the PD-sym group scores significantly higher on the TMT-A, TMT-B, and Stroop-III tests, indicating worse performance. Both PD groups have significantly lower scores on the MoCA, NLV, IQ, RAVLT IR and DR, and FEEST than the HC group, indicating worse performance. On the semantic fluency task, the PD-sym group scores significantly lower than the HC group, indicating worse performance. However, no significant difference is found between the PD-asym and the HC group for this task, indicating no difference in performance. Next, both PD groups score significantly higher on the TMT-A than the HC group, indicating worse performance. For the TMT-B, Stroop-I, and Stroop-III, the PD-sym group scores significantly higher than the HC group, demonstrating worse performance. However, the PD-asym does not obtain significantly different scores than the HC group for these latter tests, indicating comparable performance. No significant differences are found between the PD groups and HC for the JOLO.

Table 2

Neuropsychological assessment at baseline

	PD-sym (*n* = 51)	**PD-asym (*n* = 51)**	**HC (*n* = 102)**	**Test statistic**	**p-value**	**Post-hoc Bonferroni**
MoCA Mean (*SD*)	24.22 (2.91)	25.73 (2.77)	27.30 (2.77)	*H* = 46.67	< .001*	Sym < asym < HC**
NLV Mean (*SD*)	74.65 (19.25)	77.27 (17.665)	86.58 (8.058)	*H* = 21.44	< .001*	Sym = asym < HC
IQ Mean (*SD*)	100.14 (13.500)	103.18 (11.076)	108.35 (6.993)	*H* = 19.91	< .001*	Sym = asym < HC

TMT-A[a] Mean (*SD*)	51.59 (21.408)	41.14 (23.087)	32.67 (11.199)	$H = 35.61$	< .001*	Sym > asym > HC**
Stroop-I[b] Mean (*SD*)	58.31 (12.02)	53.80 (11.307)	46.72 (7.863)	$H = 42.22$	< .001*	Sym = asym < HC
TMT-B[c] Mean (*SD*)	142.35 (71.049)	90.78 (49.545)	75.27 (33.249)	$H = 43.22$	< .001*	Sym > asym = HC**
Stroop-III[d] Mean (*SD*)	131.61 (50.697)	109.47 (41.753)	93.37 (22.001)	$H = 27.41$	< .001*	Sym > asym = HC**
Sem. fluency Mean (*SD*)	20.96 (6.206)	24.37 (6.462)	25.05 (5.964)	$F = 7.75$	< .001*	Sym < asym = HC**
RAVLT IR Mean (*SD*)	32.47 (10.849)	37.56 (11.174)	43.98 (9.964)	$F = 21.50$	< .001*	Sym < asym < HC**
RAVLT DR Mean (*SD*)	6.27 (3.086)	7.82 (2.964)	9.28 (3.176)	$F = 16.42$	< .001*	Sym < asym < HC**
FEEST[e] Mean (*SD*)	43.15 (6.385)	45.41 (6.450)	48.05 (5.866)	$F = 10.88$	< .001*	Sym = asym < HC
JOLO Mean (*SD*)	24.02 (4.735)	25.02 (3.723)	25.84 (3.101)	$H = 4.32$	< .115	

Note. * = significance level α = 0.05; ** = significant difference between sym & asym. [a] HC n = 101; [b] HC n = 100; [c] HC n = 101; [d] HC n = 100; [e] PD-sym n = 48, HC n = 100.

Abbreviations: *SD*, standard deviation; *H*, Kruskal-Wallis test; *F*, ANOVA.

Additionally, this section describes the differences between the groups after including age as a covariate. There is a significant difference between the scores on the MoCA after adjusting for the effect of age, F (2, 200) = 27.88, p < .001. The PD-sym and PD-asym groups significantly differ (p = 0.036), with the PD-sym group scoring lower than the PD-asym group, indicating worse performance. Significant differences are also present between the HC and the PD-sym (p < .001) and the PD-asym (p < .001), indicating that both PD groups are performing worse than the HC. A significant difference is also found in the TMT-B after controlling for age, F (2, 199) = 24.478, p < .001. The PD-sym group scores significantly higher than the PD-asym group, indicating worse performance (p < .001). The PD-sym group also scores significantly higher than the HC (p < .001). However, no significant difference exists between the PD-asym group and the HC (p = 0.083). No other differences are found in performance between the PD groups after including age as a covariate.

