Brain network characteristics and cognitive performance in motor subtypes of Parkinson’s disease: a resting state fMRI study

Amée F. Wolters*ab, Stijn Michielseab, Mark L. Kuijfab, Luc Defebvrecd, Renaud Lopesce, Kathy Dujardincd, Albert F.G. Leentjensb,f

a Department of Neurology, Maastricht University Medical Center, Maastricht, the Netherlands
b Department of Neurosurgery, School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, the Netherlands
c Univ. Lille, Inserm, Lille Neuroscience & Cognition, F-59000 Lille, France
d CHU Lille, Neurology and Movement Disorders, F-59000 Lille, France
e Univ. Lille, CNRS, Inserm, CHU Lille, Institut Pasteur de Lille, US 41 - UMS 2014 - PLBS, F-59000 Lille, France
f Department of Psychiatry and Neuropsychology, Maastricht University Medical Center, Maastricht, the Netherlands

*These authors contributed equal to this paper and are shared first authors.

*Corresponding author: Department of Neurology, Maastricht University Medical Centre, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands; amee.wolters@mumc.nl; +31(0)43-387 7056.

Key words: Parkinson’s disease, magnetic resonance imaging, fMRI, resting-state networks, cognition, subtypes.
Abstract:

**Introduction**: Parkinson’s disease (PD) is a heterogeneous disorder with great variability in motor and non-motor manifestations. It is hypothesized that different motor subtypes are characterized by different neuropsychiatric and cognitive symptoms, but the underlying correlates in cerebral connectivity remain unknown. Our aim is to compare brain network connectivity between the postural instability and gait disorder (PIGD) and tremor-dominant (TD) subtypes, using both a within- and between-network analysis.

**Methods**: This cross-sectional resting-state fMRI study includes 81 PD patients, 54 belonging to the PIGD and 27 to the TD subgroup. Group-level spatial maps were created using independent component analysis. Differences in functional connectivity were investigated using dual regression analysis and inter-network connectivity analysis. An additional voxel-based morphometry analysis was performed to examine if results were influenced by grey matter atrophy.

**Results**: The PIGD subgroup scored worse than the TD subgroup on all cognitive domains. Resting-state fMRI network analyses suggested that the connection between the visual and sensorimotor network is a potential differentiator between PIGD and TD subgroups. However, after correcting for dopaminergic medication use these results were not significant anymore. There was no between-group difference in grey matter volume.

**Conclusion**: Despite clear motor and cognitive differences between the PIGD and TD subtypes, no significant differences were found in network connectivity. Methodological challenges, substantial symptom heterogeneity and many involved variables make analyses and hypothesis building around PD subtypes highly complex. More sensitive visualisation methods combined with machine learning approaches may be required in the search for characteristic underpinnings of PD subtypes.
1. Introduction

Parkinson’s disease (PD) is a heterogeneous neurodegenerative disorder, that shows a rapid increase in worldwide incidence and prevalence over the past two decades [1]. A great variability in presentation exists, not only in motor manifestations, but also in cognitive functioning, autonomic symptoms, prognosis, and treatment response [2]. This is why the National Institutes of Health state that obtaining more insight in the heterogeneous nature and defining different subtypes of PD, is one of the top three research priorities in PD [3]. Although the scientific validity of PD subtypes is questioned [4], in clinical practice, the subdivision of patients into a tremor-dominant (TD) and postural instability and gait disorder (PIGD) subtype is often used to describe the main motor phenotypes [5, 6].

The different clinical presentations of PD may be related to the involvement of different neuronal pathways and alterations in neurotransmitter activities. Bradykinesia and rigidity are thought to be mainly related to dopaminergic deficits, whereas it has been suggested that serotonin plays an important role in tremor. In addition, cholinergic modulations seem to influence gait disorders in PD [7]. This suggests that different pathophysiological processes and various functional brain networks may be involved in different PD subtypes. However, results vary greatly between studies. For example, one study showed an increased functional connectivity density in the cerebellum and a decreased functional connectivity density in the frontal lobes of TD patients compared to PIGD PD patients [8], whereas others have reported an increased connectivity between the basal ganglia and the ventral somatomotor network in TD subjects and a decreased connectivity between the basal ganglia and the fronto-parietal network in non-TD subjects [9]. Moreover, cerebral activity within the default mode network has been described as distinctive between TD and akinetic-rigid PD patients [10]. Most studies have focused on specific regions of interest while, in order to elucidate the underlying pathophysiology of PD motor subtypes, it might be more relevant to study complex whole-brain interactions and functional brain organization at a global network level [11]. Advances in
functional magnetic resonance imaging (fMRI) analysis offer the possibility to study the overall resting-state function of brain networks using both within- and between-network analysis. This may open the perspective of modelling the pathways of pathology spreading in PD, which might precede structural damage, and to characterize the most vulnerable networks [11]. Furthermore, knowledge of the pathophysiology of distinct PD subtypes might eventually lead towards more specific and reliable clinical biomarkers and personalized medicine in the future.

