PREDICTING PARKINSON'S DISEASE SUBTYPES USING NEUROIMAGING

Assessing Dopamine Availability and Grey Matter Volume

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ABSTRACT

Introduction Parkinson's disease (PD) is highly heterogeneous and different subtypes can be discriminated. The objective of this study was to predict PD subtype by dopamine availability and grey matter (GM) volumes and to relate pathology to PD symptoms. **Methods** A linear discriminant analysis (LDA) was conducted with neuroimaging predictors of 66 PD patients screened at the VU University medical center, divided into three symptom-based subtypes. Correlations were conducted between neuroimaging measures and symptoms. Post hoc, a LDA was conducted with right hemisphere neuroimaging predictors only. **Results** Volumes of the bilateral hippocampus, dlPFC, IFG and insula and dopamine in the putamen were unable to predict PD subtype, but right insular volume had discriminative value. Lower hippocampal volume related to lower verbal memory performance. **Discussion** The discriminative value of right insular volume might be due to its directive role in cognition. Future research should continue to explore pathology heterogeneity in PD within larger patient groups, with special attention to insular involvement and by use of network imaging.

KEYWORDS: Parkinson's disease, heterogeneity, neuroimaging, dopamine, atrophy, insula

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INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder, with resting tremor, rigidity, bradykinesia and postural instability considered its cardinal symptoms (Jankovic, 2008). However, various non-motor symptoms are common, and greatly impact the quality of life of PD patients (Barone et al., 2009). Cognitive impairments in executive functioning (EF), memory and visuospatial abilities are common in early stage patients (Bosboom, Stoffers, & Wolters, 2004) leading to mild cognitive impairment (MCI) in 25% of patients (Aarsland et al., 2010). Moreover, after 20 years of PD, 83% of patients regress into PD related dementia (PDD) (Hely, Reid, Adena, Halliday, & Morris, 2008). Additionally, psychiatric symptoms including depression, anxiety, impulse control disorders and hallucinations are common in PD (de la Riva, Smith, Xie, & Weintraub, 2014). Considering this wide range of possible symptoms and high interindividual variation in their occurrence, PD is highly heterogeneous (Foltynie, Brayne, & Barker, 2002). Previous research distinguished various clinical subtypes (Lewis et al., 2005; van Rooden et al., 2010), raising the question whether underlying disease pathologies differ between these subtypes. Consequently, Levodopa – the standard pharmacological treatment for PD patients (Mercuri & Bernardi, 2005) – may not be universally effective for the variety of PD symptoms.

Several pathological processes have been related to PD. An important diagnostic hallmark is the degeneration of dopaminergic neurons in the substantia nigra pars compacta. This leads to dopamine deficiency within the striatum, particularly in the putamen and caudate nucleus (Dexter & Jenner, 2013). The consequence is altered functioning of three cortico-striato-thalamocortical (CSTC) circuits (Vriend et al., 2014). These circuits incorporate connections between the striatum, thalamus and cortical regions and are implicated in goal-directed behaviour (Groenewegen & Uylings, 2010). The motor, associative and limbic CSTC circuits are implicated in motor activity, cognition (specifically

EF) and emotion, respectively (Groenewegen & Uylings, 2010). Their functioning is dependent on sufficient dopamine availability (DeLong & Wichmann, 2007). For a simplified diagram of the involved brain structures, see Figure 1.

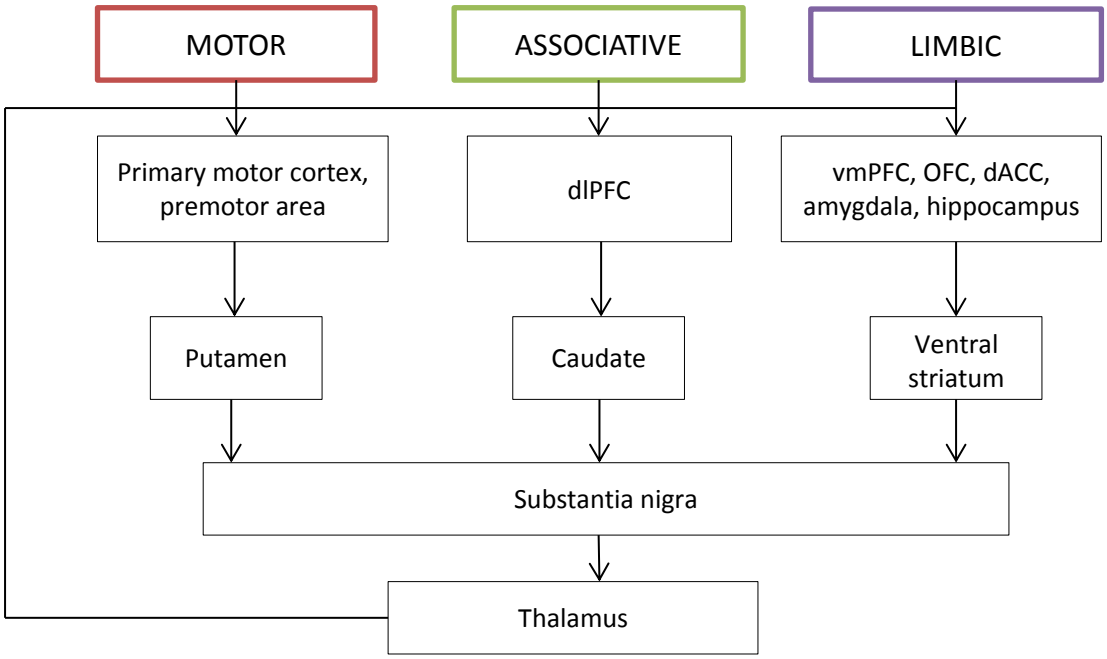

Figure 1. Simplified schematic representation of the cortico-striato-thalamocortical circuits. Modified from (Kaasinen & Rinne, 2002). Abbreviatons: dlPFC = dorsolateral prefrontal cortex, vmPFC = ventromedial prefrontal cortex, OFC = orbitofrontal cortex, dACC = dorsal anterior cingulate cortex.

Alterations in the CSTC circuits due to dopaminergic depletion have been linked to several PD symptoms. As the involvement of the putamen in the motor circuit suggests, a relationship between motor symptoms and dopaminergic depletion in the striatum, but most notably in the putamen, has been established (Garnett, Nahmias, & Firnau, 1984; Nahmias, Garnett, Firnau, & Lang, 1985). Subsequently, dopaminergic therapy effectively decreases these motor symptoms, at least during the early stages of treatment (LeWitt, 2009; Nagatsua & Sawadab, 2009; Horstink et al., 2006). Similarly, dopaminergic deficiency in the caudate has been associated with impaired EF and working memory (WM) (Bruck et al., 2001; Marie et al., 1999; Rinne et al., 2000), which may be reversed with dopaminergic therapy (Chaudhuri & Schapira, 2009; Cools, Stefanova, Barker, Robbins, & Owen, 2002).

Furthermore, the caudate has been suggested to relate to psychiatric symptoms, with decreased dopamine relating to PD depression, and increased dopamine to PD impulse control disorders (Vriend et al., 2014). Considering this broad involvement of the CSTC circuits in PD symptomology, one explanation for the heterogeneity in symptoms might be differences in the pattern and extent of damage to the circuits between patients (Lewis & Barker, 2009). However, the effects of striatal dopamine depletion cannot fully account for the broad range of PD symptoms. For instance, dopaminergic treatment may worsen memory performance (Miah, Olde Dubbelink, Stoffers, Deijen, & Berendse, 2012).

An additional pathological characteristic in PD could be grey matter (GM) atrophy in various brain structures (Ibarretxe-Bilbao, Junque, Marti, & Tolosa, 2011). GM loss has been reported in PD, most consistently in the hippocampus (Camicioli et al., 2003; Tam, Burton, McKeith, Burn, & O'Brien, 2005; Laakso et al., 1996). Hippocampal atrophy has been related to impaired memory performance in early stage (Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Beyer et al., 2013) as well as demented PD patients (Laakso et al., 1996; Beyer & Aarsland, 2008; Tam et al., 2005). Additionally, decreased prefrontal cortex (PFC) volume was found in early stage, non-demented patients (Bruck et al., 2004; Tessa et al., 2014) as well as patients with PD-MCI (Danti et al., 2015) and PDD (Melzer et al., 2012). This is interesting, considering the crucial role of the PFC in EF (Alvarez & Emory, 2006). The dorsolateral PFC (dlPFC) has been linked most consistently to EF - specifically to WM (Alvarez & Emory, 2006; Kane & Engle, 2002) - and PD atrophy in this region was associated with decreased nonverbal intelligence (Nagano-Saito et al., 2004). The inferior frontal gyrus (IFG) and insula – involved in inhibition (Cieslik, Mueller, Eickhoff, Langner, & Eickhoff, 2015) – show GM loss in non-demented PD patients (Nagano-Saito et al., 2005; Pereira et al., 2009) and PD-MCI and PDD patients (Danti et al., 2015). For an overview of atrophy studies in PD, see table 1. In conclusion, some, but not all patients seem to be subject

to GM atrophy. Differences in atrophy between patients might provide another explanation for non-motor symptom heterogeneity.