Differences in cognitive decline over three years

Demographic and clinical characteristics

The demographic and clinical characteristics of the patients that participated in the follow-up session are shown in Table 3. Both PD groups consist of $n = 34$ participants. The baseline and follow-up data averages are depicted, considering the demographic differences between the entire baseline group and the group that attended the follow-up three years later. Only for the MDS-UPDRS III at follow-up are significant differences found, with PD-sym scoring higher than the PD-asym, indicating more severe motor functioning. No other significant differences are found, including no differences in medication dosages.

Table 3

Clinical characteristics and demographics of PD patients that participated in follow-up

	PD-sym (*n* = 34)	**PD-asym (*n* = 34)**	**Test statistic**	**p-value**
Age_BL Mean (*SD*)	66.03 (7.594)	62.79 (8.026)	t (*df*) = 1.707 (66)	0.092
Age_FU Mean (*SD*)	69.09 (7.609)	65.85 (8.038)	t (*df*) = 1.704 (66)	0.093
Sex female *n* (%)	11 (32.4%)	9 (26.5%)	χ^2 (*df*)= 0.283 (1)	0.595
Education Median [IQR]	5 [1]	5 [1]	χ^2 (*df*) = 7.083 (6)	0.313
LEDD[a] Mean (*SD*)	587.19 (274.802)	640.17 (347.463)	U = 482.00	0.794
MDS-UPDRS III_BL Mean (*SD*)	30.53 (11.346)	26.65 (8.831)	t (*df*) = 1.574 (66)	0.120
MDS-UPDRS III_FU[b] Mean (*SD*)	30.06 (13.700)	23.06 (9.082)	t (*df*) = 2.473 (65)	0.016*
Hoehn & Yahr_BL Median [IQR]	2 [0]	2 [1]	χ^2 (*df*) = 5.356 (3)	0.148
Hoehn & Yahr_FU Median [IQR]	2 [0]	2 [1]	χ^2 (*df*) = 7.691 (4)	0.104

Note. * = significance level $\alpha = 0.05$. [a] PD-sym $n = 32$, PD-asym $n = 29$; [b] PD-sym $n = 33$. Abbreviations: BL, baseline; FU, follow-up; *SD*, standard deviation; *n*, sample size; IQR, interquartile range; *t*, independent sample t-test; *df*, degrees of freedom; *U*, Mann-Whitney U test; χ^2, Chi-square test.

Neuropsychological assessment

First, Table 4 provides an overview of the neuropsychological assessment at baseline of PD patients participating in the follow-up session. Significant higher scores are obtained by PD-sym for the TMT-A and -B, indicating worse performance on these tests. For the semantic fluency task, the PD-sym group scores significantly lower, indicating worse performance. No significant differences are found between the groups for the other cognitive tasks. Comparing this with the results in Table 2, fewer significant differences are found among patients that participated in the follow-up since the baseline group shows differences in the MoCA, TMT-A and TMT-B, Stroop-III, semantic fluency, and RAVLT IR and DR.

Table 4

Neuropsychological assessment at baseline of PD patients that participated in follow-up

	PD-sym BL (*n* = 34)	**PD-asym BL (*n* = 34)**	**Test statistic**	**p-value**
MoCA Mean (*SD*)	24.85 (2.787)	25.68 (2.847)	*t (df)* = -1.205 (66)	0.232
NLV Mean (*SD*)	79.88 (14.738)	77.32 (2.847)	*U* = 568.00	0.902
IQ Mean (*SD*)	103.56 (11.668)	103.26 (11.013)	*U* = 611.50	0.680
TMT-A Mean (*SD*)	46.68 (20.416)	36.47 (12.101)	*U* = 413.50	0.044*
Stroop-I Mean (*SD*)	56.35 (12.860)	51.91 (9.965)	*U* = 468.00	0.177
TMT-B Mean (*SD*)	122.68 (60.477)	79.50 (27.808)	*U* = 321.50	0.002*
Stroop-III Mean (*SD*)	113.24 (36.029)	104.06 (28.516)	*U* = 499.50	0.336
Sem. fluency Mean (*SD*)	22.24 (6.729)	25.32 (5.693)	*t (df)* = -2.043 (66)	0.045*
RAVLT IR Mean (*SD*)	35.62 (10.560)	37.82 (11.164)	*t (df)* = -0.837 (66)	0.406
RAVLT DR Mean (*SD*)	7.03 (3.176)	7.94 (45.29)	*t (df)* = -1.212 (66)	0.230
FEEST[a] Mean (*SD*)	44.27 (6.151)	45.29 (6.279)	*t (df)* = -0.672 (66)	0.504

JOLO Mean (*SD*)	24.82 (3.826)	24.79 (3.666)	*U* = 574.00	0.961

Note. * = statistically significant different distribution. [a] PD-sym *n* = 33. Abbreviations: *SD*, standard deviation; *n*, sample size; *t*, independent sample t-test; *df*, degrees of freedom; *U*, Mann-Whitney U test.