The main aim of the present study was to compare brain network organization between PIGD and TD subtypes using resting-state fMRI. Furthermore, our secondary aim is to associate potential significant differences in cerebral connectivity with alterations in cognitive performance. Based on previous studies, we expect the PIGD subtype to show altered connections in brain regions that are part of the default mode network, while the TD subtype is expected to show alterations mainly in the fronto-parietal network [11]. In addition, we expect the PIGD subtype to be more prone to develop cognitive decline in general, particularly in visuospatial, executive and memory domains [7].

2. Materials and methods

The present study is based on a previous published cross-sectional observational resting-state fMRI study, in which cognitive phenotypes of PD were investigated. This study is extensively described elsewhere [12, 13].

2.1. Participants

The study consisted of 156 PD patients. All patients met the United Kingdom Brain Bank criteria for idiopathic PD [14]. We excluded patients with a diagnosis of a neurological disease other than PD, moderate and severe dementia (defined as a score >1 on the Clinical Dementia Rating [15] and according to the Movement Disorders criteria [16]) and an age older than 80 years. Participants were
recruited among the outpatients of two European movement disorder centres, in Lille, France and Maastricht, the Netherlands. All participants gave informed consent prior to participation in the study. The study was approved by the local institutional review boards (CPP Nord-Ouest IV, 2012- A 01317-36 and METC AZM/UM 12-3-064 and registered at clinicalTrials.gov: NCT01792843) and performed in accordance with the principles of the Declaration of Helsinki (Fortaleza, Brazil, 2013).

Detailed demographic and disease related variables were documented, including the antiparkinsonian medication and levodopa equivalent daily dose (LEDD) [17]. All participants were assessed after having received their usual anti-parkinsonian medication (“ON” state). Severity of motor symptoms was assessed by the score on the Movement Disorders Society - Unified Parkinson Disease Rating Scale (MDS-UPDRS III) and disease stage by the Hoehn & Yahr score (H&Y) [18].

Based on a numerical ratio derived from the mean tremor score and mean-PIGD score at the MDS-UPDRS III, two subgroups were defined, namely a TD and PIGD subgroup. This classification is based on a previously described method [6], in which the tremor score is determined by assessing 11 items, derived from the MDS-UPDRS (Item 2.10, 3.15a, 3.15b, 3.16a, 3.16b, 3.17a, 3.17b, 3.17c, 3.17d, 3.17e and 3.18). The mean of these items is divided by the mean of the five items that are used to assess the PIGD score (item 2.12, 2.13, 3.10, 3.11, 3.12). Participants with a ratio ≤0.9 were classified as a PIGD subtype, while patients with a ratio ≥1.15 were classified as TD subtype. Patients with a ratio between 0.90 and 1.15, were classified as indeterminate. Only PD patients with a PIGD or TD subtype classification were included in the present analysis.

The cognitive assessment battery that was performed in this study was extensively described elsewhere [12]. Overall cognitive function was assessed with the Mattis Dementia Rating Scale (Mattis DRS). Additionally, a comprehensive neuropsychological assessment was performed evaluating five cognitive domains: 1) attention and working memory (Digit span forward and backward Symbol Digit Modalities Test), 2) executive functions (Trail Making Test B/A ratio, the
interference index and the number of errors in the interference condition of a 50-item version of the Stroop word colour test and a 1-minute phonemic word generation task performed in single and alternating conditions), 3) verbal episodic memory (Hopkins verbal learning test), 4) language (the 15-item short form of the Boston naming test and animal names generation task in 1 minute), 5) visuospatial functions (the short version of the judgment of line orientation test).

