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ASSESSING HETEROGENEITY IN AND THE RELATION BETWEEN THE NEUROPSYCHIATRIC AND COGNITIVE PROFILE IN PARKINSON'S DISEASE

A Data-Driven Approach

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ABSTRACT
Introduction *Parkinson's disease (PD) is a disease with a high heterogeneity in symptoms. The objective of this study was to assess heterogeneity in neuropsychiatric and cognitive symptoms of PD, and examine if neuropsychiatric disorders were related to specific cognitive domain impairments.* **Methods** *A hierarchical cluster analysis (HCA) was conducted on clinical data of 226 PD patients screened at the VU University medical center using elaborate measurement of cognitive, neuropsychiatric and motor symptoms. Subsequently, a linear discriminant analysis (LDA) was conducted to assess which constructs could explain the clusters.* **Results** *The HCA resulted in four clusters: a young-age, unimpaired cluster (*N = 86*), an older age cluster with severe impairements overall (*N = 15*), a cluster with executive function (EF) impairment (*N = 46*) and a cluster with motor symptoms and memory impairment (*N = 79*).* **Discussion** *Cluster 1 and 2 may represent the early and late – demented – stages of PD, respectively. The latter two clusters have similar demographics, and could subsequently represent different pathways of disease progression. Future research should focus on comparing particularly cluster 3 and 4 on pathophysiological measures and monitor differences in disease progression.*

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INTRODUCTION

Parkinson's disease (PD) is a chronic, idiopathic, neurodegenerative disease, second most common after Alzheimer's disease (Wirdefeldt, Adami, Cole, Trichopoulos & Mandel, 2011). PD was first described almost 200 years ago by James Parkinson in his monograph "An Essay on the Shaking Palsy" (1817). The core symptoms of PD, often referred as 'motor symptoms', include resting tremor (i.e. 'involuntary shaking'), rigidity, bradykinesia (i.e. slowness of movement) and postural instability (Dauer & Przedborski, 2003; Jankovic, 2008). Over the years, many studies have been conducted on the symptomatology and pathophysiology of PD. Dopaminergic cell loss in the substantia nigra was identified in 1919 by Trétiakoff in his thesis (Drach, Wach & Bohl, 1996) as one of the cardinal features of PD. Subsequently, suppletion with the dopamine precursor L-Dopa ((S)-2-Amino-3-(3,4-dihydroxyphenyl)-propanoic acid) was found to relief motor symptoms in mice and rabbits by Carlsson and colleagues (1957). This discovery led to the development of pharmacological treatment of PD in humans. To this date, L-Dopa is still the treatment of choice in PD (Bloem et al., 2010). After five to ten years of chronic pharmacological treatment, motor complications, including dyskinesias and motor fluctuations, occur in 50-80% of the patients (Olanow et al., 2004). Like in Alzheimer's disease, six neuropathological stages of the neurodegenerative process in PD are distinguished, both before onset of the motor symptoms and after onset (Braak, Ghebremedhin, Rüb, Bratzke & Tredici, 2004). The stages vary from lesions in olfactory structures in the early stages of the disease, to involvement of the neocortical areas in the final stages. Furthermore, protein aggregates named 'Lewy bodies' – named after neurologist Frederic Lewy – are often associated with the neurodegeneration as seen in PD and related parkinsonisms (Spillantini et al., 1997). In summary, there have been many advancements in research in PD, focusing mainly on the associated motor symptoms and its relief.

While originally PD was seen as a movement disorder, attention for non-motor symptoms (NMS) has increased in the past decades. Ninety-eight percent of the PD patients experiences one or more NMS (Barone et al., 2009). Depression, anxiety, rapid eye movement sleep behavioral disorder (RBD) and olfactory dysfunction even seem to precede the onset of the PD motor symptoms (Fulda & Manconi, 2013; Ishihara and Brayne 2006; Ross et al., 2008; Tan, Salgado & Fahn, 1996). NMS frequently associated with PD are neuropsychiatric symptoms (i.e. depression, anxiety, apathy, impulse control disorders (ICDs) and psychosis), and cognitive disorders leading to mild cognitive impairment (MCI) or Parkinson's disease dementia (PDD). Table 1 gives an overview of these symptoms in PD. In

Table 1 Overview of Frequently Prevalent Non-Motor Symptoms in PD.

Symptom Domain		Prevalence	Source
Neuropsychiatry	Depressive Symptoms	30-35%	Aarsland, Påhlhagen, Ballard, Ehrt & Svenningsson, 2012
	Anxiety Symptoms	40-50%	Aarsland, Marsh & Schrag, 2009; Leentjens et al., 2011; Nègre-Pagès et al., 2010
	Apathy	-60%	Gallagher & Schrag, 2012
	Psychotic Symptoms	25-40%	Chaudhuri et al., 2006; Papapetropoulos & Mash, 2005; Rabey, 2009
	Impulse Control Disorders	14%	Weintraub et al., 2010
Cognition	MCI*	25.8%	Aarsland et al., 2010
	PDD	32%	Aarsland, Zaccai & Brayne, 2005
Sleep Disorders		60-98%	Comella, 2007
Autonomic Symptoms		>50%	Hou & Lai, 2007

