Biomarkers and non-motor symptoms as a function of motor symptom asymmetry in early Parkinson’s disease

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ABSTRACT

Introduction: The longitudinal trajectories of cognitive-neuropsychiatric symptoms from the early stages of Parkinson’s disease, as a function of motor symptom asymmetry at the onset of the disease, remain to be fully explored. Moreover, the relationship to biomarkers warrants further investigation.

Methodology: Non-motor and biospecimen data from 413 patients with Parkinson’s disease, dissociating predominantly left-sided motor symptoms patients (n = 179), predominantly right-sided motor symptoms patients (n = 234), and matched healthy controls (n = 196), were extracted from the Parkinson’s Progression Marker Initiative database during a 3-Year follow-up. Non-parametric and conservative corrections for multivariate comparisons were carried out on neuropsychiatric and biomarker data.

Results: A decline for global cognitive efficiency scores in predominantly right-sided motor symptoms patients was observed, whereas depressive and anxiety symptoms were greater overtime for predominantly left-sided motor symptoms patients. Biomarker analysis revealed that predominantly right-sided patients expressed decreased levels of total-tau and phospho-tau over time, while left-sided patients didn’t differ from healthy controls.

Conclusion: From the early course of the disease, the existence of different clinical phenotypes is proposed, associated to emerging evidences of distinct pathological pathways and a left-hemispheric vulnerability for cognitive decline.

1. Introduction

Non-motor symptoms (NMS), such as cognitive impairments and neuropsychiatric disorders, are common to patients with Parkinson’s disease (PD), but their presence appears to be subjected to inter- and intra-individual variability (Schapira et al., 2017). The reason of this heterogeneity remains to be fully discovered, but clinical variables, such as motor symptom asymmetry, are increasingly the subject of research (Borhammer, 2021; Marinus et al., 2018).

As far as neuropsychological functions are concerned, reduced cognitive performances in patients with predominantly right-sided motor symptoms (RPD) have been previously documented in comparison to patients with predominantly left-sided motor symptoms (LPD) (Agosta et al., 2020; Huber et al., 1992; Katzen et al., 2006). These deficits concern global cognitive efficiency (Agosta et al., 2020), long-term verbal memory (Amick et al., 2006; Cubo et al., 2010; Foster et al., 2016; Huber et al., 1992; Starkstein et al., 1987; Starkstein and Leiguarda, 1993), language (Blonder et al., 1989; Mohr et al., 1992; Spicer et al., 1988; Starkstein et al., 1987) and for some specific authors, executive functions (Huber et al., 1992; Voruz et al., 2020; Voruz et al., 2022). Some have even suggested that RPD patients may be more vulnerable to the onset of dementia associated with PD in the long term (Harris et al., 2013). That being said, the literature isn’t unanimous about the effect of motor symptom asymmetry on neuropsychological

Abbreviations: α-syn, alpha-synuclein; Aβ42, β-amyloid 1–42; CSF, cerebrospinal fluid; FDR, false discovery rate; GDS, geriatric depression scale; GEE, generalized estimating equations; HC, healthy controls; HVLT, Hopkins verbal learning test; LEDD, Levodopa Equivalent Daily Dose; LPD, patients with predominantly left-sided motor symptoms; MDS-UPDRS, Movement Disorders Society Unified Parkinson’s Disease Rating Scale; MoCA, Montreal Cognitive Assessment; NMS, non-motor symptoms; PD, Parkinson’s disease; PPMI, Parkinson’s Progression Marker Initiative; p-tau, phospho-tau; t-tau, total-tau; RPD, patients with predominantly right-sided motor symptoms; STAI, State-Trait Anxiety Inventory; UA, uric acid.

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functions, such as executive or visuospatial functions (for review see, Riederer, et al., 2018; Verreyt et al., 2011). Some studies failed to report any significant differences for visuospatial functions (Kurlawala et al., 2021; Verreyt et al., 2011), while others have observed worsened visuo-spatial performances in LPD patients as compared to RPD (Amick et al., 2006; Starkstein et al., 1987; Tømer et al., 1993). In this sense, the literature also suggested that inhibitory functions were underpinned by networks in the right hemisphere, thus implying a possible effect of motor symptom asymmetry in PD, with potentially greater deficits in LPD patients. Despite these theoretical assumptions, recent studies that focused on the early stages of PD (Di Caprio et al., 2020), or the more advanced stages of the disease, revealed no differences between LPD and RPD for reactive inhibitory control. Also, only bilateral DBS, and not unilateral DBS, was able to restore reactive inhibitory control to a near-normal level, in this clinical population (Mancini et al., 2017; Mirabella et al., 2015; Mirabella et al., 2012).

Taken together, these results go against a lateralization of inhibitory functions in the right hemisphere. That said, these heterogeneous results could be partially explained by hemispheric specialization during cognitive tasks. Visuo-spatial abilities, known to besubtracted by the right hemisphere, would be more vulnerable to dysfunction in LPD, while verbal material would be more deteriorated in RPD due to the left hemisphere dominance of language. Moreover, another factor that may be invoked regarding the heterogeneity of the majority of these studies is the inclusion of patients at different stages of the disease and the lack of longitudinal studies starting from the early stages of the disease. For example, some studies reported no difference between LPD and RPD in the early stages of PD, but rather a significant impact of motor symptom asymmetry as the disease progresses (Adwani et al., 2016; Poletti et al., 2013).

Regarding neuropsychiatric symptoms, LPD patients seem to specifically display mood disorders, as compared to RPD patients who seem more unscathed of these disorders (Coundouris et al., 2020). In this sense, a number of studies have shown an increase in depressive symptoms (Foster et al., 2011; Foster et al., 2013; Pellicano et al., 2015), anxiety (Foster et al., 2011; Foster et al., 2010; Kurlawala et al., 2021; Modestino, Amenechi, Reinhofer and O’Toole, 2017; Voruz et al., 2020), sleep impairment (Zhu et al., 2021), psychosis (Cubo et al., 2010), but also emotion recognition deficits (Voruz et al., 2020) in LPD. That being said, and as for cognitive functions, some authors have shown increased symptoms of apathy in RPD patients (Harris et al., 2013), which may suggest the existence of dissociated neurological pathways in the apparition of neuropsychiatric symptoms. However, these studies mainly focused on patients either in advanced or mixed stages of PD, whereas early stages of the disease have been less investigated. In early stage PD, a limited number of cognitive functions were assessed, such as attentional functions, showing no differences according to the asymmetry of motor symptoms (Di Caprio, Modugno, Mancini, Olivola and Mirabella, 2020).