2.2. MRI acquisition

Patients were scanned at two sites (Maastricht and Lille) using 3T Philips Achieva MRI scanners with matching software versions and MR sequences. All participants were scanned in medication “ON” state. 3D T1-weighted images were acquired with a magnetization-prepared gradient echo sequence (voxel size: 1 x 1 x 1 mm\(^3\); repetition time (TR): 7.2 ms; echo time (TE): 3.3 ms; matrix size: 176 x 256 x 256 voxels, flip angle: 9°). Resting-state fMRI was performed with a T2*-weighted echo-planar imaging (EPI) sequence lasting 10 minutes (Maastricht: Voxel size: 3 x 3 x 3 mm\(^3\); TR: 2400 ms; TE: 30 ms; matrix size: 80 x 80 x 40 voxels; flip angle: 90° / Lille: Voxel size: 3 x 3 x 3 mm\(^3\); TR: 2400 ms; TE: 30 ms; matrix size: 64 x 64 x 40 voxels; flip angle: 90°). Patients were instructed to close their eyes, remain quiet and stay awake. All images were visually inspected and incomplete or disturbed brain images, with largely incomplete brain coverage, ghosting or large motion artefacts (defined as ≥3 mm displacement in any of the translation parameters), were excluded.

2.3. MRI pre-processing

After conversion from raw data to nifti format, structural T1-weighted images were pre-processed using Freesurfer v7.1.0 software (http://surfer.nmr.mgh.harvard.edu/). This included the processing steps of non-uniform signal correction, signal and spatial normalizations, skull stripping and brain tissues segmentation.
fMRI images were pre-processed with FSL software v6 (fsl.fmrib.ox.ac.uk/fsl). First, the first three image volumes were removed to avoid T1 equilibration effects. Motion was corrected using mcflirt function with the middle volume as the reference volume [19]. Furthermore, a noise filter was applied at level 0.66 and with noise AR (auto-correlation) at 0.34, as well as high-pass temporal filtering to reduce nuisance related to respiratory and pulsation processes. After this, slice-timing correction and spatial smoothing with 6 mm full width at half maximum (FWHM) were performed. fMRI images were registered to the anatomical T1 data by using non-linear and boundary-based registration (BBR) in FSL [20]. Both fMRI images and anatomical T1-images were normalised to standard MNI space, with a resampling resolution of 3 mm³.

134 participants had an MRI scan. Based on severe head motion (defined as ≥3 mm displacement in any of the translation parameters), 17 datasets were excluded from analysis. In addition, participants were excluded because of an incomplete MRI acquisition (2 participants), poor quality of the anatomical images (5 participants) or ischemic cerebral lesions (5 participants). This resulted in 105 participants for the current study.

2.4. Analysis of resting-state data

Group-level spatial maps, called resting-state networks, were created by performing MELODIC group independent component analysis (ICA). In advance, ICA’s were performed for each participant on a single subject level using automatic dimensionality. These typically displayed 50 to 70 components per individual subject. Therefore, the group ICA was performed with a dimensionality of 75. All 75 spatial maps were visually inspected and classified as either displaying resting-state activity or noise components, in accordance with the guidelines for ICA component classification [21]. Eventually, 51 components were discarded as noise components (movement artifacts, MRI artifacts, white matter, physiological noise) and 24 were classified as resting-state activity. A dual-regression analysis was performed to derive subject-specific time series for each of these spatial maps [22]. First, for each
subject, the group-average set of spatial maps was regressed (as spatial regressors in a multiple regression) into the subject’s 4D space-time dataset. This resulted in a set of subject-specific timeseries, one per group-level spatial map. Next, those timeseries were regressed (as temporal regressors, again in a multiple regression) into the same 4D dataset, resulting in a set of subject-specific spatial maps, one per group-level spatial map. We then tested for group differences using FSL’s randomise permutation-testing tool. Between-group effects were considered significant if they reached two-tailed p-values of <0.001 (family-wise error (FWE) corrected at the voxel level with Threshold-Free Cluster Enhancement (TFCE) and Bonferroni-corrected for two-sided testing in 24 spatial maps).