Table 1

Overview of Studies into Atrophy in Parkinson's Disease

Brain structure	**Finding**	**Study**
Hippocampus	Atrophy progresses from PD to PD-MCI patients	Laakso et al., 1996; Camicioli et al., 2003
	Similar extent of atrophy in PD and PDD patients	Tam et al., 2005
	Atrophy in early stage PD relates to impaired memory	Bruck et al., 2004; Beyer et al., 2013
PFC	No frontal atrophy in PD	Worker et al., 2014; Camicioli et al., 2003
	Decreased PFC volume in early stage PD patients	Bruck et al., 2004; Tessa et al., 2014
	Frontal thinning in PD-MCI, but not in PD patients	Danti et al., 2015; Melzer et al., 2012
dlPFC	Atrophy in the dlPFC in PD is associated with decreased nonverbal intelligence	Nagano-Saito et al., 2004
IFG	Atrophy in PD patients	Nagano-Saito et al., 2005; Pereira et al., 2009
	Atrophy in PDD	Beyer & Aarsland, 2008
Insula	Atrophy of the left insula in PD-MCI and PDD patients	Danti et al., 2015
	Atrophy of the left insula in PDD patients	Beyer & Aarsland, 2008

Abbreviations: PD = Parkinson's disease, MCI = mild cognitive impairment, PDD = Parkinson's disease related dementia; PFC = prefrontal cortex, dlPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus.

In sum, previous findings suggest that different PD symptoms relate to different pathologies, including dysfunctional CSTC circuits and GM atrophy. One promising way to discover more about pathological heterogeneity is to build on previously found symptom-based PD subtypes. One recent study related subtypes with severe motor symptoms to lower

dopamine availability in the putamen, but failed to take into account cognitive functioning as a clinical characteristic, and GM atrophy as a pathological characteristic (Erro et al., 2016). Van Balkom et al. (2016) distinguished four patient clusters with differing clinical profiles. Cluster 1 (C1: young patients with mild symptoms) and Cluster 2 (C2: older patients with severe overall symptom severity) were hypothesized to represent the opposite ends of disease trajectory. Interestingly, patients in C3 and C4 were of the same age, but their symptoms differed. C3 was characterized by deficiencies in EF while motor symptoms were mild; C4 experienced verbal memory dysfunction and more severe motor symptoms. An overview of these patient groups can be found in Box 1. The differences in motor and cognitive symptoms between the two last mentioned subtypes suggest different underlying pathologies.

Box 1. Characteristics of the Four Patient Clusters (van Balkom et al., 2016).

Cluster 1

C1 consisted of relatively young patients, with a young age at disease onset. These patients experienced low motor symptoms, were cognitively unimpaired and their psychiatric symptoms (anxiety and depression) were below clinical threshold.

Cluster 2

C1 consisted of relatively old patients, with a high age at disease onset. They had high symptom severity within all categories. Motor symptoms were severe, cognitive performances indicated MC, and psychiatric symptoms were well above clinical threshold.

Cluster 3

C3 consisted mainly of female patients, mean age 65 years. Patients had relatively low disease stage and low motor symptom severity. Neuropsychological tests indicated EF impairments. Psychiatric symptoms were above clinical threshold.

Cluster 4

C4 consisted mainly of male patients, mean age 65 years. Patients had relatively high disease stage, and motor symptoms were worse than in C1 and C3. EF was comparable with that of a healthy populations, but problems appeared in verbal memory. Psychiatric symptoms were above clinical threshold.

The current study is the first attempt to predict PD subtype by use of dopamine availability and GM volumes. In C3, we expect diminished dopamine in the caudate and atrophy of the dlPFC, IFG and insula to underlie their EF deficiencies. In C4, motor symptoms are expected to be caused by diminished dopamine in the putamen and verbal memory problems by hippocampal atrophy. Furthermore, we will explore relationships between dopamine availability and GM volumes on the one hand, and symptoms on the other, to validate earlier findings. Motor symptom severity is expected to relate negatively to dopamine availability in the putamen and EF is expected to relate positively to dopamine availability in the striatum. Furthermore, verbal memory capacity is expected to relate positively to hippocampal volume, and EF to relate positively to GM volume of the dlPFC, IFG and insula. Additional information regarding the underlying pathology of different symptoms in PD should give rise to alternative treatment strategies. There is a great need for the amelioration of PD non-motor symptoms. The recognition of pathological subtypes should ultimately lead to better disease course prognosis and personalized treatment.

METHODS

Participants

Data from 135 PD patients were extracted from a database containing extensive measurements regarding motor symptoms, cognitive functioning and neurological assessment of PD patients. All patients were referred to the outpatient clinic for movement disorders of the VU University Medical Center between May 2008 and June 2014 for routine clinical practice. Informed consent was obtained to use their clinical data for scientific purposes. Patients were diagnosed with idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank criteria (Hughes, Daniel, Kilford, & Lees, 1992) by movement disorder specialists. They were divided into four patient clusters of motor, cognitive and neuropsychiatric symptoms (N_{C1}=56, N_{C2}=6, N_{C3}=27, N_{C4}=46) according to a previous cluster analysis within the same patient sample (van Balkom et al., 2016). A detailed description of these clusters can be found in box 1. In short, the characteristics of the clusters were: C1: young, relatively unimpaired patients, C2: older patients, with overall high symptom severity, C3: deficiencies in EF, mild motor symptoms, C4: verbal memory deficiencies, severe motor symptoms. For a subset of these patients, a MRI or/and DaT SPECT scan was made for diagnostic purposes. These patients were selected for inclusion. The amount of patients included differed between the analyses, depending on the availability of imaging data. The samples are specified per analysis under *Results.*

Measurements

Structural imaging. 93 patients underwent a T1-weighted magnetic resonance imaging (MRI) scan. Scans were obtained from a GE Signa HDxt 3.0-Tesla MRI-scanner with an 8-channel head coil, using a sagittal 3-dimensional gradient-echo T1-weighted sequence (256 x 256 matrix; field of view = 25cm; slice thickness = 1mm; voxel size = 1 x

0.98 x 0.98mm; TR = 7.8ms; TE = 3.0ms; view angle = 12°) (Gerrits et al., 2016). The brain was segmented into cortical and subcortical regions, based on the Desikan-Killiany atlas, using Freesurfer Software v.5.3.0 (http://surfer.nmr.mgh.harvard.edu). An outlier analysis was performed on all structures to identify possible inaccurate segmentation, based on a deviate size of the regions. We performed a visual quality check (QC) on our ROIs (i.e. hippocampus, dlPFC, IFG and insula) to ensure accurate segmentation, with special attention devoted to outlier regions. For the cortical areas, this was performed on models of the surface area (SA) and cortical thickness (CT), see Figure 2. All areas that were excluded based on its surface area, were also excluded for analysis of cortical thickness and vice versa. The dlPFC was composed of the caudal middle frontal and rostral middle frontal (Kikinis et al., 2010; Desikan et al., 2006) and the IFG of the pars opercularis, pars orbitalis and pars triangularis (Desikan et al., 2006). The final outcome measures were the CT in mm, and SA and volume of the subcortical ROI (i.e. hippocampus) in mm².

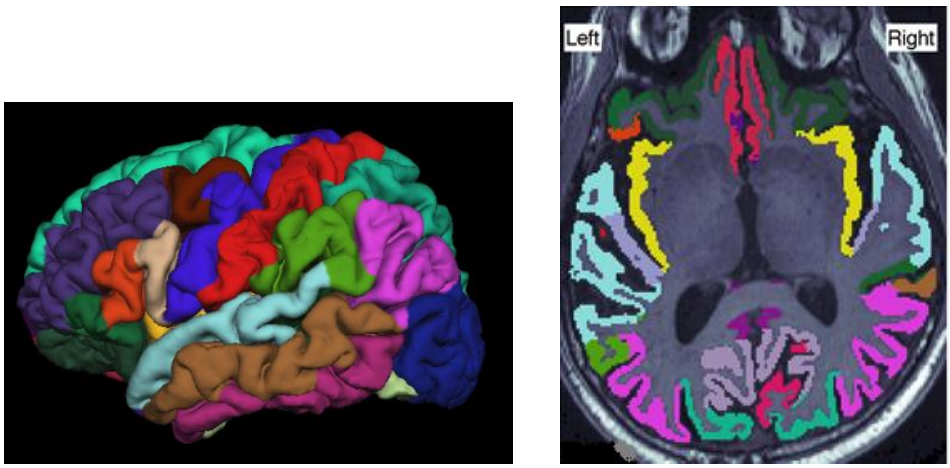

Figure 2. Models of cortical surface area (left) and cortical thickness (right), provided by Freesurfer software. These models allowed for the performed visual quality check.