In the context of a high degree of heterogeneity regarding PD literature, it is unsurprising that the question of the impact of motor symptom asymmetry on biomarkers (and their relationship with NMS) remains to be fully explored at different stages of the disease. Interestingly, in PD (Clausen et al., 2016), fronto-temporal dementia (Whitwell and Josephs, 2012), Alzheimer’s disease (Dixon et al., 2002), and Huntington’s disease (Ross et al., 2002), studies have highlighted the presence of a greater vulnerability for the left hemisphere, associated to clinical and pathogenic evidence of a neurodegenerative process. More specifically, studies on Alzheimer’s disease have indicated more marked biopspecimen alterations (e.g., 17beta-hydroxysteroid dehydrogenase or nitric oxide mediator system) in the left-hemisphere, as well as asymmetric depositions of β-amyloid associated to cognitive dysfunctions (Fring et al., 2015). This has also been observed for primary progressive aphasia (Rabinovici et al., 2008). The potential left hemispheric vulnerability for cognitive disorders in neurodegenerative pathologies could therefore be reinforced in PD by motor symptom asymmetry (Harris et al., 2013). This would lead to a more aggressive and rapid neurodegenerative process in the sub-group of patients with a right predominance of motor symptoms (i.e., RPD). As such, the levels of biomarkers associated with these non-motor impairments would also depend on motor symptom asymmetry. In that matter, a recent study has suggested an association between asymmetric dopamine transporter loss of the putamen and biomarkers of neurodegenerative diseases (Fiorinzato et al., 2021). In this study, the authors observed reduced β-amyloid levels in PD patients with a predominant left hemisphere dopamine transporter loss as compared to patients with a predominant right hemisphere dopamine transporter loss. These differences were present since the first year of disease onset and maintained over the first 4 years of longitudinal evolution.

In this context, the aim of this study was to evaluate the presence of NMS (cognitive and neuropsychiatric) as well as the differences in biomarkers at the early stages of the disease, according to motor symptom asymmetry at disease onset, and investigate their evolution over time in the first 3 years following diagnosis. To this end, we extracted motor, NMS and radiological data from a large cohort of patients with PD (n = 413), differentiating them according to the predominant laterality of their motor symptoms (LPD, n = 179 vs RPD, n = 234), and from a healthy control group (HC, n = 196). We focused on biomarkers known to be associated to PD, i.e., alpha-synuclein (α-syn) (Schirinzii et al., 2019) and uric acid (UA) (Wen et al., 2017), but also those associated with neurodegenerative pathologies (tau protein [total-tau (t-tau), phospho-tau (p-tau)] and β-amyloid 1–42 (Aβ42) (Alves et al., 2015; Simuni et al., 2018a, b). Finally, we also controlled longitudinally for the effect of dopa replacement therapy on NMS. The realization of this study was made possible thanks to the multicenter Parkinson’s Progression Marker Initiative (PPMI) funded by the Michael J. Fox Foundation for Parkinson’s Research and funding partners (Marek et al., 2011).

First, regarding cognition, we predicted a significantly reduced performance as well as a more pronounced progressive deterioration of long-term performances in RPD as compared to both LPD and HC (Harris et al., 2013). For neuropsychiatric outcomes, significant inter- and intra-group differences were also expected, with LPD displaying more depressive and anxious symptoms as compared to both RPD and HC. Secondly, we expected to observe a significant difference between RPD and LPD patients on biomarker levels, with more pronounced effects in RPD considering the hypothesis of a left cerebral hemisphere vulnerability.

2. Methodology

2.1. Power analysis

Power analysis on behavioral data. The power analysis was based on the results for apathy in Harris et al. (2013), who measured neuropsychiatric differences according to motor symptom asymmetry, and who suggested that RPD patients may be vulnerable to dementia in the long term. To achieve the desired statistical power (1 - β) of 90% and a risk of Type I error (α) of 0.05, results indicated that for a one-sided hypothesis, 17 participants would be needed in each group, while for a two-sided hypothesis 20 participants would be needed in each group.

Power analysis on biomarkers data. The power analysis was based on the results for Aβ42 in Fiorenzato et al. (2021), who measured biomarkers differences according to dopamine active transporter (DAT) binding asymmetry. To achieve the desired statistical power (1 - β) of 90% and a risk of Type I error (α) of 0.05, results indicated that for a one-sided hypothesis, 159 participants would be needed in each group, while for a two-sided hypothesis 195 participants would be needed in each group.

2.2. Participants (Table 1)

The data used for the present article was obtained from the PPMI, an
asymmetry and those with a discrepancy between motor and DAT binding asymmetry). Nevertheless, intergroup analysis revealed significant differences between LPD and RPD for the DAT binding asymmetry index (calculated on the basis of methodology validated in previous studies [Fiorenzato et al., 2021; Kaasinen, 2016]) of the caudate (LPD: 0.097 ± 0.078; RPD: 0.074 ± 0.079 [z = −15.29, p < .001]), striatum (LPD: 0.115 ± 0.083; RPD: 0.099 ± 0.091 [z = −15.80, p < .001]) and putamen (LPD: 0.161 ± 0.151; RPD: 0.158 ± 0.169 [z = −14.42, p < .001]), demonstrating the statistical difference between both PD groups. Moreover, Spearman correlation analyses on each PD subgroup revealed positive association between the motor asymmetry index measured with the lateralized UPDRS-III items and the basal ganglia structure asymmetry index measured by the DAT binding, confirming a link between these two measures of asymmetry in PD. Finally, no significant differences were observed between the 3 groups (LPD; RPD; HC) for sociodemographic outcomes (except for handedness, with a higher percentage of ambidextrous participants in the HC group as compared to RPD). Also, no significant clinical differences for PD symptomatology were observed between PD subgroups (LPD; RPD), except for motor symptom lateralization, as well as no significant difference for the Total Levodopa Equivalent Daily Dose (LED) and type of medication (see Supplementary Table 1).

2.2.1. Ethics

The PPMI study is registered with ClinicalTrials.gov (NCT01141023). Each participating PPMI site received approval from an ethical standards committee on human experimentation before study initiation. This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines after approval of the local ethics committees of the participating sites. Written informed consent for research was obtained from all individuals participating in the study.