Finally, the differences in cognitive performance between the PD groups at follow-up are assessed, as depicted in Table 5. The PD-sym group achieves a significantly lower difference score on the Stroop-III, indicating a more considerable decline in performance for this task. No significant differences are found for the other cognitive tasks, indicating no cognitive decline differences between the PD-sym and PD-asym groups over three years.

Table 5

Neuropsychological assessment of PD-patients at follow-up

	PD-sym (*n* = 34)	**PD-asym (*n* = 34)**	**Test statistic**	**p-value**
MoCA Mean (*SD*)	0.50 (2.863)	-0.18 (2.938)	*t* (*df*) = 0.961 (66)	0.340
NLV Mean (*SD*)	-0.15 (6.204)	-3.62 (13.769)	*U* = 507.50	0.385
IQ Mean (*SD*)	-0.71 (5.654)	-1.09 (7.864)	*U* = 563.50	0.859
TMT-A Mean (*SD*)	-4.18 (20.355)	-3.09 (12.266)	*U* = 531.50	0.568
Stroop-I Mean (*SD*)	-3.85 (9.774)	-2.97 (12.174)	*U* = 646.50	0.400
TMT-B[a] Mean (*SD*)	-18.03 (57.885)	-29.35 (62.082)	*U* = 490.00	0.373
Stroop-III Mean (*SD*)	-18.41 (37.125)	-4.79 (24.121)	*U* = 753.00	0.032*
Sem. fluency Mean (*SD*)	1.56 (4.692)	0.56 (6.170)	*t* (*df*) = 0.752 (66)	0.455
RAVLT IR Mean (*SD*)	1.77 (6.081)	1.59 (7.743)	*t* (*df*) = 0.105 (66)	0.917
RAVLT DR Mean (*SD*)	0.68 (2.114)	0.38 (2.349)	*t* (*df*) = 0.543 (66)	0.589
FEEST[b] Mean (*SD*)	1.88 (4.441)	0.26 (5.282)	*t* (*df*) = 1.336 (64)	0.186

JOLO Mean (*SD*)	0.44 (3.125)	0.24 (3.438)	*t* (*df*) = 0.221 (66)	0.825

Note. * = significance level α = 0.05. [a] PD-sym *n* = 33; [b] PD-sym *n* = 32. Abbreviations: *SD*, standard deviation; *n*, sample size; *t*, independent sample t-test; *df*, degrees of freedom; *U*, Mann-Whitney U test.

Discussion

The current study aimed to assess differences in cognitive functioning in all cognitive domains at the time of diagnosis and to evaluate differences in cognitive decline over time among patients with probable brain-first and body-first PD. Probable brain-first and body-first subtypes were assessed with the respectively asymmetric and symmetric distribution of dopaminergic deficiencies at the *de novo* stage, which might be a suitable proxy (Boertien et al., in preparation). Previous research suggested a higher pathology burden was observed in body-first subtypes of PD. In addition to that, research on the SOC model suggested that the body-first type of PD showed faster disease progression and accelerated cognitive decline over time (Borghammer, 2021; Borghammer et al., 2022). In the current study, we expected the symmetrical subgroup to show worse performance at baseline and present faster deterioration at follow-up than the asymmetrical subgroup. With an increased understanding of PD's origin site and progression, as the SOC model explains, better diagnosis and good therapy choices can be made to provide appropriate and personally constructed treatments.

Differences in cognitive functioning at the time of diagnosis

First, this research assessed the differences in demographic characteristics in *de novo* PD patients with symmetrical versus asymmetrical dopaminergic deficiency and healthy controls. The PD-sym group had a significantly higher age than the PD-asym group and the healthy control group at the time of diagnosis. A higher age in the probable body-first group was expected, considering the distribution of alpha-synuclein pathology and the long prodromal phase (Borghammer et al., 2022). Thus, this finding is in line with the SOC hypothesis. Next, the PD-sym group had a significantly higher disease severity and more pronounced motor symptoms than the PD-asym group. This indicates that the probable body-first group shows a higher burden of Lewy body pathology of the disease. Previous research found that body-first PD showed more motor symptoms at the *de novo* stage due to a more significant overall

burden enabled by symmetrical pathology involvement (Borghammer, 2021). Again, this is in concordance with the SOC model. Education and gender distribution did not significantly differ between the PD subgroups, indicating that differences between the PD groups were not attributed to these factors. However, both PD groups included significantly more men than the control group, and in addition to that, PD-asym had a significantly lower education level than the healthy controls. This difference in education may have influenced the performance on the cognitive tasks because PD patients with higher education are associated with higher cognitive functioning in domains such as attention, executive functioning, memory, and visuospatial functioning (Hindle et al., 2014).