Dopaminergic imaging. Dopamine transporter (DaT) single-photon emission computed tomography (SPECT) scans with FP-CIT SPECT tracer were achieved from 125 patients. FP-CIT is known to bind at presynaptic dopamine receptors and consequently

provides a measurement of the density of dopaminergic neurons within the caudate and putamen (Vriend et al., 2014b). FP-CIT was injected intravenously with a mean dose of 185MBq, three hours before the scan was accomplished (Vriend et al., 2014b). DaT SPECT scans were normalized with the use of a standardized MRI brain to allow for interindividual comparison. The QC consisted of reorienting the hair cross, to ensure that the left and right regions were aligned. The cerebellum is known to have minimal dopamine receptors and served as reference region (Scherfler et al., 2007). Therefore, we could control for possible non-specific binding within the ROIs (i.e. head of the caudate and putamen). Typical examples of DaT SPECT scans for a healthy subject and PD patient can be found in Figure 3.

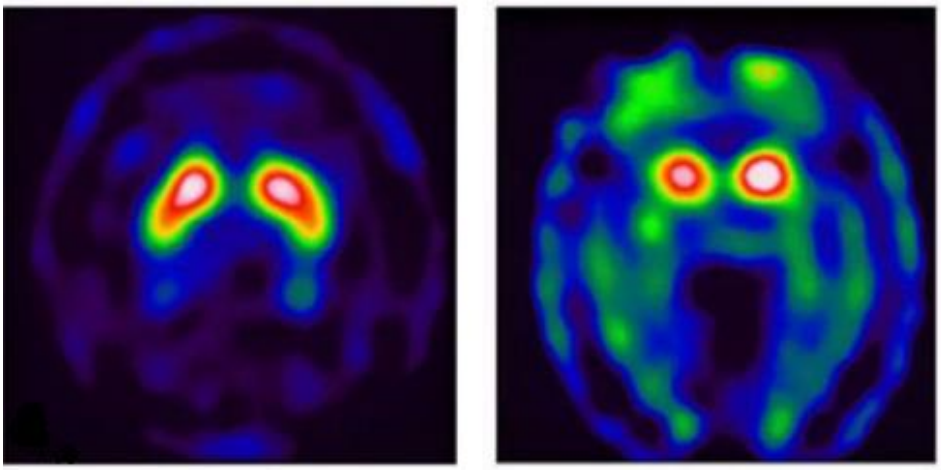

Figure 3. Typical DaT SPECT scan for healthy subject (left) and PD patient (right). Reduced dopaminergic binding in the bilateral putamen is visible in the PD patient. Derived from Huang, Yen & Lu (2012).

Cognitive functioning. In the current study, we included neuropsychological measurements on which patients in C3 and C4 scored differently. These were measurements of executive functioning, working memory and verbal memory (Van Balkom et al., 2016). The Stroop task completion time for card III minus the completion time for card II, served as assessment of interference susceptibility (Hammes, 1971). The Trail Making Task (TMT) completion time for task B minus completion time for task A, assessed cognitive flexibility (Reitan & Wolfson, 1985). The total score on the backwards subtask of the Digit Span Task

of the WAIS-III assessed working memory (Wechsler, 2000). Lastly, to assess verbal episodic memory, the total delayed free recall score of the Dutch version of the Rey Auditory Verbal Learning Test (15 Words Task) was used (Saan & Deelman, 1986). For a description and illustration of the neuropsychological tasks, see Appendix 1.

Motor symptoms & disease stage. Motor symptom severity was assessed with section three of the Unified Parkinson's Disease Rating Scale (UPDRS-III) (Fahn & Elton, 1987). This constitutes clinical assessment of motor symptoms including rigidity, tremor, postural instability and bradykinesia. A higher score indicates more, or more severe motor symptoms. Disease stage was assessed by the Hoehn & Yahr scale (Hoehn & Yahr, 1967*)*. This scale describes eight disease stages based on the present motor symptoms, ranging from 'no signs of disease' to 'bound to wheelchair or bed unless helped'. As such, a higher score indicates a later disease stage.

Psychiatric symptoms. Beck Depression Inventory (BDI) has been used to measure symptoms of depression (Beck, Ward, Mendelson, Mock & Erbaugh, 1961). We considered a threshold of 14-15 as clinically relevant symptoms (Visser, Leentjens, Marinus, Stiggelbout, & van Hilten, 2006). For the assessment of anxiety symptoms, the Beck Anxiety Inventory (BAI) (Beck, Brown, Epstein & Steer, 1988) was administered, with a threshold of 12-13 for clinically relevant symptoms (Leentjens et al., 2011). An overview of all measurement instruments is provided in Table 2.

Table 2

Measurement Instruments

Structural imaging	T1-weighted magnetic resonance imaging (MRI) scan
Dopaminergic imaging	Dopamine transporter (DaT) single-photon emission computed tomography (SPECT) scan
Disease stage	Hoehn & Jahr Scale
Motor symptoms	Unified Parkinson's Disease Rating Scale-III
Cognitive functioning	
Executive functioning	Stroop card III **|** card II
	TMT part B **|** part A
Working memory	Digit Span backwards
Verbal Episodic Memory	15 Word Task delayed free recall
Psychiatric symptoms	
Depression	Beck Depression Inventory
Anxiety	Beck Anxiety Inventory

Statistical Analyses

ROI volumes. The equations to arrive at the corrected, bilateral mean ROI volumes are listed in Box 2. If an analysis was conducted using the left and right ROI volumes separately, these were divided by the intracranial volume separately.

Box 2. Equations for Corrected ROI Volumes.

The mean volumes of the caudal middle frontal (CMF), rostral middle frontal (RMF), pars opercularis (POP), pars orbitalis (POR) and pars triangularis (PT) were calculated as follows:

$$(1) \quad M\ volume = \left\{\frac{(\text{left SA} * \text{left CT})}{2}\right\} + \left\{\frac{(right\ SA * right\ CT)}{2}\right\}$$

The mean hippocampal and insular volume were calculated similarly:

$$(2) \quad)\ M\ volume = \frac{(\text{left volume} + \text{right volume})}{2}$$

Next, the mean volumes of the CMF and RMF were summed to arrive at dorsolateral prefrontal cortex (dlPFC) volume. Similarly, the POP, POR and PT were summed for the inferior frontal gyrus IFG). Lastly, mean volumes of the dlPFC, IFG, insula and hippocampus were divided by their individual intracranial volume (ICV), to correct for interindividual differences.

Abbreviations: M = Mean, SA = surface area, CT = cortical thickness

Dopamine binding ratios. The dopamine availability within the head of the caudate and putamen were corrected for nonspecific binding by use of the FP-CIT binding within the cerebellum. The specific to nonspecific binding ratio was calculated with the following equation:

$$(3)\ Specific\ binding\ ratio = \frac{BR\ ROI - BR\ REF}{BR\ REF}$$

Abbreviations: BR = binding ratio, ROI = region of interest, REF = reference region (i.e., cerebellum).

Clinical symptoms. Neuropsychological test results were corrected for education level (Digit span backwards) or, if necessary, for age, gender and education level (Stroop, TMT, 15WT). Test scores were converted to T-scores, which have a mean of T = 50 and standard deviation of SD = 10, using the Dutch norms of Schmand, Houx and De Koning (2012). The total score of the BDI and BAI served as psychiatric outcome measures. Data from these questionnaires were imputed if 1/6 or less of the items were missing.

Detection of outliers and skewed distributions. The following statistical analyses have been performed in IBM SPSS Statistics 22 (IBM Corp., 2013). Since the samples differed between the analyses, an outlier screening and investigation of the distributions were performed for each sample. A score of 2.2 × interquartile range (IQR) beneath the 25th percentile or above the 75th percentile was considered an outlier. Normality of distributions was tested with a Kolmogorov-Smirnov test and visual inspection.

Linear Discriminant Analysis (LDA) with clinical predictors. The LDA with clinical predictors of the original study (Van Balkom et al., 2016) was replicated in the current sample. Due to a small sample size (N < 10), C2 was excluded (Hair, Black, Babin & Anderson, 2010). The included predictor variables were the z-scores of the following measurements: UPDRS-III, BAI, DS backwards, 15WT delayed recall, TMT part B | A and Stroop Card III |II. The BAI was normally distributed after a square root transformation. The

unequal cluster sizes were corrected for by adjustment of the prior classification probabilities.

Linear Discriminant Analysis with imaging predictors. A LDA was conducted to assess whether z-scores of volumes of the dlPFC, IFG, insula and hippocampi and dopamine BR in the caudate and putamen can predict cluster membership. The assumption of homogeneous variances within the clusters was tested with use of Levene's test. For all predictor variables, the variances were equal for C1, C3 and C4 with $\alpha = .01$. Furthermore, the equality of the variance-covariance matrices between the groups was ensured by Box's M. Spearman correlations were conducted to assess the relationships amongst the predictor variables. The dopamine BR within the caudate and putamen too highly related to include both, $r = .94$, $p < .001$ (Evans, 1996). To still allow our data to predict motor symptom severity, we chose to maintain the dopamine BR within the putamen. To our knowledge, this study is the first to use imaging variables to predict PD phenotype, so a stepwise method was appropriate (Hair, Black, Babin & Anderson, 2010). In order to maximize the use of the available data, the Mahalanobis D2 method was used (Hair et al., 2010). The unequal cluster sizes were corrected for by adjustment of the prior classification probabilities. A two-sided test with $\alpha < .05$ was conducted.