2.3. Measured outcomes

PD participants and HC underwent comprehensive clinical and imaging assessments, as well as bioampling. Amongst clinical assessments, the Movement Disorders Society Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) ([Goetz et al., 2007]) was used to evaluate motor aspects. The geriatric depression scale (GDS) (Yesavage et al., 1982) and State-Trait Anxiety Inventory (STAI) (Spilberger et al., 1983) were used to assess neuropsychiatric symptoms. Cognitive testing comprised of the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), Hopkins verbal learning test (HVLT) – revised (Benedict et al., 1998), Benton judgment of line orientation (Benton et al., 1978), semantic fluency (Spreen, 1977), letter number sequencing (Wechsler and Edition, 1997), and symbol digit modalities test (Smith, 1973). Biospecimen collection was undertaken from cerebrospinal fluid and urine in order to measure levels of α-syn, amyloid, tau and urate. Data used in the preparation of this article were obtained from the Parkinson’s Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit http://www.ppmi-info.org/.” Details regarding data collection procedures and measured variables have been previously published and are available at http://www.ppmi-info.org/ ([Marek et al., 2011]).

2.4. Data analysis

The Shapiro-Wilk test was used to assess normal distribution of outcome variables. Given non-negligible deviations from normality for an important number of variables, nonparametric statistics were employed to measure between- and within-subjects effects of continuous variables.

Kruskal-Wallis tests were used to assess the presence of differences between groups on raw scores, as well as on Delta scores (used to assess the progression of symptoms) between the follow-ups and Baseline (Delta score Year 1 – Baseline; Delta score Year 3 – Baseline), followed by individual Man-Whitney U tests and Chi-square tests that were performed for 2 × 2 comparisons. Benjamini-Hochberg False discovery rate (FDR) corrections were applied for each domain (motor; cognition; psychiatry; biospecimen) and at each time point (Baseline; Year 1; Year 3; Delta score Year 1 – Baseline; Delta score Year 3 – Baseline) [thresholds are available under the tables in supplementary material]. Wilcoxon tests were used to compare baseline and yearly follow-up assessments within each group in order to assess the longitudinal evolution of NMS symptoms and biomarkers for each PD subgroup, using also Benjamini-Hochberg FDR corrections [thresholds are available under the tables].

Post-hoc generalized estimating equations (GEE) were carried out, using LEDD as predictor, and NMS as response variables for each PD subgroup (p < .05), to control for the effect of dopa replacement therapy on cognition and neuropsychiatric symptoms. NMS were selected as dependent variables, independently of the results of inter- and intra-group analyses. Given the non-parametric distribution of our dependent variables and the presence of repeated measures, we performed a GEE Gamma logit model on longitudinal data. Moreover, post-hoc Spearman correlations were performed at each time point, as function of the groups, to control for the potential effect of sociodemographic variables significantly differing between groups. Here as well, NMS were selected as dependent variables, independently of the results of inter- and intra-group analyses.

Statistical analyses were performed on SPSS © version 27.
2.5. Data availability

All data is extracted from the Parkinson’s Progression Marker Initiative funded by the Michael J. Fox Foundation for Parkinson’s Research and funding partners.

3. Results

FDR corrected intergroups comparisons on raw scores were carried out for Total Levodopa Equivalent Daily Dose (LEDD) and motor severity symptoms (see Table 2, Supplementary results 1, and Supplementary Table 1), NMS (see Tables 3 and 4, Supplementary results 2, and Supplementary Tables 3 and 5), as well as biomarkers (see Table 5, Supplementary results 2 and Supplementary Table 7) as a function of motor asymmetry.

3.1. NMS and biospecimen progression (delta scores between follow-ups and baseline) as a function of motor symptom asymmetry

Cognition (see Table 3, and Supplementary Table 3). For RPD, intergroup analysis of the progression of cognitive impairments (delta score) after FDR correction revealed no significant differences when compared to LPD for the progression of cognitive impairments at Year 1. However, the analysis revealed a significant decrease in the performance for HVLT – Immediate/Total recall (p = .013) between LPD and RPD patients at Year 3, suggesting over time an increase in performance for LPD, with a slight decrease for RPD. When the PD patient groups (LPD and RPD) were compared to HC, the analysis did not reveal a significant progression of cognitive symptoms at Year 1. However, at Year 3, the analysis revealed a greater alteration in the Symbol Digit test for both groups (LPD vs HC: <.001; RPD vs HC: p = .016), suggesting greater progression of attentional impairment in patients with PD.

Neuropsychiatry (see Table 4, and Supplementary Table 5). Comparisons between LPD and RPD revealed no significant differences. When the PD patient groups (LPD and RPD) were compared to HC, analysis revealed a higher progression of apathy symptoms (p = .008) measured on the UPDRS I in LPD patients as compared to HC at Year 1. A higher progression was revealed for RPD patients when compared to HC solely for cognitive symptoms (p < .001) and hallucinations/psychosis symptoms (p < .001) on the UPDRS I at Year 3, potentially suggesting a higher increase of neuropsychiatric symptoms, especially for hallucinations/psychosis in RPD patients over time.

Biospecimen (see Table 5 and Supplementary Table 7). Comparisons between LPD and RPD revealed no significant differences. When the PD patient groups (LPD and RPD) were compared to HC, analysis after FDR correction revealed solely at Year 1 a significant progression in RPD patients of α-syn (p = .002), t-tau/α-syn ratio (p = .002) and, p-tau/α-syn ratio (p = .006), while no significant differences after FDR correction were observed between LPD and HC. No differences between the three groups were noted at Year 3.

3.2. NMS and biospecimen longitudinal evolution as a function of motor symptom asymmetry

Cognition (Supplementary Table 4 and Fig. 1). For RPD, after FDR correction, a decrease over time for the following domains was observed: cognitive global efficiency as measured by MoCA (Baseline vs Year 1, p < .001 and Baseline vs Year 3, p < .001) and visuo-spatial abilities with the Benton Judgement of Line (Baseline vs Year 1, p = .001, but not significant a Year 3). In parallel, longitudinal analyses revealed that the sub-domains of cognition that declined in the LPD group at Year 1 were visuo-spatial abilities (Baseline vs Year 1 for Benton Judgement of Line, p = .001, but not significant at Year 3) and global efficiency (Baseline vs Year 1 for MoCA, p = .004, but not significant at Year 3), whereas a significant improvement at Year 3 was revealed for verbal episodic memory (HVLT – Immediate recall/Total Recall).