The subject-specific time series from each component of interest were used as input for FSLnets v0.6, in order to study inter-network connectivity. FSLnets is a network modelling tool in which the brain is represented as a network consisting of a collection of nodes and edges. The resting-state network components of interest are indicated as nodes, while the connections between these nodes are called edges. A correlation matrix was calculated, demonstrating the correlation strength between all components of interest. Partial correlations (Ridge Regression, rho = 0.1), representing direct connections between different components, were calculated. The resulting correlation r-values were transformed into Z-scores with Fisher’s transformation for further analysis. Subsequently, a group-level analysis was performed to assess group differences in inter-network connectivity. For this, FSL-randomize was used with 5000 permutations, in order to FWE (family-wise error) correct for multiple comparisons across all edges. Results were considered significant when demonstrating a FWE-corrected p-value < 0.05. Outcomes were corrected for demographic characteristics that significantly differed between study centres (years of formal education, PD side of onset and sex). Although LEDD values did not significantly differ between groups, dopaminergic medication is known to influence cerebral network connectivity [23]. For this reason, a correction was also applied for the use of dopaminergic medication by adding the LEDD as a co-variate.
2.5. Voxel-based morphometry

In order to investigate voxel-wise differences in grey matter volume the anatomical T1-weighted images were analysed with FSL-VBM, an optimised voxel-based morphometry (VBM) protocol carried out with FSL tools [24]. First, structural images were brain-extracted and grey matter-segmented before being registered to the MNI 152 standard space using non-linear registration [25]. The resulting images were averaged and flipped along the x-axis to create a left-right symmetric, study-specific grey matter template. Second, all native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 8 mm. Finally, voxel wise general linear model (GLM) was applied using permutation-based testing, correcting for multiple comparisons across space by threshold-free cluster enhancement at p < 0.05.

2.6. Statistical analysis

Demographic variables were analysed using IBM SPSS version 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp). Demographic and disease-related variables were compared with Pearson’s chi-squared test for categorical variables (non-parametric test), the Mann-Whitney U Test for ordinal variables and non-normally distributed continuous variables and the student’s t-test for normally distributed continuous variables. The Kolmogorov-Smirnov test was used to assess the normality of the data. An analysis of covariance (ANCOVA) with LEDD and HAM-D (Hamilton depression rating scale) total score as covariates, was performed to compare both groups on cognitive performance. The statistical significance threshold was set to p < 0.05.
3. Results

3.1. Demographic, Clinical and Neuropsychological Characteristics

Initially, 105 participants were included in the current analysis. After assessing the motor subtype based on the numerical ratio of the MDS-UPDRS score, 24 participants were classified as indeterminate subtype and were excluded from analysis. Therefore, 81 PD patients were included in the study. This involved 54 PIGD patients and 27 TD patients. Details regarding the demographic and clinical features can be found in Table 1. The Hoehn & Yahr stage of the PIGD subgroup (mean 2.2 ± 0.6) was significantly higher, compared to the TD subgroup (mean 2.0 ± 0.3, p = 0.024). Furthermore, the distribution of PIGD and TD differed significantly between centres, in Lille there were less TD patients than in Maastricht (p < 0.001). No significant differences in other demographic variables were found between the two groups. When comparing the TD and PIGD subgroups between the two centres, it appeared that the between-centre difference was largely driven by three variables, namely years of formal education, PD side of onset and sex. However, for the PIGD subgroup there was also a significant difference for the MDS-UPDRS III and Mattis DRS scores (Supplementary data, Table 1 and 2).

Cognitive performance was compared between the two groups. No significant difference was found between the PIGD and TD subgroups on the Mattis DRS: total score (p = 0.155). However, the PIGD subgroup performed worse on tests related to attention and working memory (Mattis DRS: Attention subscale, p = 0.033; WAIS-R backward digit, p = 0.042; Symbol digit modalities test, p = 0.002; Trail Making Test-A, p = 0.023), executive functions (Trail Making Test-B, p = 0.002; Stroop: interference index, p = 0.031; Stroop: errors, p = 0.038), memory (Mattis DRS: Memory subscale, p = 0.027), language (Boston naming test, p = 0.016) and visuospatial function (Mattis DRS: Construction subscale, p = 0.013). None of the assessed cognitive domains displayed higher scores in the PIGD
subgroup compared to the TD subgroup. Details regarding the neuropsychological assessment can be found in Table 2.

3.2. Resting-state fMRI dual regression analysis

For details regarding the selected independent components see Figure 1 (and Supplementary data, Table 3). The dual regression analysis showed a significant difference between the two motor subtypes for several independent components (p-value <0.05). These independent components were located in the occipital pole (IC 1), intracalcarine cortex/lingual gyrus (IC 2), angular gyrus/supramarginal gyrus (IC 10), precentral gyrus (IC 11), precentral gyrus/postcentral gyrus (IC 13), middle temporal gyrus/angular gyrus (21) and inferior frontal gyrus (23). However, after correction for multiple comparisons (p-value <0.001), none of the results remained significant when comparing the TD and PIGD subgroups (Supplementary data, Table 3).