Correlations. Two-sided correlations were conducted to investigate if GM volume and dopamine BR within the mentioned ROIs are related to cognitive functioning and motor symptoms. Pearson correlations were conducted for those variables with a normal, and Kendall's tau correlations for those with a skewed distribution. We adjusted the α of the correlations that included a volumetric measure for multiple comparisons and mutual correlations (SISA; http://www.quantitativeskills.com/sisa/calculations/bonfer.htm), resulting in a critical value of $\alpha < .013$ (mutual correlation coefficient: .26, 6 ROIs). Since we used only one ROI to assess dopamine BR, the critical value for this correlation was $\alpha < .05$.

Post hoc testing. To assess whether our three clusters differed on the imaging variables, ANOVAs were conducted. To correct for multiple comparisons within unequal sample sizes, we used Gabriel's pairwise test procedure. We investigated whether taking a mean bilateral measurement of the volume of our ROIs might have caused us to overlook any relationship between clinical characteristics and imaging variables, by conducting correlations with left and right ROIs separately. Furthermore, we conducted correlations between the dopamine BR in the caudate and the BAI. Pearson correlations were conducted for those variables with a normal, and Kendall's tau correlations for those with a skewed distribution. The correlations that included a volumetric measure were corrected for multiple comparisons and mutual correlations (SISA), resulting in a critical value of $\alpha < .013$ (mutual correlation coefficient: .34, 6 ROIs). After correction for the correlations that included a dopaminergic BR measures, (mutual correlation coefficient: .78, 4 ROIs), the critical value resulted in $\alpha < .037$.

Lastly, a LDA was conducted with the ROIs of the right hemisphere only, which showed the strongest correlation with the clinical variables. Right IFG volume correlated too highly with right hippocampal volume to include both ($r > .6$; Evans, 1996). We chose to include the right hippocampus, because it is the only measure we expected to relate to verbal episodic memory. The Mahalanobis D2 method was used, with correction for the unequal cluster sizes.

RESULTS

Demographic and descriptive characteristics

The final sample consisted of 135 PD patients (age *M* = 63.3, age *SD* = 10.1 , female % = 36.3, H&Y median = 2). The patients were divided into the four subtypes, according to Van Balkom et al. (2016), N_{C1}=56, N_{C2}=6, N_{C3}=27, N_{C4}=46. Only the patients with both a MRI scan and DaT SPECT were included for the linear discriminant analyses (LDAs). Patients with any missing values were excluded from the LDAs. The quality check of the cortical areas led to the exclusion of eleven patients. In addition, one participant was excluded after the subcortical quality check. This exclusion process is depicted in Figure 4. The demographics of the final LDA sample, categorized by cluster, can be found in Table 3.

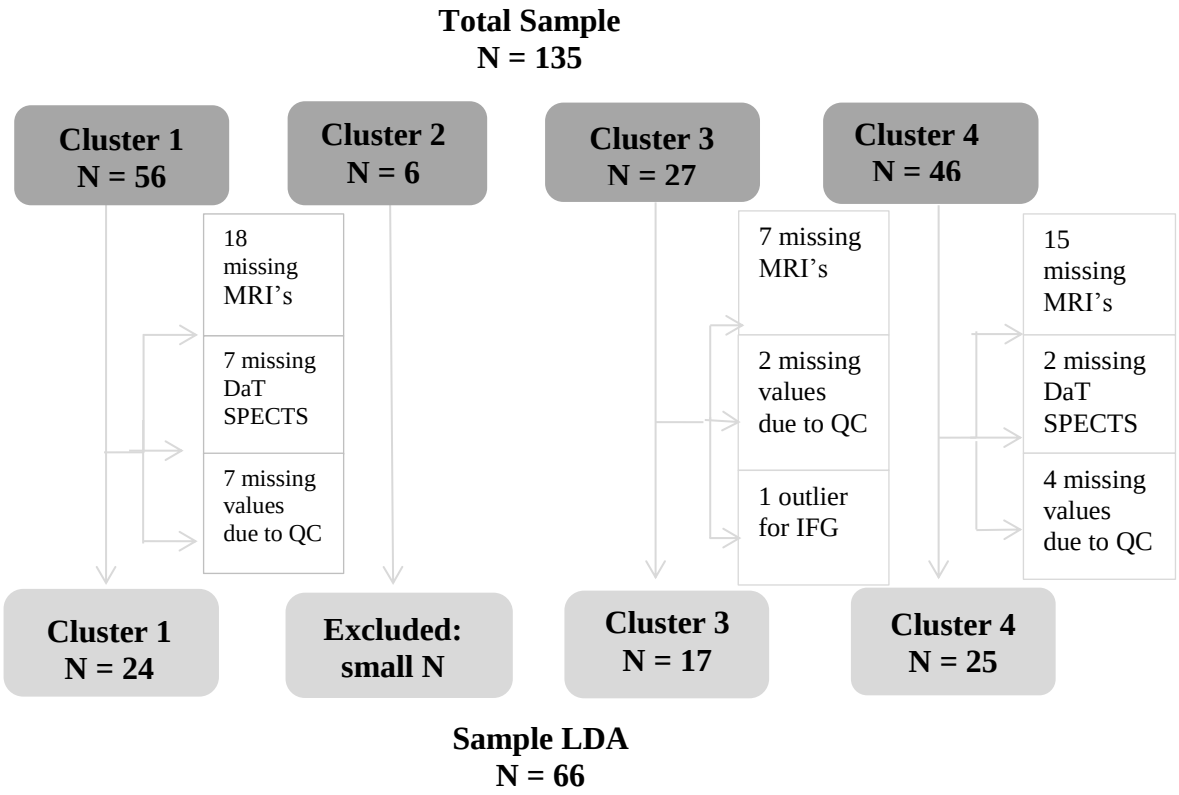

Figure 4. Flowchart of the Final Total Sample (upper part) and the Final LDA Sample (lower part).

Table 3

Mean (SD), Median (range) or Frequency of Descriptive Characteristics, Categorized by Cluster.

Descriptive characteristic (N = 66)	**C1** (N = 24)	**C3** (N = 17)	**C4** (N = 25)
Age, mean years (*SD*)	57.5 (10.3)	65.8 (8.7)	65.7 (9.3)
Age of disease onset, mean years (*SD*)	54.7 (11.3)	61.5 (9.2)	62.1 (9.2)
Female, N (*%*)	29.2.%	70.6%	16%
Hoehn & Yahr disease stage, median (*range*)	2 (0-3)	2 (1-3)	2 (2-3)
Education level*, median (*range*)	6 (3-7)	5 (3-7)	6 (3-7)
Elementary school or lower (<6 years), frequency (%)	0 (0)	0 (0)	0 (0)
Elementary/middle school finished (6 years)	0 (0)	0 (0)	0 (0)
Junior high school (7-8 years)	1 (4.2)	2 (11.8)	3 (12)
Senior middle/high school (9 years)	1 (4.2)	5 (29.4)	4 (16)
First year high school (10 years)	6 (25)	4 (23.5)	5 (20)
Second year high school/high school finished/applied sciences (11-12 years)	7 (29.2)	4 (23.5)	4 (16)
University	9 (37.5)	2 (11.8)	9 (36)

* Dutch Verhage Classification (Verhage, 1964)

Part I – Linear Discriminant Analyses

LDA with Clinical Predictors

The original LDA with clinical characteristics as predictor variables (see Appendix II: C3 and C4 were originally discriminated by the TMT part B|A, Stroop III|II and DS backwards) was replicated in the current, smaller sample (*N* = 66, *age M* = 62.8, *SD* = 10.3, *female %* = 34.8, *H & Y median* = 1). An overview of the clinical characteristics of each cluster is shown in Appendix III. The LDA resulted in two discriminant functions. Function 1 discriminated C3 from C4. Within this function, the most important discriminating variable was the UPDRS-III (*r* = .83), followed by the TMT (*r* = .3). Function 2 discriminated C1 from both C3 and C4. The most important discriminative variable within this function was the BAI (*r* = .75). Moreover, the TMT part B|A (*r* = -.69) and the UPDRS-III (*r* = .55) discriminated these clusters. The Stroop III|II, DS Backwards and 15WT delayed recall did not contribute to the

LDA. The two discriminative functions and the contribution of the individual variables have been illustrated in Figure 5. The first function explained 65.7% of the variance, canonical R^2 = .71 and the second one explained 34.3% of the variance, canonical R^2 = .62. Combined, the functions significantly discriminated the clusters, Λ = .28, $\chi^2(6)$ = 79.73, p < .001. Removing the first function, the second function still significantly discriminated the clusters, Λ = .61, $\chi^2(2)$ = 30.43, p < .001. By use of these functions, 75.8% of the participants could be classified correctly. To conclude, C3 and C4 were originally discriminated by TMT part B|A, Stroop III|II and DS backwards and currently by UPDRS-III, TMT B|A and the BAI.