Table 1: Sociodemographic and clinical variables at baseline for each group (LPD; RPD; HC). Legend. Chi²: Chi-squared test; F: female; FDR: false discovery rate; HC: healthy controls; LPD: patients with Parkinson’s disease (PD) who exhibit predominantly left-sided motor symptoms; M: male; NA: not applicable; RPD: patients with PD who exhibit predominantly right-sided motor symptoms; K-W: Kruskal–Wallis test; M-W: Mann–Whitney U test; SD: standard deviation.

| Variable                      | LPD (n = 179) | RPD (n = 234) | HC (n = 196) | K-W and Chi² | LPD vs RPD | LPD vs HC | RPD vs HC |
|-------------------------------|---------------|---------------|--------------|-------------|------------|----------|----------|
| Age in Years (mean ± SD)      | 60.38 (±10.02) | 58.20 (±9.36) | 60.82 (±11.23) | .109        | –          | –        | –        |
| Education in Years (mean ± SD)| 15.42 (±2.97) | 15.61 (±3.01) | 16.04 (±2.89) | .154        | –          | –        | –        |
| Gender                        | M: 58.70%     | M: 69.70%     | M: 64.30%    | .062        | –          | –        | –        |
| Handedness                    | R: 84.90%     | R: 89.70%     | R: 81.00%    | .034*       | .052       | .058     | .038*    |
| | L: 13.40%     | L: 6.90%      | L: 12.30%     |             |            |          |          |
| | Amb: 1.70%    | Amb: 3.40%    | Amb: 6.70%    |             |            |          |          |
| Age of onset in Years (mean ± SD)| 59.86 (±10.03) | 58.20 (±9.36) |             | .049        | –          | NA       | NA       |
| Age diagnostic in Years (mean ± SD)| 59.86 (±10.03) | 58.20 (±9.36) |             | .049        | –          | NA       | NA       |
| Initial symptom (at diagnosis)| 70.99%        | 76.54%        |             | .330        | –          | NA       | NA       |
| Resting tremor                | Yes: 22.91%   | Yes: 23.46%   |             |             | –          | .924     | NA       |
| NMS                           | 16.24%        | 15.64%        |             |             | –          | .063     | NA       |
| | No: 83.76%    | No: 84.36%    |             |             |            |          | NA       | NA       |

For RPD, after FDR correction, no significant progression was revealed for RPD patients when compared to HC.
|                  | Baseline | Year 1 | Year 3 | Delta score Year 1 - Baseline | Delta score Year 3 - Baseline |
|------------------|----------|--------|--------|-----------------------------|-------------------------------|
|                  | LPD (n = 179) | RPD (n = 234) | HC (n = 196) | LPD (n = 165) | RPD (n = 222) | HC (n = 185) | LPD (n = 154) | RPD (n = 203) | HC (n = 167) | LPD (n = 165) | RPD (n = 222) | HC (n = 185) | LPD (n = 154) | RPD (n = 203) | HC (n = 167) |
| Categorical H&Y  |          |        |        |                             |                               |
| (OFF State)      | 39.11%   | 49.15% | 1.01%  | 27.14%                      | 31.38%                        | 15.65%                       | 19.86%                       | 0.60%                      |                     |                     |                     |                     |                     |                     |                     |
| stage 0          | 59.78%   | 50.85% | 0.00%  | 69.29%                      | 63.83%                        | 2.16%                        | 79.13%                       | 69.50%                      | 0.60%                      |                     |                     |                     |                     |                     |                     |
| stage 1          | 1.12%    | 0.00%  | 0.00%  | 3.57%                       | 4.26%                         | 0.00%                        | 5.22%                        | 10.64%                      | 0.00%                      |                     |                     |                     |                     |                     |                     |
| stages 2–5       |          |        |        |                             |                               |
| Categorical H&Y  |          |        |        |                             |                               |
| (ON State)       | 39.11%   | 49.15% | 1.01%  | 27.27%                      | 25.91%                        | 1.62%                        | 22.86%                       | 23.08%                      | 0.60%                      |                     |                     |                     |                     |                     |                     |
| stage 0          | 59.78%   | 50.85% | 0.00%  | 70.78%                      | 66.82%                        | 2.16%                        | 72.14%                       | 70.77%                      | 0.60%                      |                     |                     |                     |                     |                     |                     |
| stage 1          | 1.12%    | 0.00%  | 0.00%  | 1.95%                       | 2.88%                         | 0.00%                        | 4.29%                        | 6.15%                       | 0.00%                      |                     |                     |                     |                     |                     |                     |
| stages 3–5       |          |        |        |                             |                               |

UPDRS III (OFF) (mean ± SD)

|                  |          |        |        |                             |                               |
| UPDRS III (ON) (mean ± SD)
|                  |          |        |        |                             |                               |
| UPDRS IV score (mean ± SD)
|                  |          |        |        |                             |                               |
| UPDRS Total score (OFF) (mean ± SD)
|                  |          |        |        |                             |                               |
| Total Rigidity score (OFF) (mean ± SD)
|                  |          |        |        |                             |                               |

UPDRS Total score (ON) (mean ± SD)

|                  |          |        |        |                             |                               |
| Total Rigidity score (ON) (mean ± SD)
|                  |          |        |        |                             |                               |

Medication

|                  |          |        |        |                             |                               |

(continued on next page)
Table 2 (continued)

| Year 3 - Baseline | Year 1 - Baseline | Delta score | Delta score | Delta score |
|-------------------|-------------------|-------------|-------------|-------------|
| 9.15%             | 8.14%             | 6.90%       |
| 5.40%             | 4.37%             | 1.03%       |
| 8.14%             | 0.45%             | 7.79%       |
| 7.79%             | 0.45%             | 7.34%       |
| 6.90%             | 1.03%             | 5.87%       |
| 8.14%             | 0.45%             | 7.79%       |
| 7.79%             | 0.45%             | 7.34%       |
| 6.90%             | 1.03%             | 5.87%       |

Legend. HC: healthy controls; HY: Hoehn & Yahr; LEDD: Levadopa Equivalent Daily Dose; LPD: patients with Parkinson’s disease (PD) who exhibit predominantly left-sided motor symptoms; NA: not applicable; RPD: patients with PD who exhibit predominantly right-sided motor symptoms; SD: standard deviation; SDAP: Modified Schwab & England Activities of Daily Living Scale; Modified UPDRS: Modified Unified Parkinson’s disease Rating Scale; Modified SAE ADL: Modified Schwab & England Activities of Daily Living Scale.

Biospecimen (see Supplementary Table 8 and Fig. 2). For each time point, we controlled whether there was a significant proportion of patients with high levels of CSF hemoglobin, as recent studies have shown a potential biasing effect on biomarker concentrations in case of high hemoglobin concentration in the CSF sample (Paciotti et al., 2021). The results showed no significant difference between groups at Baseline (LPD vs HC: \( p = .769 \); RPD vs HC: \( p = .870 \); LPD vs RPD: \( p = .641 \)) and Year 1 (LPD vs HC: \( p = .302 \); RPD vs HC: \( p = .420 \); LPD vs RPD: \( p = .766 \)). However, at Year 3, significant differences occurred between LPD and HC (\( p = .015 \)), as well as RPD and LPD (\( p = .009 \)), showing higher levels of CSF hemoglobin in RPD and HC than in LPD; no differences were observed between HC and RPD (\( p = .900 \)). Therefore, in order to control for a potential bias in observed results by high levels of CSF hemoglobin, as previously validated (Paciotti et al., 2021), we ran the analysis on biospecimen by removing the patients with high hemoglobin from all groups at Year 3. The results obtained were comparable to the analysis including patients with high hemoglobin levels. Therefore, the results presented below include the whole sample.