3.3. Network analysis

Following the dual regression analysis, network analysis was performed with FSLnets. A network hierarchy of the 24 selected independent components, clustered based on their covariance structure, was created (Supplementary data, figure 1). Furthermore, a clustering method was used to group the independent components together based on these correlations. This network hierarchy confirms that components of the major larger resting-state brain networks were involved in our analysis.

When comparing the PIGD and TD subgroups, a significant higher functional connectivity was found between the lateral occipital cortex (IC 5) and the pre- and post-central gyrus (IC 13) in the PIGD group, compared to the TD group (p = 0.034). Since differences between study centre were mainly driven by three variables (years of formal education, PD side of onset and sex), the analysis was repeated including these variables as co-variates. With the inclusion of these co-variates, again the
edge between the lateral occipital cortex and the pre- and post-central gyrus showed a significant difference (PIGD > TD, \(p = 0.033\)). However, after the introduction of LEDD as a covariate this result did not remain significant (\(p = 0.068\)).

3.4. Voxel-based morphometry analysis

The VBM analysis, performed both with and without the co-variates described above (LEDD, years of formal education, PD side of onset and sex), did not reveal any cortical brain areas with a significant difference in local grey matter volume between PIGD and TD patients (corrected \(p\)-value > 0.05).

4. Discussion

This is the first study performing a whole-brain, inter-network, resting-state fMRI analysis of PD motor subtypes. The main aim of this study was to investigate if PD patients with a PIGD subtype show different functional network characteristics compared to the TD subtype. A significantly higher connectivity was found between the lateral occipital cortex and the pre- and post-central gyrus in PIGD patients compared to the TD subgroup. However, after the correction for dopaminergic medication use, this result was not significant anymore. Moreover, no significant differences in grey matter volume between the two motor subgroups are found.

In addition, cognitive performance was compared between PIGD and TD patients. Our results show that PIGD patients did perform worse in nearly all cognitive domains, especially on tests for attention, working memory and executive function. These findings correspond with the results of several earlier studies, that showed that cognitive dysfunction is more pronounced in PIGD patients compared to TD patients [7]. Moreover, it has been shown earlier that lower cognitive scores predict fall risk after five years, suggesting that cognitive decline itself may among other things lead to the gait deficits in the PIGD subgroup [26].
However, with this study we were unable to confirm our initial hypothesis that the PIGD and TD subtypes would be characterized by changes in different network configurations which in turn could also explain cognitive differences between the subtypes. It has been suggested that different motor subtypes of PD may be characterized by alterations in subcortical grey matter nuclei rather than by differences in large brain networks [27]. Furthermore, pathological studies suggest a different degeneration pattern of the substantia nigra and locus coeruleus in TD patients compared to PIGD patients [28]. Future studies, using more sensitive ultra-high field MRI, may prove to be more efficacious in visualising these subcortical structures and could help to elucidate the underlying pathophysiology of PD motor subtypes.

These negative findings are in contrast with results from earlier studies that report a variety of alterations in cerebral connectivity between a wide number of brain areas, as recently reviewed by Boonstra et al. [29]. Although several resting state fMRI studies have focused on differences on functional connectivity between motor subtypes, the results of these studies vary widely, are incomparable and do not allow for an overall conclusion with regard to specific changes in connectivity per subgroup. The substantial variability of these results may be partially explained by the relatively small number of participants in these studies. Study samples typically vary between 10 and 40 PD patients [29]. Such small studies are more likely to produce less robust results compared to large samples, due to a high sampling variability, and tend to have an increased probability of reporting false positive results [30]. In addition, these studies are not well comparable due to different definitions of subtypes. Whereas all studies define a TD subgroup, the definition of non-TD groups varies, with some studies defining a PIGD subgroup, an akinetic-rigid (AR) group, or both; other studies defined a ‘mixed group’ or simply group all non-TD patients together. The difficulties in defining PD subtypes were recently the focus of a Movement Disorder Society (MDS) task force that concluded that subtyping has substantial methodological shortcomings and questionable clinical
applicability [4]. Moreover, since PD is a heterogeneous disorder, involving a wide range of both motor and non-motor symptoms, subtyping based solely on motor symptoms is probably too simplistic. However, new classification methods have not yet been developed and validated. At present, the subtyping of patients into a TD, indeterminate and PIGD subtype is most commonly used [5, 6]. It has also been shown that the TD, mixed and PIGD subtyping is more sensitive for the identification of non-motor abnormalities than the TD, mixed and AR classification [31]. We therefore believe that, while awaiting new classification methods, it is acceptable to use the PIGD and TD motor subtyping classification. The application of the same criteria by different studies, also ensures the possibility to compare results among different reports.