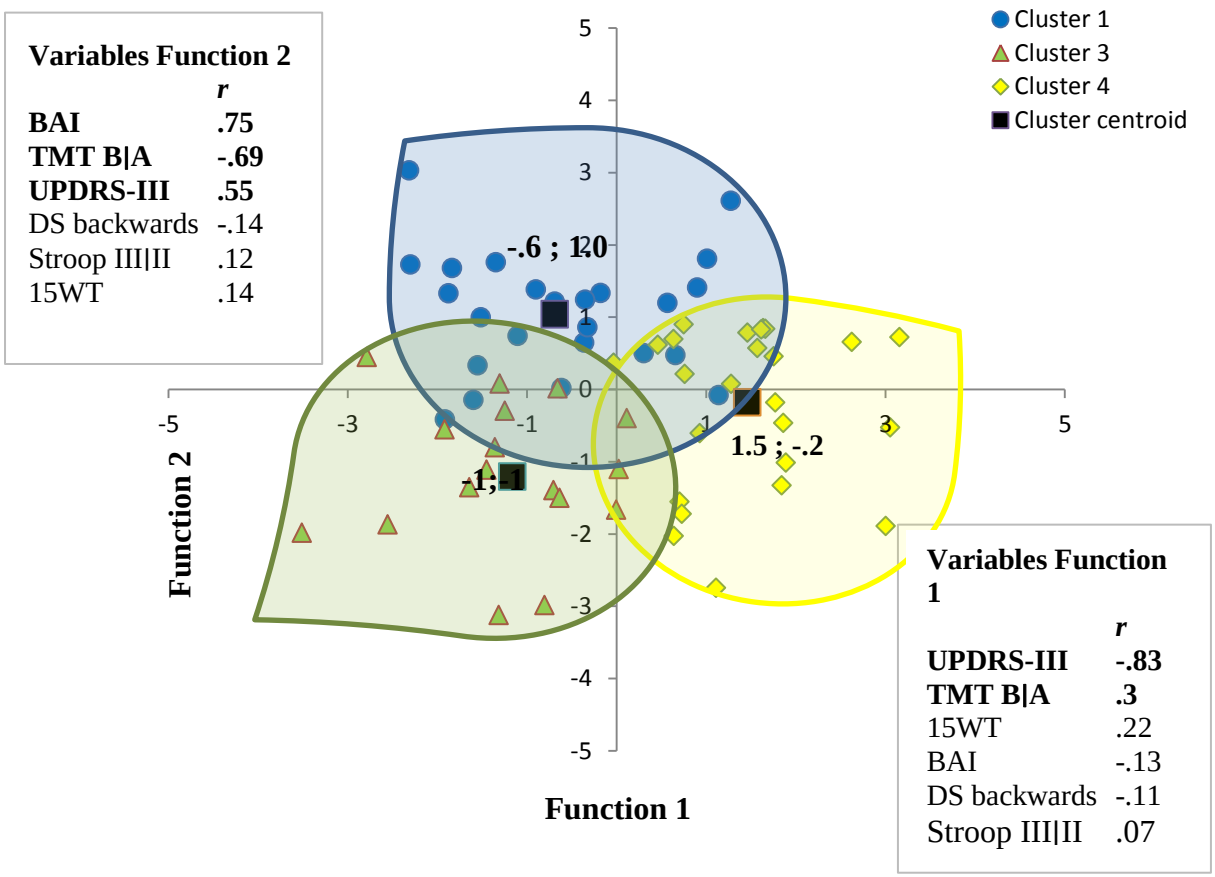

Figure 5. Discriminating Functions 1 and 2 in the LDA with Clinical Predictors Between Three Clusters, with the Cluster Centroids for each Cluster. The Boxes represent the Correlation between the Clinical Variables and the Discriminating Functions. Abbreviations: BAI = Beck Anxiety Inventory, TMT = Trail Making Task, UPDRS-III = Unified Parkinson's Disease Rating Scale – III, DS = Digit Span, 15WT = 15 Words Test.

LDA with neuroimaging predictors

A stepwise LDA was conducted to assess which of the imaging variables contributed to the discrimination of C1, C3 and C4. The sample consisted of 66 PD patients (age M = 62.8, SD = 10.3, female % = 34.8, H & Y median = 1). An overview of the mean values of the imaging characteristics of the clusters is provided in Table 4.

Table 4

Mean (SD) of Imaging Characteristics, Categorized by Cluster

Imaging variables		**Cluster 1 (N = 24)**	**Cluster 3 (N = 17)**	**Cluster 4 (N = 25)**
Volume dlPFC	in mm^2	1.21E-02 (1.02E-03)	1.16E-02 (6.50E-04)	1.18E-02 (8.36E-04)
Volume IFG	in mm^2	5.57E-03 (4.78E-04)	5.42E-03 (5.38E-04)	5.41E-03 (5.21E-04)
Volume insula	in mm^2	4.23E-03 (2.96E-04)	4.08E-03 (3.56E-04)	4.31E-03 (2.62E-04)
Volume hippocampus	in mm^2	2.70E-03 (2.64E-04)	2.53E-03 (3.42E-04)	2.54E-03 (3.12E-04)
Dopamine BR putamen		1.92E+00 (3.47E-01)	1.69E+00 (4.65E-01)	1.95E+00(2.17E-01)

Abbreviations: dlPFC = dorsolateral prefrontal cortex, IFG = inferior frontal gyrus, BR = binding ratio.

The LDA revealed no discriminant functions that were able to significantly differentiate between the clusters. As such, none of the variables were identified as significant predictors. By default, the minimal *F*-value required for entering the model was 3.84. An overview of the *F*-values of each hypothesized predictor is provided in Table 5. An LDA including the dopamine BR within only the posterior part of the putamen led to similar results.

Table 5

F-values of the Hypothesized Predictors

Predictor variable	**F-value**
Volume dlPFC	1.613
Volume IFG	.739
Volume insula	2.958
Volume hippocampus	2.285
Dopamine BR putamen	3.213

Abbreviations: dlPFC = dorsolateral prefrontal cortex, IFG = inferior frontal gyrus, BR = binding ratio.

Part II – Correlations

Correlations between GM volume and dopamine availability within the mentioned ROIs on the one hand and clinical characteristics on the other hand were conducted within the entire sample of 135 PD patients. The samples varied per conducted correlation, depending on the availability of data and the outcome of the quality check and outlier screening. The exact samples and correlations are shown in Table 6. Hippocampal volume correlated significantly with the 15WT delayed recall, $r = .28$, $p = .006$ (N = 92), see Figure 6. These correlations show the expected positive correlation between hippocampal volume and 15WT, but not those between frontal volumes and EF measures.

Table 6

Pearson's (r) or Kendall's Tau correlations (τ) between Clinical Characteristics and Imaging Variables

	15WT	**TMT**	**Stroop**	**DS bw**	**UPDRS-III**
DA BR putamen					$\tau = -.04$
(N = 125)					$p = .50$
Volume insula		$\tau = .13$ (N = 83)	$r = .003$	$\tau = -.04$	
(Stroop, DS bw: N = 86)		$p = .09$	$p = .98$	$p = .60$	
Volume dlPFC		$\tau = .16$ (N = 79)	$r = .15$	$\tau = .11$	
(Stroop, DS bw: N = 81)		$p = .04$	$p = .17$	$p = .17$	
Volume IFG		$\tau = .11$(N = 83)	$\tau = .05$	$\tau = .11$	
(Stroop, DS bw: N = 85)		$p = .14$	$p = .54$	$p = .16$	
Volume hippocampi	$r = .28^{*}$				
(N = 92)	$p = .006$				

* Significant at the $\alpha < .01$ level

Abbreviations: 15WT = 15 Word Task, TMT = Trail Making Task part B | A, DS bw = Digit Span backward, UPDRS-III = Unified Parkinson's Disease Rating Scale – III, DA = dopamine, BR = binding ratio, dlPFC = dorsolateral prefrontal cortex, IFG = inferior frontal gyrus.

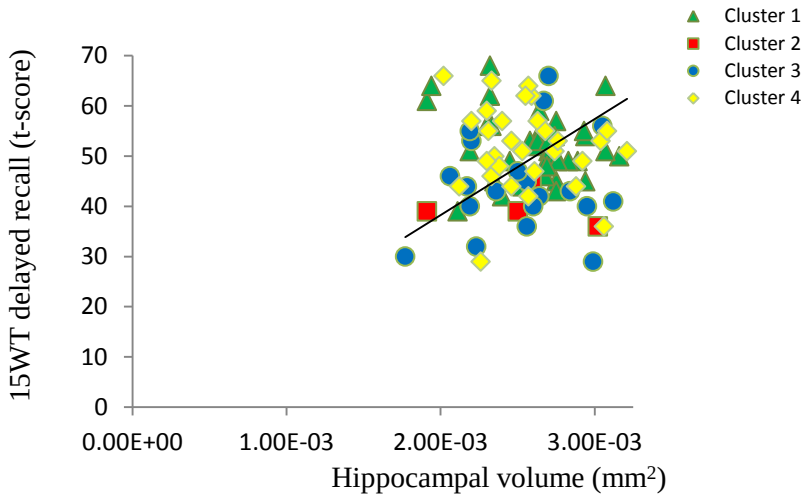

Figure 6. Relationship between hippocampal volume and 15WT delayed recall.