Interestingly, significant modifications in biomarker concentrations were observed for both groups after FDR correction. For LPD, analysis revealed a significant increase of the p-tau/\( \beta \)-tubulin ratio at Year 1 (Baseline vs Year 3, \( p < .001 \)) and p-tau/\( \alpha \)-syn ratio (Baseline vs Year 3, \( p = .004 \)). For RPD, analysis revealed an increase of the p-tau/\( \alpha \)-syn ratio (Baseline vs Year 1, \( p = .003 \), but not significant at Year 3), along with a significant increase of the t-tau/\( \alpha \)-syn ratio (Baseline vs Year 1, \( p = .001 \), as well as a significant increase of t-tau/p-tau ratio at Year 1 (Baseline vs Year 1, \( p = .004 \)), which persisted at Year 3 (Baseline vs Year 3, \( p = .005 \)). All other intra- and inter-groups comparisons involving PD subgroups were not significant before or after FDR correction. The results of inter-groups comparisons between HC and PD patients are displayed in Supplementary Table 7.

3.3. Relationship between NMS and LEDD as a function of motor symptom asymmetry

Due to the possible effects of dopaminergic therapy on NMS (for review see, Garcia-Ruiz et al., 2014), and despite the fact that effects of dopaminergic therapy were not observed in the PPMI cohort in a previous study (Simuni et al., 2018a, b), we still evaluated the effects of LEDD on NMS (MoCA; semantic fluency Total; HVLT – Immediate recall; HVLT retention; Benton Judgment of Line; GDS; STAI-State) as a function of motor symptom asymmetry. For LPD, a significant longitudinal association was only observed between depressive symptoms (GDS) and LEDD (\( B = 0.000 \), [0.000; 0.001], \( R^2 = 8.002 \), \( p < .005 \)) [logarithmic relationship with LEDD, \( R^2 = 0.026 \), \( F = 6.554 \), \( p = .011 \)]). All other associations were non-significant for LPD (\( p < .064 \)). For RPD, no significant longitudinal associations were observed between NMS and LEDD (\( p > .101 \)).

3.4. Relationship between NMS and significant sociodemographic variables as a function of motor symptom asymmetry

The analysis of sociodemographic variables between the groups revealed only a significant difference between the HCs and RPD for recall, \( p = .010 \). All other intra- and inter-groups comparisons involving PD subgroups were not significant before or after FDR correction (all \( p > .017 \)). The results of inter-groups comparisons between HC and PD patients are displayed in Supplementary Table 3.

Neuropsychiatry (see Supplementary Table 6 and Fig. 1). A significant increase of depressive symptoms (GDS) in LPD patients was revealed after FDR correction (Baseline vs Year 3, \( p = .035 \)), whereas no significant modifications were observed for RPD over time for all neuropsychiatric data after FDR correction (\( p > .063 \)). All other intra- and inter-groups comparisons involving PD subgroups were not significant after FDR correction (all \( p > .063 \)). The results of inter-groups comparisons between HC and PD patients are displayed in Supplementary Table 5.

Analysis revealed an increase of the p-tau/\( \beta \)-tubulin ratio at Year 1 (Baseline vs Year 1, \( p < .001 \)) and p-tau/\( \alpha \)-syn ratio (Baseline vs Year 3, \( p < .001 \)) and p-tau/\( \alpha \)-syn ratio (Baseline vs Year 3, \( p < .001 \)). The results of inter-groups comparisons between HC and PD patients are displayed in Supplementary Table 3.

The relationship was only observed between depressive symptoms (GDS) and LEDD (\( R^2 = 0.026 \), \( F = 6.554 \), \( p = .011 \)) [logarithmic relationship with LEDD, \( R^2 = 0.026 \), \( F = 6.554 \), \( p = .011 \)]). All other associations were non-significant for LPD (\( p < .064 \)). For RPD, no significant longitudinal associations were observed between NMS and LEDD (\( p > .101 \)).

### Table 2

| Year 3 - Baseline | Year 1 - Baseline | Delta score | Delta score | Delta score |
|-------------------|-------------------|-------------|-------------|-------------|
| 9.15%             | 8.14%             | 6.90%       |
| 5.40%             | 4.37%             | 1.03%       |
| 8.14%             | 0.45%             | 7.79%       |
| 7.79%             | 0.45%             | 7.34%       |
| 6.90%             | 1.03%             | 5.87%       |
| 8.14%             | 0.45%             | 7.79%       |
| 7.79%             | 0.45%             | 7.34%       |
| 6.90%             | 1.03%             | 5.87%       |