Cognitive impairment is common and already visible in the early and untreated stages of PD, so cognitive performance in *de novo* patients and healthy controls was assessed (Aarsland et al., 2009; Muslimović et al., 2005). It was hypothesized that PD-sym would score worse than PD-asym groups for the cognitive domains, especially on tasks measuring executive functioning and memory. The PD-sym group did perform significantly lower than the PD-asym group on the cognitive screening and tasks measuring attention and processing speed, executive functioning, language, and memory. This indicates more cognitive dysfunctions in the PD-sym group than in the PD-asym group. No differences were discovered between the PD groups for premorbid functioning and the domains measuring social cognition and visuospatial functioning. For tasks measuring executive functioning and language, the PD-asym group performed not statistically different from the HC group. However, it appeared that the averages of the PD groups were slightly worse. This may suggest worse executive functioning and language performance in the PD groups than in the HC group. No differences were found between the three groups for measuring visuospatial functioning. The JOLO might not be sensitive enough to establish differences in visuospatial functioning, or this domain may not be significantly affected in the *de novo* stages of PD. Attention, executive

functioning, and memory are more affected in *de novo* stages than visuospatial functioning because over 50% of patients have preserved visuospatial skills (Pfeiffer et al., 2014). Other research did not find differences between PD groups and healthy controls on visuospatial functioning, even suggesting that these abilities are preserved (Magnante et al., 2022).

Nevertheless, the differences in cognitive functioning could be partially explained by the PD-sym group's higher age than the PD-asym group. However, the ANCOVA results should be interpreted cautiously because not all assumptions were met. Parametric tests are often more potent than nonparametric tests. Thus, parametric tests have a higher chance of finding a statistically significant result if this result exists. Therefore, the results of the ANCOVA for these significant results are biased and may not accurately represent the actual effects. As a result, these significant findings may no longer hold when using nonparametric tests in the future, and even no differences in test performance may be detected.

The SOC model proposes that the body-first subtype in *de novo* stages is related to a higher burden of pathology and faster disease progression (Borghammer et al., 2022). Since the α-synuclein pathology is expected to arise in the ENS, it has more time to distribute through the spinal cord to the brain, leading to a higher age of onset. Next, the pathology can spread bilaterally, affecting both hemispheres (Borghammer, 2021; Horsager et al., 2020; Knudsen et al., 2021). According to the brain plasticity theory (Hebb, 1949), this implies that the pathology of the body-first type will cause more damage, leaving less space for other brain areas to reinstate functions.

It was predicted that the PD-sym group would achieve lower cognitive scores. Without correcting for age, the PD-sym group performed significantly lower than the PD-asym group on various cognitive domains. However, when age was included as a covariate in the analyses, only significant differences were observed in the cognitive screening task, as shown in preliminary evidence from previous research (Boertien et al., in preparation) and a task

measuring executive functioning. Additionally, this executive functioning task involved motor skills, and the PD-sym group showed already more pronounced motor symptoms than the PD-asym group. Thus, this indicates that motor symptoms may also have affected performance, but further investigation is necessary to confirm this hypothesis. Subsequently, it is possible that overall cognitive functioning is worse in PD-sym, but when examining per domain, only slightly different scores are observed between the PD groups. When considering the average test scores only, the symmetrical group seems to perform worse on each test, but these discrepancies are mostly not found as significant differences. Unfortunately, this is one of the first studies to examine the cognitive functioning between PD-sym and PD-asym intensively, and this poses difficulties in confirming or rejecting any speculations about the obtained results. In conclusion, these findings demonstrate that inserting age as a covariate only provides limited evidence for the SOC hypothesis. Additionally, nonparametric tests may reveal more reliable results detrimental to the SOC model.

The current discoveries partly agree with previous ideas on differences in cognitive functioning, as proposed by the SOC hypothesis (Borghammer, 2021). As predicted by prior investigation, patients with symmetrical dopaminergic deficiency had a higher age and more motor symptoms than patients with asymmetrical dopaminergic deficiency. After correcting for age, the body-first group scored only significantly worse on cognitive screening and executive functioning than the brain-first patients. Additionally, these results are preliminary, and nonparametric statistical tests may find even less significant results. No differences were discovered in other domains. These latter findings do not align with the SOC hypothesis. In conclusion, these outcomes illustrate limited evidence of cognitive differences between body-first and brain-first PD at baseline and provide diminished support for the SOC hypothesis.