Part III – Post hoc testing

Analyses of Variance

ANOVAs with cluster membership (C1, C3, C4) as factor were conducted to explore whether the clusters differed on each of the five imaging variables (N = 66, age M = 62.8, SD = 10.3, female % = 34.8, H & Y median = 1). No significant volume differences were observed for dlPFC ($F(2, 63) = 1.61$, $p = .21$), IFG ($F(2, 63) = .74$, $p = .48$), insula $F(2, 63) = 2.96$, $p = .06$, and hippocampus ($F(2, 63) = 2.29$, $p = .11$), nor in the dopamine BR within the putamen, *Welch's* $F(2, 35) = 2.27$, $p = .12$. The differences in insular volume between C3 ($M = -.46$, $SD = 1.15$) and C4 ($M = .28$, $SD = .85$) revealed a trend towards significance, detected with Gabriel's pairwise post hoc test procedure. This is depicted in Appendix IV. Hence, no differences existed in neuroimaging measures between the patient clusters.

Correlations between clinical characteristics and left and right ROIs separately

The correlations between clinical characteristics and ROIs were conducted again with left and right ROIs separately within the entire sample of 135 PD patients. Again, the exact samples varied per conducted correlation. Considering the increased discriminative value of the BAI

within the current sample, the caudal dopamine BR has been included to investigate possible relationships with the BAI. With the left and right hippocampus separated, only the right correlated significantly with the 15WT, $r = .31$, $p < .003$, N = 92. For an illustration of this relationship and an overview of the conducted correlations, see Appendix V and VI. This analysis showed that the relationship between 15WT and hippocampal volume was restricted to the right hemisphere and that no other relationships existed when hemispheres were assessed separately.

LDA with right neuroimaging predictors

A final LDA was conducted with the right DLPFC, right insula, right hippocampus and right putamen dopamine BR as predictor variables (N = 66, age M = 62.8, SD = 10.3, female % = 34.8, H & Y median = 1). An overview of the mean values of the predictor variables per cluster is provided in Appendix VII. The LDA revealed that the right insular volume could discriminate C1 and C4 from C3. This predictor explained 11% of the variance, canonical R^2= .33, thereby significantly differentiating C3 from C4, $\Lambda = .89$, $\chi^2(2) = 7.25$, $p < .05$. With the right insular volume, 45.5% of the participants could be classified correctly. Thus, right insular volume contributed to patient cluster discrimination.

DISCUSSION

The objective of the current study was to predict PD subtypes by use of dopamine availability in the striatum and GM volumes. The heterogeneity in PD symptomology suggest different underlying pathologies. This might be a consequence of the disruption of the CSTC circuits on the one hand and GM loss on the other hand (Ibarretxe-Bilbao, Junque, Marti, & Tolosa, 2011). We were mainly interested in two clusters with patients of similar ages but different clinical profiles. C3 consisted of patients with EF impairments, while patients in C4 experienced more severe motor symptoms and verbal memory impairments.

First, we replicated the LDA of Van Balkom et al. (2016) to examine whether our subsamples of the original patient groups were clinically representative of the original ones. Originally, C3 and C4 were distinguished by cognitive flexibility, inhibition and WM. Our subsets were distinguished by cognitive flexibility, motor symptoms and anxiety. Hence, only cognitive flexibility remained a discriminating EF factor, while motor symptoms and anxiety were of increased importance. In answer to the main research question, bilateral measures of dopamine availability in the putamen and volumes of the dlPFC, IFG, insula and hippocampus appeared unable to predict PD subtypes. Moreover, we found a positive relationship between bilateral hippocampal volume and verbal episodic memory, but failed to establish relationships between frontal volumes and EF.

A possible explanation for not finding any bilateral predictors might be that our chosen brain structures were based on the original discriminating symptoms, while these appeared slightly different in our subsample. Adding an anxiety related predictor, such as the amygdala (Davis, 1992), could be promising. Lower left amygdala volume has been related to increased anxiety in PD (Vriend et al., 2016). However, we did include predictors related to EF and motor functioning. According to EF, we could not include all frontal structures related to EF, considering the sensitivity to the sample size/amount of predictors ratio of our research

method (Hair, Black, Babin & Anderson, 2010. Two additional structures that contribute to EF are the anterior cingulate cortex (ACC) (MacDonald, Cohen, Stenger, & Carter, 2000), and the orbitofrontal cortex (OFC). Atrophy in PD has been reported in the ACC (Nagano-Saito et al., 2005) and impaired decision making was related to atrophy of the OFC (Ibarretxe-Bilbao et al., 2009). Interestingly, amongst others, the OFC has connections with the dlPFC, insula, hippocampus and caudate (Elliott, Dolan, & Frith, 2000), which have all been related to PD pathology.

According to motor symptoms, the lack of relationship with dopamine availability in the putamen seemed not due to differences in dopamine agonist or SSRI use between groups (Booij & Kemp, 2008) or the gender difference (Lavalaye, Booij, Reneman, Habraken, & van Royen, 2000; van Dyck et al., 1995). Furthermore, isolating the posterior putamen, which typically shows most extensive dopamine loss (Brooks et al., 1990), did not alter the results. An interesting possibility is that dopamine in the putamen might relate to hypokinesia and rigidity, but not to tremor (Spiegel et al., 2007; Rinne et al., 1999; Benamer et al., 2000). In the current study, we used an overall measure of motor symptom severity, possibly averaging out this relationship.

To investigate whether using bilateral measures canceled out the involvement of either left or right ROI, we subsequently conducted exploratory analyses for both hemispheres separately. Verbal episodic memory now appeared to relate only to right hippocampal volume. Overall, symptoms related stronger to the right, than to the left neuroimaging measures. In PD, motor symptoms usually relate to pathology of the contralateral hemisphere (Kim et al., 2014). Therefore, the stronger relationship of motor symptoms with dopamine in the right putamen might reflect the experience of symptom dominance on the left body side within our patient sample.

The lateralization of motor symptoms has been found to relate to the experience of

cognitive symptoms. Patients with predominantly right side motor symptoms (i.e. left hemisphere pathology) are susceptible to language-related deficits, including verbal memory (Verreyt, Nys, Santens, & Vingerhoets, 2011). Indeed, verbal memory deficits in PD have been related most consistently to left hippocampal atrophy (Bruck, Kurki, Kaasinen, Vahlberg, & Rinne, 2004; Camicioli et al., 2003; Bouchard et al., 2008). However, no relationship between motor symptom lateralization and EF has been established (Verreyt et al., 2011). Our results are similar to those of Pereira et al. (2014), who found that right cortical thinning preceded MCI, after which it spread to the left hemisphere. In healthy individuals, cognitive flexibility is related mostly to left, and inhibition mostly to right frontal activity (Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002; Vanderhasselt, De Raedt, & Baeken, 2009). Considering these previous findings, the stronger relationships we found between right hemisphere measures and verbal memory and cognitive flexibility are surprising.

Building on the finding that right hemisphere measures related most to symptoms, we explored whether neuroimaging measures of the right hemisphere alone could predict PD subtype. Now, right insular volume contributed to the discrimination of our patient groups, with a trend towards lower volume in C3, the group with EF deficiencies. This presumably does not reflect the fact that this group consisted mainly of women, in contrast to the other groups. In fact, previous research into a gender effect of brain structure size shows that the GM/white matter ratio is larger in women (Cosgrove, Mazure, & Staley, 2007). Research into insular volume specifically showed no gender difference when controlling for intracranial volume (Allen, Damasio, Grabowski, Bruss, & Zhang, 2003).

The role of the insula in human behaviour is broad, with a functional distinction between the posterior insula (PI), implicated in viscera-sensory and somatosensory awareness, and the anterior insula (AI), implicated in cognition and affection (Chang, Yarkoni, Khaw, &

Sanfey, 2013). The role of the AI in cognition provides an explanation for its discriminative value, since cognitive flexibility distinguished our patient groups. The AI has extensive connections with cortical and subcortical regions (Christopher, Koshimori, Lang, Criaud, & Strafella, 2014), allowing for its role to switch between networks required for EF in reaction to salient events (Menon & Uddin, 2010). Interestingly, considering our finding, this role of directing EF has been attributed mostly to the right AI (Sridharan, Levitin, & Menon, 2008). In PD, insular GM loss and dopamine availability have been reported and showed an association with EF (Burton, McKeith, Burn, Williams, & O'Brien, 2004; Beyer & Aarsland, 2008; Ramirez-Ruiz et al., 2005). Decreased dopamine in the insula has been suggested to lead to lowered interaction with cortical areas, thus disturbing its role as hub in a functional network (Christopher et al., 2014).