Legend: HC: healthy control; HY: Hoehn & Yahr; LEDD: Levadopa Equivalent Daily Dose; LPD: patients with Parkinson’s disease (PD) who exhibit predominantly left-sided motor symptoms; NA: not applicable; RPD: patients with PD who exhibit predominantly right-sided motor symptoms; SD: standard deviation; SDAP: Modified Schwab & England Activities of Daily Living Scale; Modified UPDRS: Modified Unified Parkinson’s disease Rating Scale; Modified SAE ADL: Modified Schwab & England Activities of Daily Living Scale.
|                | Baseline       | Year 1     | Year 3     | Delta score Year 1 - Baseline | Delta score Year 3 - Baseline |
|----------------|----------------|------------|------------|------------------------------|------------------------------|
|                | LPD (n = 179)  | RPD (n = 234) | HC (n = 196) | LPD (n = 165) | RPD (n = 222) | HC (n = 185) | LPD (n = 154) | RPD (n = 203) | HC (n = 167) | LPD (n = 163) | RPD (n = 222) | HC (n = 185) | LPD (n = 154) | RPD (n = 203) | HC (n = 167) |
| MoCA (mean ± SD) | 27.13 ± 2.40  | 27.09 ± 2.26 | 28.23 ± 1.11 | 26.45 ± 2.87 | 26.23 ± 2.78 | 27.27 ± 2.19 | 26.60 ± 3.12 | 26.25 ± 2.95 | 27.45 ± 2.18 | 0.65 ± 2.67 | 0.85 ± 2.60 | 0.94 ± 2.11 | 0.60 ± 2.11 | -0.60 ± 2.14 |
| HVLT – Immediate/Total recall (mean ± SD) | 24.19 ± 4.86 | 24.62 ± 5.13 | 26.05 ± 4.50 | 23.82 ± 5.35 | 23.85 ± 5.46 | 26.34 ± 6.66 | 25.35 ± 5.60 | 24.18 ± 6.43 | 26.50 ± 5.27 | 0.80 ± 4.41 | 0.87 ± 4.75 | 0.88 ± 4.13 | 0.80 ± 5.13 | 0.84 ± 3.84 |
| HVLT – Retention (mean ± SD) | 0.85 ± 0.21 | 0.86 ± 0.20 | 0.90 ± 0.18 | 0.82 ± 0.22 | 0.85 ± 0.24 | 0.88 ± 0.19 | 0.85 ± 0.33 | 0.83 ± 0.25 | 0.88 ± 0.19 | 0.02 ± 0.24 | 0.01 ± 0.25 | 0.02 ± 0.22 | 0.03 ± 0.27 | 0.02 ± 0.06 |
| HVLT – Delayed recall (mean ± SD) | 8.20 ± 2.52 | 8.45 ± 2.54 | 9.29 ± 2.32 | 7.95 ± 2.82 | 8.21 ± 2.91 | 9.12 ± 2.50 | 8.51 ± 2.83 | 8.17 ± 3.22 | 9.21 ± 2.52 | 0.26 ± 2.46 | 0.20 ± 2.42 | 0.14 ± 2.02 | 0.12 ± 2.38 | 0.54 ± 0.085 |
| Benton Judgement of Line Orientation (mean ± SD) | 12.74 ± 2.10 | 12.76 ± 2.16 | 13.12 ± 1.98 | 12.32 ± 2.44 | 12.35 ± 2.40 | 12.65 ± 2.45 | 12.52 ± 2.27 | 12.69 ± 2.23 | 12.54 ± 2.28 | 0.53 ± 1.98 | 0.43 ± 2.07 | 0.43 ± 2.09 | 0.31 ± 2.04 | -0.27 ± 0.98 |
| Symbol Digit (mean ± SD) | 42.15 ± 10.36 | 40.51 ± 9.14 | 46.77 ± 10.53 | 41.55 ± 10.08 | 40.52 ± 10.31 | 47.56 ± 10.99 | 40.75 ± 11.61 | 39.72 ± 11.62 | 47.91 ± 11.01 | 0.78 ± 7.32 | 0.13 ± 8.41 | 0.86 ± 8.66 | -1.92 ± 8.22 | 1.05 ± 8.05 |
| Semantic Fluency – Total score (mean ± SD) | 48.37 ± 11.63 | 49.00 ± 11.76 | 51.8 ± 11.20 | 48.87 ± 12.30 | 48.87 ± 10.90 | 52.48 ± 11.22 | 48.90 ± 11.27 | 47.98 ± 11.72 | 52.83 ± 11.92 | 0.20 ± 7.77 | 0.21 ± 7.66 | 0.53 ± 7.18 | 0.97 ± 8.30 | 0.53 ± 8.65 |

Legend. HC: healthy controls; LPD: patients with Parkinson’s disease (PD) who exhibit predominantly left-sided motor symptoms; MoCA: Montreal Cognitive Assessment;; HVLT: Hopkins Verbal Learning Test; RPD: patients with PD who exhibit predominantly right-sided motor symptoms; SD: standard deviation.

*Significant after FDR correction when compared with RPD.

#Significant after FDR correction when compared with HC.

*Significant after FDR correction when compared with Baseline.
|                       | Baseline (n = 179) | Year 1 (n = 234) | Year 3 (n = 165) | Delta score Year 1 - Baseline (n = 165) | Delta score Year 3 - Baseline (n = 165) |
|-----------------------|-------------------|------------------|-----------------|----------------------------------------|----------------------------------------|
| **UPDRS I - Depression** |                  |                  |                 |                                        |                                        |
| mild                  | 0.00%             | 0.00%            | 0.00%           | NA                                     | NA                                     |
| moderate              | 0.00%             | 0.00%            | 0.00%           | NA                                     | NA                                     |
| severe                | 0.00%             | 0.00%            | 0.00%           | NA                                     | NA                                     |
| **UPDRS I - Fatigue**  |                  |                  |                 |                                        |                                        |
| mild                  | 0.00%             | 0.00%            | 0.00%           | NA                                     | NA                                     |
| moderate              | 0.00%             | 0.00%            | 0.00%           | NA                                     | NA                                     |
| severe                | 0.00%             | 0.00%            | 0.00%           | NA                                     | NA                                     |
| **UPDRS I - Hallucinations and Psychosis** | |                  |                   |                                        |                                        |
| mild                  | 0.00%             | 0.00%            | 0.00%           | NA                                     | NA                                     |
| moderate              | 0.00%             | 0.00%            | 0.00%           | NA                                     | NA                                     |
| severe                | 0.00%             | 0.00%            | 0.00%           | NA                                     | NA                                     |

**Legend.** HC: healthy controls; GDS: Geriatric Depression Scale; LPD: patients with Parkinson’s disease (PD) who exhibit predominantly left-sided motor symptoms; RPD: patients with PD who exhibit predominantly right-sided motor symptoms; SD: standard deviation; STAI: The State-Trait Anxiety Inventory; UPDRS: MDS-Unified Parkinson’s Disease Rating Scale.
|                | Baseline | Year 1          | Year 3          | Delta score Year 1 - Baseline | Delta score Year 3 - Baseline |
|----------------|----------|-----------------|-----------------|-----------------------------|-----------------------------|
|                | LPD      | RPD             | HC              | (n = 177)                  | (n = 230)                  |
|                | (n = 154)| (n = 207)       | (n = 195)       | (n = 168)                  | (n = 168)                  |
| Serum Uric Acid (mean ± SD) | 310.24 (±77.83) | 320.19 (±78.72) | 322.88 (±77.57) | 303.62 (±73.67) | 316.17 (±77.56) |
| CSF p-tau (mean ± SD) | 15.03 (±5.42) | 14.85 (±5.20) | 17.52 (±8.35) | 14.71 (±5.12) | 15.01 (±5.46) |
| CSF Aβ42 (mean ± SD) | 948.71 (±471.86) | 889.26 (±362.83) | 1019.37 (±499.46) | 925.94 (±394.76) | 872.58 (±404.15) |
| CSF α-syn (mean ± SD) | 1499.92 (±683.62) | 1525.00 (±664.03) | 1695.19 (±747.42) | 1449.61 (±592.08) | 1409.57 (±641.69) |
| CSF t-tau (mean ± SD) | 171.47 (±59.45) | 169.30 (±55.44) | 191.64 (±79.26) | 166.21 (±53.42) | 170.38 (±62.96) |
| Ratio of CSF t-tau to CSF p-tau (mean ± SD) | 0.20 (±0.09) | 0.21 (±0.10) | 0.22 (±0.15) | 0.20 (±0.1) | 0.21 (±0.12) |
| Ratio of CSF t-tau to CSF Aβ42 (mean ± SD) | 0.12 (±0.03) | 0.11 (±0.02) | 0.12 (±0.02) | 0.12 (±0.03) | 0.13 (±0.04) |
| Ratio of CSF t-tau to CSF α-syn (mean ± SD) | 0.02 (±0.01) | 0.02 (±0.02) | 0.02 (±0.02) | 0.02 (±0.01) | 0.02 (±0.02) |
| Ratio of CSF p-tau to CSF Aβ42 (mean ± SD) | 0.01 (±0.00) | 0.01 (±0.00) | 0.01 (±0.00) | 0.01 (±0.00) | 0.01 (±0.00) |
| Ratio of CSF p-tau to CSF α-syn (mean ± SD) | 0.00 (±0.00) | 0.00 (±0.00) | 0.00 (±0.00) | 0.00 (±0.00) | 0.00 (±0.00) |