In this study patients were assessed after having received their usual antiparkinsonian medication (‘ON’ state). Previous studies have already demonstrated that dopaminergic medication influences brain connectivity patterns both in a linear and non-linear way, with a tendency to normalize abnormal brain connectivity [23]. Therefore, the results of the current analysis were corrected for LEDD. However, some earlier studies did not include LEDD as a covariate [32]. Other studies try to evade this problem by scanning patients in an ‘OFF’ medication state [33]. Whereas this rules out the direct confounding effect of levodopa use, it also introduces new problems, since secondary alterations in dopaminergic transmission, such as receptor up- and downregulation take a longer time to restore and may still confound outcomes by exaggerating alterations in connectivity [34]. Due to these pharmacological effects, different study methods with regard to medication use might partially explain the variability in results between studies. The impact of dopaminergic medication was clearly illustrated by our analyses. Even though LEDD did not significantly differ between the two subgroups, significant between-group findings disappeared after correction for LEDD. Therefore, in order to reproduce reliable results, fMRI studies in PD patients ‘ON’ medication should always be corrected for LEDD.
Given the number of patients included and the correction for a number of covariates, we think these negative results are valid. They show that network analyses in PD is more complex than anticipated and that research into changes in network connectivity in PD probably requires more advanced statistical methods, such as machine learning techniques, in much larger datasets.

This study has strengths and limitations. A strength is the fact that this is the largest study so far comparing differences in functional connectivity between motor subtypes in PD. Another strength is that patients were comprehensively assessed with measures on motor symptoms and cognitive performance. Also, the statistical approach was corrected for multiple comparisons, for between group differences and for LEDD. A limitation is the fact that this study was not initially designed to compare motor subtypes. The relative proportion of these subtypes also varied between the two centres, which we could not explain. We corrected for differences between centres and, given the negative outcome of this study, do not believe the results were affected by this. Another limitation is the difficulty in defining subtypes, as mentioned before. In this study we focussed on the TD and PIGD motor subtypes of PD, aware of potential criticism to this division. Finally, although the MRI protocols performed at the two different locations were matched and the same type of 3T MRI scanner was used (Philips Achieva), minor differences in MRI output cannot be ruled out.

In conclusion, although the PIGD and TD PD subgroups clearly differ in terms of motor and cognitive performance, we were not able to demonstrate any between group differences in functional network connectivity. The resting-state fMRI network analyses suggested that the connection between the visual and sensorimotor network might differentiate between PIGD and TD subgroups. However, these results did not remain significant after correcting for LEDD. Methodological challenges, substantial individual-level symptom heterogeneity and the many involved variables and confounders make analyses and hypothesis building with respect to PD subtypes highly complex.
More sensitive visualisation methods, such as ultra-high field MRI in combination with machine learning approaches that are able to handle much more variables in much larger datasets may be more efficacious in the search for clinically reliable subtypes of PD.

5. Authors contributions

1. Research project: A. Conception, B. Organization, C. Execution.


A.F.W.: 1A, 2A, 2B, 3A.

S.M.: 2B, 2C, 3B.

M.L.K.: 1A, 2A, 2C, 3B.

L.D.: 2C, 3B.

R.L.: 1A, 1B, 1C, 2C, 3B.

K.D.: 1A, 1B, 1C, 2C, 3B.

A.F.G.L: 1A, 1B, 1C, 2A, 2C, 3B.

6. Funding sources

This work was not supported by any grant or subsidy. The study on which these analyses were based was supported by the Michael J. Fox Foundation for Parkinson’s Research (MJFF grant 23-8-2012) The sponsor was not involved in the design of this analysis, nor in data interpretation, the writing of this article or decision to submit this article for publication.
The authors report no financial disclosures relative to this study.