*Percentage of the non-demented PD patients.
Abbreviations: MCI = Mild cognitive impairment, PDD = Parkinson's disease dementia.

general, NMS are stronger predictors of the health-related quality of life compared to motor symptoms (HRQoL; Martínez-Martín, Rodriguez-Blazquez, Kurtis & Chaudhuri, 2011). More than that, depressive symptoms in PD are more frequently reported to be an important predictor of the HRQoL, compared to the motor symptoms in PD (Soh, Morris & McGinley, 2011). Furthermore, PDD (Winter et al., 2011) and even cognitive impairment in non-demented PD patients (Klepac, Trkulja, Relja & Babić, 2008) are associated with reduced HRQoL. However, 40-75% of the NMS are not recognized by physicians (Shulman, Taback, Rabinstein & Weiner, 2002). Moreover, Chaudhuri and colleagues (2010) reported that 32-65% of the NMS were not declared by the patients, possibly due to the fact that patients did not link NMS with PD. These findings emphasize the importance of adequate recognition, diagnosis and treatment of NMS in PD.

In the general population, psychiatry and cognition are greatly intertwined (Millan et al., 2012). In psychiatric disorders, cognitive impairment is a frequently described symptom. Whereas attention is generally affected in psychiatry, different patterns of impairment in other cognitive domains can be discerned between the various psychiatric disorders (Millan et al., 2012). For example, depressive disorders are associated with impaired memory, processing speed and executive function (Marazziti, Consoli, Picchetti, Carlini, Faravelli, 2010). Besides, cognitive regulation of emotion is an important process often impaired in psychiatric disorders. For example, depressed patients have more problems regulating negative emotions, and tend to make more use of rumination (Joormann & D'Avanzato, 2010). Furthermore,

there seem to be cognitive vulnerabilities for people to develop psychiatric disorders like depression (Beck, 2008, Hallion & Ruscio, 2011), anxiety disorders (Beck & Clark, 1997, Hallion & Ruscio, 2011) or psychosis (Garety, Kuipers, Fowler, Freeman & Bebbington, 2001). In sum, cognitive impairments and psychiatric disorders are not to be seen as separate processes, but are rather mental disorders with shared pathologies. Indeed, changed activation in the cortico-striato-thalamo-cortical (CSTC) circuits have been associated with, among others, impaired cognition (Groenewegen & Uylings, 2010) and psychiatric disorders such as major depression (Heller et al., 2013) and obsessive compulsive disorder (Mataix-Cols & Van den Heuvel, 2006; Van den Heuvel et al., 2010). In PD, this relationship between cognition and neuropsychiatry has been less well examined. Impaired cognitive functioning in PD seems to be related to more psychiatric symptoms (Dujardin et al., 2013). In specific, psychotic symptoms are more prevalent in patients with PDD (Factor et al., 2014; Fenelon & Alves, 2010), while ICDs are associated with EF deficit (Vitale et al., 2011). However, there is still room for improving the understanding of this relationship in PD.

As stated, the point-prevalence of dementia in PD is 32%. However, newly-diagnosed PD patients already show impaired cognitive functioning, and PD patients decline faster in comparison with 'normal' ageing (Broeders et al., 2013). Performance on executive functions (EF), memory and visuospatial abilities can be impaired in non-demented patients even in early stages of PD (Dubios & Pillon, 1997; Janvin, Aarsland, Larsen & Hugdahl, 2003; Muslimović, Post, Speelman & Schmand, 2005). While there are different hypotheses on the etiology of cognitive impairments in PD, the cortico-striato-thalamo-cortical (CSTC) circuits seem to have a large influence. The circuits are divided in three partly overlapping pathways – the sensorimotor, associative and limbic pathways – which connect cortical areas to parts of the striatum and structures of the brainstem (Vriend et al., 2014b). The sensorimotor pathways connect the premotor and motor cortices with dorsal regions of the striatum, associative pathways connect the dorsolateral prefrontal cortex with the dorsal caudatus and the limbic pathways connect the orbitofrontal cortex and anterior cingulated cortex with the ventral parts of the striatum (Gerfen & Bolam, 2010; Haber & Calzavara, 2009; Vriend et al., 2014b). A simplified overview of these CSTC circuits is displayed in Figure 1. Decreased functioning of the striatum due to the diminished dopamine availability disrupts these circuits (Bosboom, Stoffers & Wolters, 2004). Cognitive dysfunction, specifically executive dysfunction, is mediated by the associative pathways, while the limbic pathways are involved in neuropsychological features such as motivation and impulse control (Vriend et al., 2014b).