(continued on next page)
handedness ($p = .034$), with a significantly higher proportion of ambidexterity driving the results. Spearman correlation analyses (adapted to ordinal and continuous data) did not reveal significant relationships between cognitive variables and handedness across groups at any of the three time points, while for neuropsychiatric variables, significant correlations were revealed for RPD with the following UPDRS-I subscores: depression ($r = 0.146, p = .036$) and anxiety ($r = 0.162, p = .016$) at Year 1, as well as hallucinations/psychosis ($r = 0.139, p = .049$) at Year 3. For LPD, significant correlations were revealed for the UPDRS-I cognitive subscore ($r = 0.171, p = .034$) and the hallucinations/psychosis subscore ($r = 0.243, p = .002$) at Year 1, as well as the apathy subscore ($r = 0.164, p = .043$) at Year 3.

### 4. Discussion

The aim of this study was to explore the existence of inter-group and longitudinal differences, as a function of motor symptom asymmetry at the onset of the disease, over a 3 year-period from diagnosis of PD on NMS and biological data. Thanks to the PPMI database (Marek et al., 2011), we analyzed the data from $n = 179$ LPD vs $n = 234$ RPD patients, matched to $n = 196$ HC. According to the statistically robust and conservatively corrected models of analyses we built, we were able to make the following inferences.

First, for cognition, analysis between LPD and RPD wasn’t significant after FDR correction, except for the progressive alteration at Year 3 of the performances for the HVLT – Immediate recall (verbal episodic memory) for the RPD group. That said, analyses also revealed as predicted different patterns of cognitive performances for the PD groups compared to HC, as well as within the PD groups over time. At baseline, LPD patients displayed significantly more cognitive deficits than RPD when compared to HC. However, over time, the performances of the LPD plateaued. RPD patients showed increased cognitive deficits, reaching more severe deficits. More specifically, global cognitive efficiency (as measured by the MoCA or the UPDRS-I subscore of cognitive symptoms) stabilized, or even improved, over time in LPD patients, while performances in RPD patients deteriorated significantly, mainly in the memory domain, which may have affected the performance for global cognitive efficiency (e.g., recall task in the MoCA). These results were also obtained for specific cognitive domains, such as verbal episodic memory (e.g., HVLT), and executive functions (e.g., verbal fluency). Nonetheless, both LPD and RPD groups did display a decrease in attention and reaction time over time (e.g., symbol digit test) as compared to HC, with a seemingly more marked progression in the LPD group (as suggested by the within group analysis). These results suggest the existence of different cognitive phenotypes as a function of motor symptom asymmetry, corroborating the hypotheses of a greater vulnerability for the left hemisphere in neurodegenerative diseases (Claassen et al., 2016; Dixon et al., 2002; Harris et al., 2013; Whitwell and Josephs, 2012). In the long-term, RPD patients may be subject to a wider degeneration of cortico-subcortical regions of the left hemisphere, which in return could increase cognitive decline, and, in the worst cases, induce dementia associated to PD.

Secondly, for neuropsychiatric functions, no significant results after FDR correction were revealed when comparing the LPD and RPD groups. That said, our analyses revealed as predicted different patterns of outcomes when groups were compared to HC and within group over time. Significantly higher levels of anxiety, psychosis and depression, as measured by UPDRS-I, were observed in LPD patients. Moreover, in this sub-group, a significant increase of depressive symptoms over time was reported. These effects corroborate previous observations regarding neuropsychiatric symptoms in LPD patients (Coundouris et al., 2020; Foster et al., 2011; Foster et al., 2010; Modestino et al., 2017; Voruz et al., 2020), and are in line with studies that have shown a functional insufficiency of the right hemisphere in patients suffering from depression (Li et al., 2018; Rotenberg, 2004). Interestingly, a recent functional magnetic resonance imaging study in PD revealed altered connectivity...
in LPD patients, with patterns of hypoconnectivity between right hemispheric cortical-striatal and cerebellar regions, which could potentially explain their vulnerability to neuropsychiatric pathologies (Su et al., 2021). Thus, our data suggests a vulnerability of LPD and the right hemisphere for developing depressive symptoms during PD. Indeed, the functional efficiency of the right hemisphere to sustain affective functions may be more compromised in LPD as compared to RPD. The significant longitudinal association only observed in LPD patients between depressive symptoms and LEDD may suggest a specific non-linear association between neuropsychiatric symptoms and medication by dopamine replacement therapy in this subgroup. Interestingly, on the UPDRS-IV, which measures dopamine therapy dysregulations, results indicate greater dopaminergic dysregulations in LPD patients in comparison to RPD patients at Year 3. Thereby, motor symptom asymmetry, in interaction with dopaminergic medication (Hanna-Pladdy et al., 2015), could explain discrepancies observed in whole group studies investigating neuropsychiatric symptoms in early PD (Péron et al., 2012). In addition to these results concerning depressive symptoms, our analysis of the progression of neuropsychiatric symptoms revealed a significant increase of psychotic symptoms in RPD when compared to HC at Year 3 follow-up, which has been less studied in relation to motor symptom asymmetry. Notably, Cubo et al. (2010) showed greater psychosis symptoms in LPD patients, rather than RPD patients. In our case, a potential explanatory hypothesis behind the observed results would lie at the intersection between the results of Claassen et al. (2016) highlighting the earlier left hemisphere degeneration in PD, and the work of Watanabe et al. (2013) showing that in PD patients with visual hallucinations, cortical and subcortical atrophies predominated in the left hemisphere. However, further studies investigating this potential phenomenon are needed in the future, in conjunction with neuroimaging data.