Differences in cognitive decline over three years

The second research question concerned whether the clinical groups differed in the rate

of deterioration. Notably, the group that participated in the follow-up was much smaller than the group at baseline. Fewer significant differences in characteristics and demographics were demonstrated between the PD subgroups at follow-up. The whole group at baseline showed differences in age, the severity of motor functioning, and motor disability. At follow-up, the PD-sym group only experienced significantly more severe motor problems than the PD-asym group. Additionally, the results of the LEDD scores demonstrated no differences in the amount of medication taken by the patients in the PD groups. Besides this, when examining the baseline neuropsychological assessment scores of the follow-up group, fewer differences were found in performance, and the averages seemed to be slightly better than the total baseline PD groups. This suggests that the patients in the follow-up group are more similar in age, education, medication dosage, and PD progression than in the baseline group. Next, these findings suggest that the smaller follow-up group consisted of less affected patients than the total baseline group. However, statistical testing was not applied here. Thus, these ideas were only hypotheses.

It was hypothesized that the PD-sym group would demonstrate faster cognitive decline. No evidence was found for this hypothesis, except for one test measuring executive functioning. Here, the PD-sym group showed faster cognitive decline than the PD-asym group. For premorbid functioning and other domains concerning attention and processing speed, language, memory, social cognition, and visuospatial functioning, nonsignificant differences were encountered. In conclusion, these findings do not support the SOC hypothesis, which states that the symmetrical subgroup demonstrates faster cognitive deterioration (Borghammer, 2021; Borghammer et al., 2022).

Nevertheless, there may be several explanations for not finding proof. This may be explained by the idea that there are no differences in cognitive decline between the PD groups or that the groups may deteriorate more similarly. Besides this, current research focused on *de*

novo PD groups and assessed the follow-up after three years. There may be a faster progression after a more extended period, or some disparities in cognition may only be visible after a specific elapsed timeframe. Further, the number of participants in the follow-up group was smaller than in the baseline group. Concerning the mean scores exclusively, the PD-sym group appeared to score slightly worse than the PD-asym group. Larger groups may increase statistical power and may reveal more differences in functioning. Furthermore, not finding differences may result from the follow-up data not being completely gathered, which could have influenced the results. Besides this, dropouts are standard in research, and research into dropouts can provide more information about how missing data affects the results.

Considering the findings above, this study demonstrated limited evidence supporting previous findings on faster disease progression in the body-first subtype (Borghammer, 2021). This also illustrates that this research found only little evidence that aligns with the SOC hypothesis. In conclusion, these outcomes suggest hardly any differences in the velocity of cognitive decline between the body-first and brain-first PD groups after a follow-up of three years.

Limitations and recommendations

In this research, the complete follow-up data is not entirely gathered yet, and the groups may be too small to detect differences. In other words, data is missing, the analysis can lack power, and may not be entirely generalizable. It is important to note that different effects can arise when a more extensive follow-up data set is incorporated. Additionally, the follow-up data depends on whether the patients wanted to cooperate in the research again or not. It may be that the most cognitively impaired patient or the patient who deteriorates the fastest does not want to continue at follow-up. Only reassessing those patients who are still functioning relatively well and not reassessing the patients who are deteriorating the most may affect the study results.

Subsequently, not finding significant differences may be related to using raw test scores of cognitive tests in the analyses. These scores are not adjusted to age, education, or gender. Moreover, in future research, using t-scores, percentiles, or other adjusted test scores may provide more reliable outcomes. Additionally, the measures used in this research may not be sensitive enough, or the norms may be outdated.

Another limitation of this study concerns using ANCOVA when the assumptions are violated. Age can be deemed a crucial factor in cognitive functioning, and this research has shown that age is an important confounder. Future research should take nonparametric tests into account to find more substantial evidence.

Interestingly, research suggests that in the body-first type, rapid cognitive deterioration increases the risk of conversion to dementia, and this can be so high that patients may be diagnosed with dementia with Lewy Bodies (DLB) rather than PD (Borghammer, 2021). This can lead to an underestimation of body-first-type individuals in PD. However, differences in cognitive profile between DLB and PD are known. For example, PD declines faster in executive and visuospatial functioning domains, while DLB declines faster in domains concerning language and memory (Smirnov et al., 2020). Further research may provide more information about this concept and clarify the probable underestimation of the number of body-first subtypes.