Our study has several strengths. Most notably, it is the first to combine dopamine availability and GM volumes in order to predict PD subtypes. Furthermore, earlier research focused mostly on pathology of motor, cognitive or psychiatric symptoms separately, whereas we combined these measures to arrive at a more complete clinical picture and its possible pathology. This is a new step towards personalized treatment. Moreover, our study encourages further investigation of insular involvement in PD's pathology, which is in line with the aim of another PD research group (Christopher et al., 2014).

Some limitations should be mentioned as well. Most notably, our sample size was small and this had several implications. First of all, low power may have prevented us to find any bilateral predictors, if present. Second, because of the small sample size, we were limited in the amount of predictors to include. Earlier research suggests the involvement of additional brain regions. Lastly, although we found a contribution of right insular volume to the discrimination of patient groups, it should be noted that this structure explained only a small proportion of the variance. This prevents us from drawing firm conclusions.

Future research should continue studying the pathology of PD heterogeneity within a larger patient group. The present study should be regarded as an exploratory one, offering ideas for additional explorations. Our finding of particular involvement of the right insula and the functional division of AI and PI calls for separate assessment of these structures. Moreover, considering the role of AI as embedded within a functional network, a promising new approach would be to use network imaging methods such as EEG or MEG. Possibly, disruptions in functional networks underlie cognitive deficits in PD. To achieve more information regarding atrophy, one could consider to conduct voxel-based morphometry to investigate differences in GM volume between patient groups as a first step. After all, many brain structures are implicated in this complex disease. Considering we did not find many of the expected relationships between volumetric measures and clinical characteristics, cortical thickness and surface area could be investigated separately. Gerrits et al. (2016) found that in PD, these measures relate differently to cognition.

Conclusions

Right insular volume contributed to the discrimination of two symptom-based Parkinson's disease patient groups. Executive functioning problems dominated in one group, verbal episodic memory problems and motor symptoms in the other. The directing role of the anterior insula in cognition might particularly contribute to their distinction. Our results call for further investigation of heterogeneity in Parkinson's disease pathology within larger patient groups, with special attention devoted to insular involvement. Network imaging could be a promising next step. We strive for moving away from standard treatments, taking into account symptom heterogeneity and differing underlying pathologies. Ultimately, personalized treatment should lead to decreased non-motor symptoms and a better quality of life.

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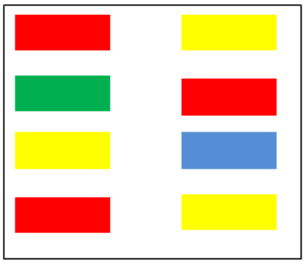
APPENDIX I Neuropsychological tasks

STROOP TASK

Card I

Rood	Geel
Groen	Blauw
Geel	Rood
Rood	Geel
Blauw	Rood

Card II



Card III

Rood	Geel
Groen	Blauw
Geel	Rood
Rood	Geel
Blauw	Rood

Instructions

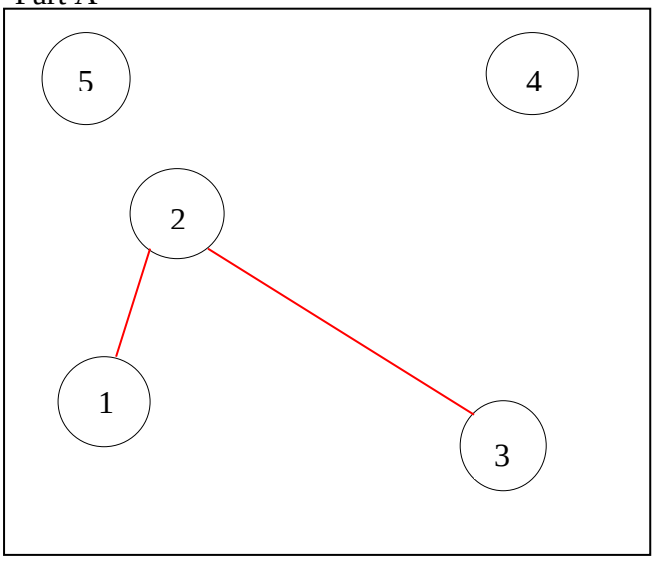
Card I: read the words aloud, as fast and accurately as possible

Card II: name the colors as fast and accurately as possible

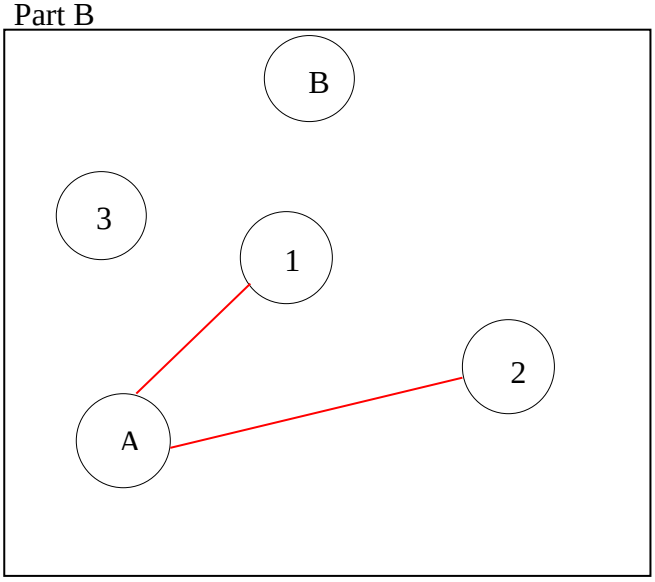
Card III: name the colors of the ink as fast and accurately as possible

TRAIL MAKING TASK

Part A



Part B



Instructions

Part A: connect the numbers in ascending order. Work as fast and accurately as possible.

Part B: connect the numbers and letters, alternately, in ascending order. Work as fast and accurately as possible.

APPENDIX I (continued)

DIGIT SPAN TASK BACKWARDS – WAIS-III

Assignment	*Correct answer*
2-6	6-2
5-8	8-5
9-3-5	5-3-9
2-4-8	8-4-2
9-3-5-6	6-5-3-9
2-4-1-3	3-1-4-2
3-6-2-4	

Instructions

I will now read you some digits. Please repeat these in reversed order.

15 WORDS TASK

Boom	Boom	Boom	Boom	Boom
Vos	Vos	Vos	Vos	Vos
Broek	Broek	Broek	Broek	Broek
Raam	Raam	Raam	Raam	Raam
…	…	…	…	…
…	…	…	….	…

Instructions

I will now read you some words. Listen carefully, I will ask you which words you remember when I'm finished.

...

We will repeat this procedure a couple of times. I will read the words to you again, then you tell me which words you remember.

APPENDIX II Graphical representation of the LDA with clinical predictors of Van Balkom et al. (2016).

Variables Function 1	*r*
UPDRS-III	**.77**
BAI	**.32**
DS backwards	-.30
15WT	-.28
TMT B | A	-.14
Stroop III | II	-.04

Variables Function 2	*r*
TMT B | A	**.71**
Stroop III | II	**.43**
DS backwards	**.37**
BAI	-.27
UPDRS-III	.26
15WT	.03