L. Defebvre gave consultancies to AbbVie and Orkyn and earned honoraria for lectures from AbbVie and UCB. A.F.G. Leentjens received a research grant from the Michael J. Fox Foundation and earned royalties from “Springer Media” and “de Tijdstroom”. All other authors have nothing to disclose.

7. Conflict of interest
The authors have no conflict of interest to report.

8. References


Olanow, I. Shoulson, et al., Variable expression of Parkinson's disease: a base-line analysis of the
dominant and postural instability/gait difficulty groups with the movement disorder society unified
Parkinson’s disease rating scale: comparison with the unified Parkinson's disease rating scale, Mov
Functional Connectivity Density in Subtypes of Parkinson's Disease, Front Hum Neurosci 11 (2017)
458.
Subtypes of Parkinson's Disease: A Dynamic Perspective, Front Aging Neurosci 13 (2021) 710735.
network differences between rigidity- and tremor-predominant Parkinson's disease, Cortex 81 (2016)
239-50.
A.F. Leentjens, Cognitive disorders in Parkinson's disease: Confirmation of a spectrum of severity,
Dujardin, Cognitive phenotypes in parkinson's disease differ in terms of brain-network organization
and connectivity, Hum Brain Mapp 38(3) (2017) 1604-1621.


[34] M. Politis, H. Wilson, K. Wu, D.J. Brooks, P. Piccini, Chronic exposure to dopamine agonists affects the integrity of striatal D2 receptors in Parkinson's patients, Neuroimage Clin 16 (2017) 455-460.
Figure 1. Spatial maps of the 24 resting-state components of interest obtained from the group independent component analysis (ICA). Spatial maps are thresholded at $3 < z < 15$. Images are shown in radiological convention (right side of the image corresponds to the left hemisphere).
Table 1. Demographic and clinical features

<table>
<thead>
<tr>
<th>Feature</th>
<th>PIGD</th>
<th>TD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>54 (67)</td>
<td>27 (33)</td>
<td></td>
</tr>
<tr>
<td>TD/PIGD ratio</td>
<td>0.3 (0.2)</td>
<td>2.5 (1.4)</td>
<td></td>
</tr>
<tr>
<td>Centre (Lille/Maastricht)</td>
<td>35/19</td>
<td>6/21</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>59.26</td>
<td>77.78</td>
<td>0.099</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.9 (8.1)</td>
<td>63.2 (8.5)</td>
<td>0.178</td>
</tr>
<tr>
<td>Handedness (% right)</td>
<td>85.2</td>
<td>85.2</td>
<td>0.368</td>
</tr>
<tr>
<td>Formal education (years)</td>
<td>11.7 (3.4)</td>
<td>12.7 (4.0)</td>
<td>0.266</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>9.7 (6.3)</td>
<td>8.2 (5.9)</td>
<td>0.234</td>
</tr>
<tr>
<td>MDS UPDRS III score</td>
<td>26.8 (12.4)</td>
<td>31.6 (10.9)</td>
<td>0.095</td>
</tr>
<tr>
<td>Hoehn &amp; Yahr stage</td>
<td>2.2 (0.6)</td>
<td>2.0 (0.3)</td>
<td>0.024*</td>
</tr>
<tr>
<td>Side of onset (% right)</td>
<td>50</td>
<td>44</td>
<td>0.969</td>
</tr>
<tr>
<td>LEDD (mg/day)</td>
<td>941.4 (422.4)</td>
<td>687.2 (832.6)</td>
<td>0.145</td>
</tr>
<tr>
<td>HAM-D</td>
<td>6.7 (5.0)</td>
<td>5.3 (3.4)</td>
<td>0.433</td>
</tr>
</tbody>
</table>

PIGD = postural instability and gait disorder; TD = tremor-dominant; MDS UPDRS III = Movement Disorders Society sponsored revision of the Unified Parkinson’s disease Rating Scale-Part III (severity of motor symptoms); LEDD = Levodopa Equivalent Daily Dose, HAM-D = Hamilton depression rating scale.