Finally, research suggests that the PD-sym and PD-asym indexes may overrepresent body-first and brain-first subtypes of PD (Boertien et al., in preparation). Additionally, separating the SAI in terciles may not be the optimal distribution to distinguish between symmetrical and asymmetrical subtypes of PD. This may result in patients being arranged in a group but not being a ‘true’ body-first or brain-first patient. Also, the SOC model proposes a differential distribution between the body-first and brain-first subtypes. However, the SAI ratios are only calculated at baseline, which says nothing about where the α-synuclein

pathology develops further. Most importantly, this indicates that the asymmetry classification index proposed by previous research may not be a suitable proxy for PD's brain- and body-first subtypes. Moreover, no firm conclusions can be drawn from the differences in cognitive functioning between probable brain-first and body-first PD.

For future research, including more follow-up results over an extended period may be enlightening. It is possible that cognitive differences between the PD subgroups are not yet visible within three years. After more data has been collected, this research can be replicated to provide more definitive and potentially more revealing evidence. Additionally, it may be valuable to investigate whether there are differences in the asymmetrical and symmetrical grouping of the FDOPA PET scans at follow-up compared to the baseline grouping. Finally, further investigation may include other cognitive tests and adjusted test scores. Dissimilarities may become more pronounced and detectable between clinical and control groups by incorporating more outcomes.

Conclusion

In brief, this research found little evidence supporting cognitive differences in probable brain-first and body-first PD. The body-first group performs worse on the cognitive screening and the domain of executive functioning after correcting for age. No differences are found in the rate of cognitive decline, except for a task measuring executive functioning, where the body-first group deteriorates faster. Hence, the findings concerning this study do not entirely support the SOC model hypothesis. Despite finding little evidence, these outcomes certainly contributed to our knowledge in this field, and these could be a stepping-stone into further research on non-motor symptoms in brain-first and body-first subtypes of PD. Therefore, further examining and gathering more follow-up data over extended periods is recommended.

References

Aarsland, D., Batzu, L., Halliday, G. M., Geurtsen, G. J., Ballard, C., Chaudhuri, K. R., & Weintraub, D. (2021). Parkinson disease-associated cognitive impairment. *Nature Reviews. Disease Primers*, *7*(1), 46. https://doi-org.proxy-ub.rug.nl/10.1038/s41572-021-00286-x

Aarsland, D., Brønnick, K., Larsen, J. P., Tysnes, O. B., & Alves, G. (2009). Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. *Neurology*, *72*(13), 1121–1126. https://doi-org.proxy-ub.rug.nl/10.1212/01.wnl.0000338632.00552.cb

Altmann, C. F., Trubelja, K., Emmans, D., & Jost, W. H. (2022). Time-course of decline in different cognitive domains in Parkinson's disease: A retrospective study. *Journal of Neural Transmission*, *129*(9), 1179–1187. https://doi-org.proxy-ub.rug.nl/10.1007/s00702-021-02441-w

Benton, A. L., Varney, N. R., & Hamsher, K. de S. (1978). Visuospatial judgment: A clinical test. *Archives of Neurology*, *35*(6), 364–7. https://doi-org.proxy-ub.rug.nl/10.1001/archneur.1978.00500300038006

Boertien, J. M., Nazmuddin, M., Klos, J., Slomp, A. C., van der Zee, S., Borra, R. J. H., van Laar, T. (in preparation). Clinical and imaging data supports brain-first and body-first subtypes in de novo Parkinson's disease.

Boertien, J. M., van der Zee, S., Chrysou, A., Gerritsen, M. J. J., Jansonius, N. M., Spikman, J. M., van Laar, T., the PPNN Study Group, Verwey, N. A., van Harten, B., Portman, A. T., Langedijk, M. J. H., Oomes, P. G., Jansen, B. J. A. M., van Wieren, T., van den Bogaard, S. J. A., van Steenbergen, W., Duyff, R., van Amerongen, J. P., & Fransen, P. S. S. (2020). Study protocol of the DUtch PARkinson Cohort (DUPARC): a prospective, observational study of de novo Parkinson's disease patients for the identification and validation of biomarkers for Parkinson's disease subtypes, progression and

pathophysiology. *BMC Neurology*, *20*(1), 1–11. https://doi-org.proxy-ub.rug.nl/10.1186/s12883-020-01811-3

Borghammer, P. (2021). The α-Synuclein Origin and Connectome Model (SOC Model) of Parkinson's Disease: Explaining Motor Asymmetry, Non-Motor Phenotypes, and Cognitive Decline. *Journal of Parkinson's Disease*, *11*(2), 455–474. https://doi-org.proxy-ub.rug.nl/10.3233/JPD-202481