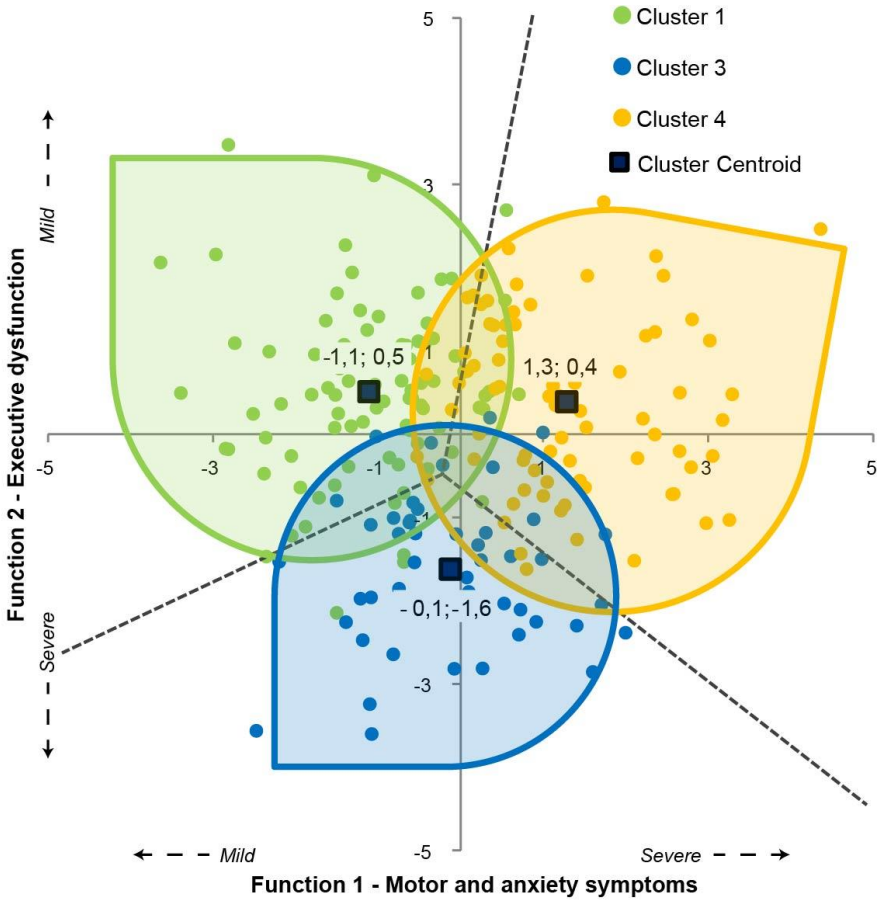


Figure 9. Discriminating Functions between the Three Clusters in the LDA. On the *X*-axis: Function 1; on the *Y*-axis: Function 2. The Coordinates of the Cluster Centroids represent Standardized Mean Scores of the Three Clusters on Function 1 and 2. The Tables present the Correlation between the Variables in the LDA and the Discriminating Functions 1 and 2. In Bold: Important Discriminating Variables ($r > .3$). Abbreviations: 15WT = 15 Words Test; BAI = Beck Anxiety Inventory; DS = Digit Span; TMT = Trail Making Task; UPDRS-III = Unified Parkinson's Disease Rating Scale – III. Derived from Van Balkom et al. (2016).

APPENDIX III Clinical characteristics of LDA sample.

Table 6

Mean (SD) of Clinical Characteristics, Categorized by Cluster

Clinical characteristic (N= 66)	**C1 (N = 24)**	**C3 (N = 17)**	**C4 (N = 25)**
Stroop interference score* [1]	51.4 (6.4)	44.8 (10.6)	52.8 (8.2)
TMT concept shifting score* [2]	52.3 (6.9)	39.7 (10.0)	50.4 (8.0)
Digit Span backwards total score*	54.8 (11.1)	47.5 (5.7)	51.4 (10.1)
15WT delayed recall score*	45.4 (10.5)	45.1 (12.7)	41.3 (10.1)
UPDRS-III total score	16.3 (7.8)	20.4 (7.5)	32.9 (7.1)
BAI total score	8.0 (5.5)	19.8 (10.7)	12.9 (6.9)

* t-score

1 = Stroop Card III | II

2 = TMT Part B | A

APPENDIX IV Insular volume, categorized by cluster

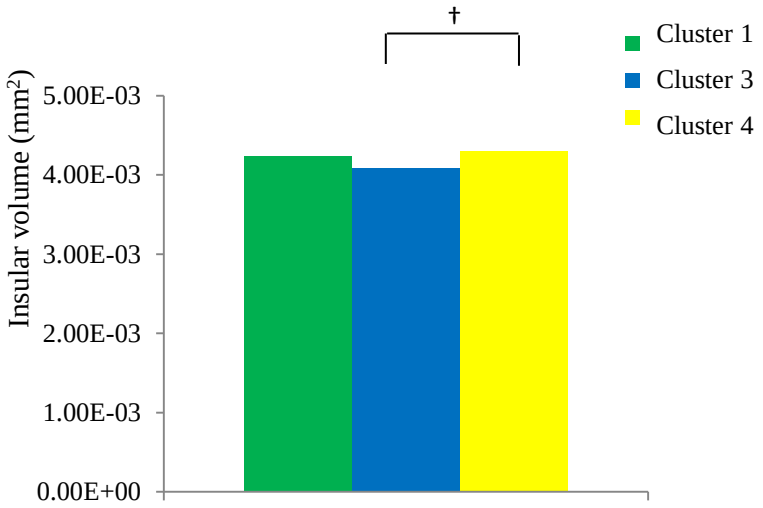


Figure 10. Mean insular volume (mm^2), categorized by cluster. † = trend toward significant difference between clusters, with $p < .1$.

APPENDIX V Correlations between clinical characteristics and left and right imaging variables.

Table 7.

Correlations between Clinical Characteristics and Imaging Variables, with Left and Right ROI's Separately.

Executive functioning	**Stroop**		**TMT**		**DS backwards**	
dlPFC_L	r = .11	(N = 83)	τ = .11	(N = 80)	τ = .08	(N = 83)
	p =.32		p = .14		p = .32	
dlPFC_R	r = .16	(N = 86)	τ = .15	(N = 84)	τ = .14	(N = 86)
	p =.15		p = .05		p = .07	
IFG_L	r = .05	(N = 86)	τ = .04	(N = 84)	τ = .03	(N = 86)
	p = .68		p = .63		p = .71	
IFG_R	r = .04	(N = 85)	τ = .17†	(N = 84)	τ = .17†	(N = 85)
	p = .70		p =.03		p = .03	
Insula_L	r = -.04	(N = 85)	τ = .09	(N = 83)	τ = -.04	(N = 85)
	p = .75		p = .25		p = .63	
Insula_R	r = .04	(N = 88)	τ = .15†	(N = 85)	τ = .02	(N = 88)
	p = .7		p = .05		p = .82	
BR_caudate_L	r = .01	(N = 125)	τ = .11	(N = 123)	τ = -.03	(N = 125)
	p = .93		p = .09		p = .67	
BR_caudate_R	r = .003	(N = 125)	τ = .10	(N = 123)	τ = -.02	(N = 125)
	p = .98		p = .11		p =.77	
BR_putamen_L (N = 123)			τ = .11			
			p = .07			
BR_putamen_R (N = 123)			τ = .12			
			p = .05			
Verbal Memory	**15WT**					
Hippoc_L (N = 92)	r = .24					
	p = .02†					
Hippoc_R (N = 92)	r = .31*					
	p = .003					
Motor symptom severity	**UPDRS-III**					
BR_putamen_L (N = 125)	τ = - .02					
	p = .81					
BR_putamen_R (N = 125)	τ = -.04					
	p =					

APPENDIX V (continued)

Psychiatric symptoms	**BAI**
BR_caudate_L	τ = -.07
	p = .23
BR_caudate_R	τ = -.11
	p = .09

* Significant at the α < .001 level

† = trend toward significance, with α < .05.

Abbreviations: dlPFC = dorsolateral prefrontal cortex, IFG = inferior frontal gyrus, L = left, R = right, Hippoc = hippocampus, BR = binding ratio, postputam = posterior putamen.

APPENDIX VI. Relationship between right hippocampal volume and 15WT

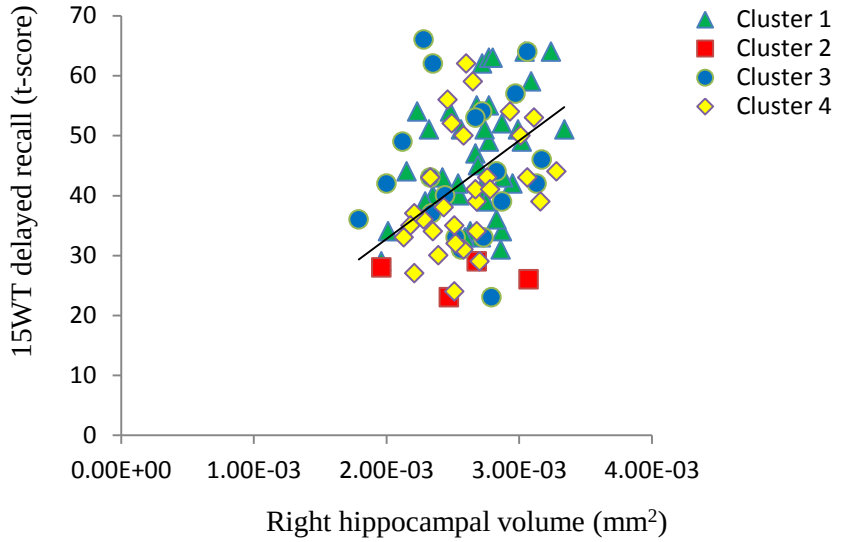


Figure 11. Relationship between right hippocampal volume and 15WT delayed recall.

APPENDIX VII Mean values of the imaging predictors per cluster

Table 8

Mean (SD) of Proposed Predictor Variables, Categorized by Cluster

Imaging variables		**Cluster 1** (n = 24)	**Cluster 3** (n = 17)	**Cluster 4** (n = 25)
Volume dlPFC_R	in mm^2	1.20E-02	1.16E-02	1.19E-02
		(1.06E-03)	(8.87E-04)	(9.15E-04)
Volume insula_R	in mm^2	4.26^{E}-03	4.07^{E}-03	4.38E-03
		(3.02^{E}-04)	(4.85E-04)	(2.88E-04)
Volume hippoc_R	in mm^2	2.78^{E}-03	2.60^{E}-03	2.59E-03
		(2.80^{E}-04)	(3.56E-04)	(3.12E-04)
BR putamen_R		1.82^{E}+00	1.59E+00	1.86E+00
		(3.55^{E}-01)	(4.60E-01)	(3.18E-01)

Abbreviations: dlPFC = dorsolateral prefrontal cortex, R= right, BR = binding ratio.