Results are represented as mean (SD), unless otherwise specified.
Table 2. Neuropsychological characteristics

<table>
<thead>
<tr>
<th></th>
<th>PIGD (n = 54)</th>
<th>TD (n = 27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall cognition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mattis DRS: Total score (1-144)</td>
<td>135.9 (6.2)</td>
<td>138.1 (6.8)</td>
<td>0.155</td>
</tr>
<tr>
<td>- Attention subscale (1-37)</td>
<td>35.6 (1.4)</td>
<td>36.3 (1.0)</td>
<td>0.033*</td>
</tr>
<tr>
<td>- Initiation/perseveration subscale (1-37)</td>
<td>34.5 (2.7)</td>
<td>35.3 (2.8)</td>
<td>0.349</td>
</tr>
<tr>
<td>- Construction subscale (1-6)</td>
<td>5.81 (0.4)</td>
<td>6.00 (0.0)</td>
<td>0.013*</td>
</tr>
<tr>
<td>- Conceptualization subscale (1-39)</td>
<td>37.6 (1.9)</td>
<td>36.9 (2.9)</td>
<td>0.324</td>
</tr>
<tr>
<td>- Memory subscale (1-25)</td>
<td>22.4 (2.6)</td>
<td>23.6 (2.0)</td>
<td>0.027*</td>
</tr>
<tr>
<td>Attention and working memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAIS-R forward digit (0-14)</td>
<td>7.3 (2.5)</td>
<td>8.1 (2.3)</td>
<td>0.197</td>
</tr>
<tr>
<td>WAIS-R backward digit (0-14)</td>
<td>5.2 (1.9)</td>
<td>6.2 (1.8)</td>
<td>0.042*</td>
</tr>
<tr>
<td>SDMT: Number in 90sec</td>
<td>36.5 (12.0)</td>
<td>46.8 (11.3)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Trail Making Test – A (sec)</td>
<td>58.6 (29.9)</td>
<td>42.7 (16.8)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Executive functions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trail Making Test – B (sec)</td>
<td>157.8 (71.7)</td>
<td>102.4 (57.3)</td>
<td>0.002*</td>
</tr>
<tr>
<td>Stroop: interference index</td>
<td>2.0 (0.7)</td>
<td>1.7 (0.4)</td>
<td>0.031*</td>
</tr>
<tr>
<td>Stroop: errors</td>
<td>5.8 (10.0)</td>
<td>1.7 (3.0)</td>
<td>0.038*</td>
</tr>
<tr>
<td>Phonemic fluency (60 sec)</td>
<td>12.7 (4.5)</td>
<td>13.6 (5.7)</td>
<td>0.539</td>
</tr>
<tr>
<td>Alternating fluency (60 sec)</td>
<td>10.2 (4.8)</td>
<td>12.6 (5.5)</td>
<td>0.053</td>
</tr>
<tr>
<td>Memory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVLT Learn1 (/12)</td>
<td>6.0 (2.0)</td>
<td>6.6 (2.1)</td>
<td>0.308</td>
</tr>
<tr>
<td>HVLT Learn total (/36)</td>
<td>24.4 (4.6)</td>
<td>26.3 (5.3)</td>
<td>0.135</td>
</tr>
<tr>
<td>HVLT number of intrusions (/36)</td>
<td>1.8 (2.3)</td>
<td>0.9 (1.5)</td>
<td>0.107</td>
</tr>
<tr>
<td>HVLT delayed recall (/12)</td>
<td>8.8 (2.3)</td>
<td>8.8 (3.0)</td>
<td>0.728</td>
</tr>
<tr>
<td>HVLT recognition hits (/12)</td>
<td>11.3 (1.0)</td>
<td>11.2 (1.2)</td>
<td>0.957</td>
</tr>
<tr>
<td>Language</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boston naming test (/15)</td>
<td>11.8 (2.7)</td>
<td>13.3 (1.7)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Semantic fluency (animals in 60 sec)</td>
<td>17.7 (6.6)</td>
<td>20.7 (6.1)</td>
<td>0.086</td>
</tr>
<tr>
<td>Visuospatial functions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Judgement of line orientation</td>
<td>10.7 (3.2)</td>
<td>12.2 (2.1)</td>
<td>0.084</td>
</tr>
</tbody>
</table>

**MMSE = Mini-mental state examination; Mattis DRS = Mattis Dementia rating scale; WAIS-R = Wechsler for adults intelligence scale revised; SDMT = Symbol digit modalities test; HVLT = Hopkins verbal learning test.**

Results are represented as mean (SD).
Highlights

- PIGD and TD PD patients clearly differ in terms of motor and cognitive performance
- No differences in network connectivity were found between PIGD and TD patients
- Analyses and hypothesis building around PD subtypes is highly complex