Borghammer, P., Just, M. K., Horsager, J., Skjærbæk, C., Raunio, A., Kok, E. H., Savola, S., Murayama, S., Saito, Y., Myllykangas, L., & Van Den Berge, N. (2022). A postmortem study suggests a revision of the dual-hit hypothesis of Parkinson's disease. *NPJ Parkinson's disease*, *8*(1), 166. https://doi.org/10.1038/s41531-022-00436-2

von Coelln, R., & Shulman, L. M. (2016). Clinical subtypes and genetic heterogeneity: of lumping and splitting in Parkinson disease. *Current Opinion in Neurology*, *29*(6), 727–734. https://doi-org.proxy-ub.rug.nl/10.1097/WCO.0000000000000384

Ekman, P., & Friesen, W. V. (1976). *Pictures of facial affect*. Palo Alto, California: Consulting Psychologists Press.

Goedert, M. (2001). Alpha-synuclein and neurodegenerative diseases. *Nature Reviews Neuroscience*, *2*, 492–501. https://doi.org/10.1038/35081564

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., Olanow, C. W., Rascol, O., Schrag, A., Teresi, J. A., van Hilten, J. J., & LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, *23*(15), 2129–2170. https://doi-org.proxy-ub.rug.nl/10.1002/mds.22340

Halliday, G. M., Leverenz, J. B., Schneider, J. S., & Adler, C. H. (2014). The neurobiological

basis of cognitive impairment in Parkinson's disease. *Movement disorders: official journal of the Movement Disorder Society*, *29*(5), 634–650. https://doi.org/10.1002/mds.25857

Hammes, J. G. W. (1971). *De Stroop Kleur-Woord Test: Handleiding*. Lisse: Swets & Zeitlinger.

Hawkes, C. H., Del Tredici, K., & Braak, H. (2007). Parkinson's disease: a dual-hit hypothesis. *Neuropathology and Applied Neurobiology*, *33*(6), 599–614. https://doi-org.proxy-ub.rug.nl/10.1111/j.1365-2990.2007.00874.x

Hebb, D. (1949). *The organisation of behaviour*. New York, NY: John Wiley and Sons.

Hindle, J. V., Martyr, A., & Clare, L. (2014). Cognitive reserve in Parkinson's disease: A systematic review and meta-analysis. *Parkinsonism & Related Disorders*, *20*(1), 1–7. https://doi-org.proxy-ub.rug.nl/10.1016/j.parkreldis.2013.08.010

Horsager, J., Andersen, K. B., Knudsen, K., Skjærbæk, C., Fedorova, T. D., Okkels, N., Schaeffer, E., Bonkat, S. K., Geday, J., Otto, M., Sommerauer, M., Danielsen, E. H., Bech, E., Kraft, J., Munk, O. L., Hansen, S. D., Pavese, N., Göder, R., Brooks, D. J., & Berg, D. (2020). Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. *Brain: A Journal of Neurology*, *143*(10), 3077–3088. https://doi-org.proxy-ub.rug.nl/10.1093/brain/awaa238

Hoehn, M. M., & Yahr, M. D. (2001). Parkinsonism: Onset, progression and mortality. *Neurology*, *17*(5), 427–442.

Jozwiak, N., Postuma, R. B., Montplaisir, J., Latreille, V., Panisset, M., Chouinard, S., Bourgouin, P. A., & Gagnon, J. F. (2017). REM Sleep Behavior Disorder and Cognitive Impairment in Parkinson's Disease. *Sleep*, *40*(8), zsx101. https://doi.org/10.1093/sleep/zsx101

Kaasinen, V. (2015). Ipsilateral deficits of dopaminergic neurotransmission in Parkinson's disease. *Annals of Clinical and Translational Neurology*, *3*(1), 21–26. https://doi-

org.proxy-ub.rug.nl/10.1002/acn3.268

Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *Lancet, 386*(9996), 896–912. https://doi-org.proxy-ub.rug.nl/10.1016/S0140-6736(14)61393-3

Knudsen, K., Fedorova, T. D., Horsager, J., Andersen, K. B., Skjærbæk, C., Berg, D., Schaeffer, E., Brooks, D. J., Pavese, N., Van Den Berge, N., & Borghammer, P. (2021). Asymmetric Dopaminergic Dysfunction in Brain-First versus Body-First Parkinson's Disease Subtypes. *Journal of Parkinson's disease, 11*(4), 1677–1687. https://doi.org/10.3233/JPD-212761