Thirdly, as for neuropsychiatric measures, reduced levels of...
b biomarkers at Baseline (p-tau and p-tau/t-tau ratio levels) and at Year 3 (α-syn and p-tau/t-tau ratio levels) were observed for both groups when compared to HC, as well as similar patterns of evolution over time (t-tau/α-syn ratio). Nevertheless, our analyses have allowed us to highlight differentiated patterns of biomarker levels as a function of motor symptom asymmetry in PD groups when compared to HC, suggesting potentially differentiated neurodegenerative pathways. For LPD, at Baseline, lower levels of α-syn were observed, while no significant differences were observed for RPD as well as the p-tau/α-syn ratio who decreased significantly over time. As the LPD expressed less cognitive deficits over time, a lower level of α-syn in the first stages may suggest a role of α-syn in cognitive functions. For RPD, at Year 3, lower levels of t-tau, p-tau and α-syn were observed, as well as a progression of α-syn levels, t-tau/α-syn ratio and p-tau/α-syn ratio at Year 1 when compared to HC, while the p-tau/t-tau ratio decreased significantly in RPD patients. Our results confirm previous observations for Aβ42 using the DAT binding asymmetry of the putamen (Fiorenzato et al., 2021) and reveal new patterns of results. Interestingly, lower concentrations of t-tau have been previously associated with PD (Kang et al., 2013), but also with other neurodegenerative disease (e.g., frontotemporal lobar degeneration (Bian et al., 2008)), and could explain the decrease in cognitive functions observed for RPD patients. Specific pathophysiological pathways of neurodegeneration, which to date are debated and mainly unknown (Kang et al., 2013), in RPD patients in comparison to LPD, could be suggested by the present results and needs to be further analyzed in the future. A specific neurodegenerative pathway over time could occur in RPD and may explain the heterogeneity of results for NMS and biomarkers in longitudinal studies of PD. The presence of such neurodegenerative pathways in RPD may suggest a greater vulnerability of the left hemisphere to neurodegeneration, as previously observed for PD (Claassen et al., 2016; Harris et al., 2013) and other neurodegenerative diseases (Dixon et al., 2002; Whitwell and Josephs, 2012).

Taken together, our results underlie the possible existence of two sub-profiles of PD based on motor symptom asymmetry at the onset of the disease, with implications for research and clinical management of PD. First, a cognitive-PD (RPD), with greater cognitive deficits, associated in parallel to changes in the t-tau and p-tau markers linked to neurodegeneration, and a second neuropsychiatric-PD (LPD), with greater neuropsychiatric deficits. It will be interesting in the future to replicate these results on other cohorts of patients, but also to assess longitudinally NMS and biomarkers in PD while considering the asymmetry of motor symptoms. From a global perspective, these two profiles could have distinct implications in terms of quality of life in the early stages of the disease, as already observed by Elkurdi et al. (2021), with a worsened quality of life for LPD patients during the first stages of the disease. These observations seem to be recently confirmed by Voruz et al. (2022) in the advanced stages of the disease, highlighting the distinction in the quality of life of pre- and post-DBS patients according to the asymmetry of motor symptoms, suggesting a better improvement in the quality of life of RPD patients. Based on our results, we could hypothesize that the distinct evolution of cognitive and neuropsychiatric symptoms could have a distinct impact on the quality of life of patients, but also of family caregivers. That said, our data showing the evolution of NMS over a period of 3 years following diagnosis, it is possible that these distinct patterns in the early phase of the disease may disappear in a follow-up at 7–10 years post-diagnosis. However, recent studies on cohorts of pre-deep brain stimulation patients suggest that in the long term, these profiles seem to be maintained, which has also been observed for other functions such as emotional processing (Voruz et al., 2020; Voruz et al., 2022). These behavioral observations have been corroborated by local field potential studies, demonstrating lateralization effects in the electrophysiological activity of the subthalamic nucleus during an emotional task (Béris et al., 2020; Péron et al., 2017).

Limitations. Our study suffers from the potential limitation of having included all participants, thus considering those with a low level of symptom asymmetry, which may be comparable to what would be observed in a control group, and also a percentage of patients with an ipsilateral putamen DAT binding, contravening the classic contralateral pathogenic pattern. Nevertheless, as described in a previous study, there are limitations to the DAT methods in PPML, with firstly a dependence on the criteria of significant asymmetry, but also by the fact that the scans were performed in different centers, with different scanners presenting different resolutions. Moreover, LPD and RPD patients differed significantly on the asymmetry index of the putamen, caudate and striatum. On the basis of these considerations, and wanting to evaluate the effect of asymmetry of motor symptoms assessed by UPDRS III at the beginning of the disease, we made the choice to include the whole sample (except those with a symmetrical score at UPDRS III), while including these binding variables as control covariates. Nevertheless, these results, which discriminate between motor asymmetry and dopaminergic binding asymmetry, challenging the classical pathogenic contralateral model, are of great interest and imply future studies of comparisons between different groups for NMS. Moreover, despite the attempt to match the groups on sociodemographic data, the analyses revealed a slight difference between the groups for handedness, with a greater proportion of ambidextrous HC as compared to the RPD group. However, post-hoc control analyses did not reveal any relationship between cognitive variables and handedness, while some significant correlations were observed for neuropsychiatric subscors in the UPDRS-I. Concerning the neuropsychological evaluations, not all cognitive functions have been assessed, such as mental flexibility, inhibitory control or language which have been highlighted in the literature as potentially differing according to the asymmetry of motor symptoms. Thus, other significant differences could be potentially observed in future studies with more exhaustive neuropsychological testing. Finally, to the best of our knowledge, no visual sensory examination was performed, and therefore an alteration could have had an influence on the cognitive performances of our patients.

5. Conclusion

Our results highlight the presence of possible cognitive-neuropsychiatric, but also biological, distinct trajectories in PD as a function of motor symptom asymmetry at the onset of the disease. Distinct pathological trajectories, as well as a left-hemisphere vulnerability in PD seem to emerge from our results, but remain to be confirmed by future investigations. This opens the way to the development of personalized cognitive and neuropsychiatric remediation management, depending on motor symptom asymmetry in PD patients.
Sample Credit author statement

Philippe Voruz: Conceptualization, Methodology, Software, Data curation, Writing – original draft preparation; Ioana Constantin: Data curation, Validation, Writing- Reviewing and Editing; Julie Peron: Conceptualization, Methodology, Supervision, Writing- Reviewing and Editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2022.108419.

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Appendix B. Author statement

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