Kong, W. L., Huang, Y., Qian, E., & Morris, M. J. (2020). Constipation and sleep behaviour disorder associate with processing speed and attention in males with Parkinson's disease over five years follow-up. *Scientific Reports, 10*(1), 19014. https://doi-org.proxy-ub.rug.nl/10.1038/s41598-020-75800-4

Lawson, R. A., Yarnall, A. J., Duncan, G. W., Khoo, T. K., Breen, D. P., Barker, R. A., Collerton, D., Taylor, J.-P., & Burn, D. J. (2014). Severity of mild cognitive impairment in early Parkinson's disease contributes to poorer quality of life. *Parkinsonism & Related Disorders, 20*(10), 1071–1075. https://doi-org.proxy-ub.rug.nl/10.1016/j.parkreldis.2014.07.004

Lezak, M. D., Howieson, D. B., Bigler, E. D., & Tranel, D. (2012). *Neuropsychological assessment* (5th ed.). Oxford University Press.

Magnante, A. T., Ord, A. S., Holland, J. A., & Sautter, S. W. (2022). Neurocognitive functioning of patients with early-stage parkinson's disease. *Applied Neuropsychology: Adult*. https://doi-org.proxy-ub.rug.nl/10.1080/23279095.2022.2106865

Muslimović, D., Post, B., Speelman, J. D., & Schmand, B. (2005). Cognitive profile of patients with newly diagnosed Parkinson disease. *Neurology, 65*(8), 1239–1245. https://doi-org.proxy-ub.rug.nl/10.1212/01.wnl.0000180516.69442.95

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x

Pfeiffer, H. C. V., Løkkegaard, A., Zoetmulder, M., Friberg, L., & Werdelin, L. (2014). Cognitive impairment in early-stage non-demented Parkinson's disease patients. *Acta Neurologica Scandinavica*, *129*(5), 307–318. https://doi-org.proxy-ub.rug.nl/10.1111/ane.12189

Postuma, R. B., Aarsland, D., Barone, P., Burn, D. J., Hawkes, C. H., Oertel, W., & Ziemssen, T. (2012). Identifying prodromal Parkinson's disease: Pre-Motor disorders in Parkinson's disease. *Movement Disorders*, *27*(5), 617–626. https://doi-org.proxy-ub.rug.nl/10.1002/mds.24996

Reichmann, H. (2010). Clinical criteria for the diagnosis of Parkinson's disease. *Neuro-degenerative diseases*, *7*(5), 284–290. https://doi.org/10.1159/000314478

Reitan, R. (1956). *Trail Making test: Manual for administration, scoring, and interpretation*. Bloomington: Indiana University.

Saan, R. J., & Deelman, B. G. (1986). *De 15-Woordentests A en B. Een voorlopige handleiding* (Intern rapport). Groningen: AZG, afd. Neuropsychologie.

Schmand, B. A., Bakker, D., Saan, R. J., & Louman, J. (1991). De Nederlandse Leestest voor Volwassenen: een maat voor het premorbide intelligentieniveau. *Tijdschrift voor Gerontologie en Geriatrie*, *22*(1), 15–19.

Smirnov, D. S., Galasko, D., Edland, S. D., Filoteo, J. V., Hansen, L. A., & Salmon, D. P. (2020). Cognitive decline profiles differ in Parkinson disease dementia and dementia with Lewy bodies. *Neurology*, *94*(20), e2076–e2087. https://doi-org.proxy-ub.rug.nl/10.1212/WNL.0000000000009434

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology*, *18*(6), 643–662. https://doi.org/10.1037/h0054651

Tomlinson, C. L., Stowe, R., Patel, S., Rick, C., Gray, R., & Clarke, C. E. (2010). Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement Disorders*, *25*(15), 2649–2653. https://doi-org.proxy-ub.rug.nl/10.1002/mds.23429

Venda, L. L., Cragg, S. J., Buchman, V. L., & Wade-Martins, R. (2010). α-Synuclein and dopamine at the crossroads of Parkinson's disease. *Trends in neurosciences*, *33*(12), 559–568. https://doi.org/10.1016/j.tins.2010.09.004

Yang, N., Ju, Y., Ren, J., Wang, H., Li, P., Ning, H., Tao, J., & Liu, W. (2022). Prevalence and affective correlates of subjective cognitive decline in patients with de novo Parkinson's disease. *Acta Neurologica Scandinavica*, *146*(3), 276–282. https://doi-org.proxy-ub.rug.nl/10.1111/ane.13662