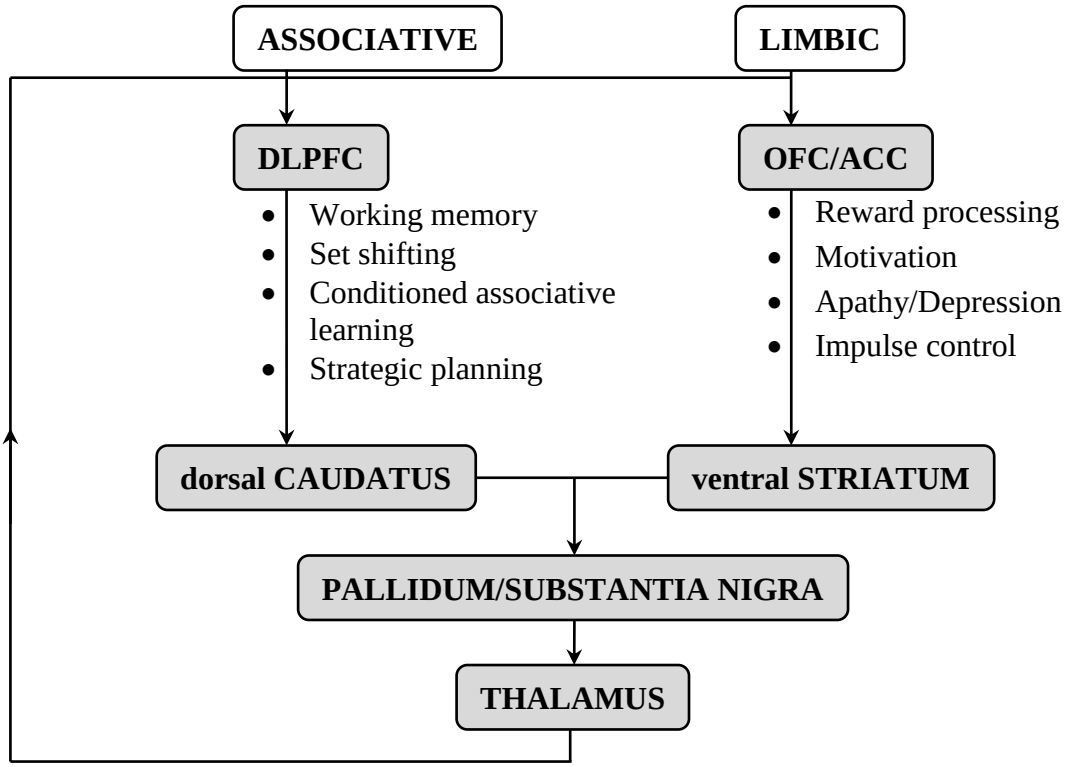


Figure 1 Cortico-Striato-Thalamo-Cortical Circuits and the Neuropsychological Functions Associated With Each Cortical Area (Alexander et al., 1986; Haber & Calzavara, 2009; Vriend et al., 2013; Zgaljardic, Borod, Foldi & Mattis, 2003). Abbreviations: DLPFC = Dorsolateral Prefrontal Cortex; OFC = Orbitofrontal Cortex; ACC = Anterior Cingulate Cortex.

Interestingly, dopaminergic treatment has not exclusively been found effective in relieving cognitive impairments in PD. A striking result found in one study, was a double dissociation between the effect of dopamine replacement therapy (DRT) on specific cognitive domains (Cools, Barker, Sahakian & Robbins, 2001). Whereas DRT withdrawal had a negative influence on the performance on a set-switching task, DRT withdrawal actually improved performance on a reversal learning task. The 'dopamine overdose theory' (Cools et al., 2001; Swainson et al., 2000) was postulated as an explanation for these results. In the early stages of PD predominantly the dorsal part of the striatum is affected while the ventral part is relatively intact. DRT will therefore have different effects on these regions (Vaillancourt, Schonfeld, Kwak, Bohnen & Seidler, 2013). Functioning of the dorsal part will be enhanced by DRT, while the ventral part will be 'overdosed'; that is, overstimulated. The dopamine system also influences neuropsychiatric symptoms found in PD. Depression is associated with OFC disruption (Zgaljardic et al., 2003). Furthermore, Vriend and colleagues (2014c) found an association between decreased dopamine transporter (DaT) availability, a marker for striatal dopamine denervation, in the (right) caudate nucleus and depressive

symptoms in PD. In addition, depression in PD seems to be well treatable by DRT (Aarsland et al., 2012). Other neuropsychiatric disorders in PD associated with dopamine include ICDs (Vriend et al., 2014a) and psychotic symptoms (Chaudhuri et al., 2006). However, not all variability in cognitive and neuropsychiatric symptoms can be explained by dopamine depletion. For instance, dementia (Ahlskog, 2005) and psychosis (Wolters & Berendse, 2001) generally do not improve by DRT. Consequently, there are additional factors influencing these symptoms. Proposed factors are non-dopaminergic systems like the serotonergic, noradrenergic and cholinergic systems, but also detrimental effects of Lewy bodies on cortical areas such as the parietal and temporal lobes and genetic predisposition (Robbins & Cools, 2014). Altogether, an array of factors contribute to the various cognitive and neuropsychiatric symptoms in PD. However, there is a large heterogeneity in PD manifestation (Foltynie, Brayne & Barker, 2002). Thus, subtype recognition is an important objective, which can indicate similar pathophysiology and can lead to individualized disease treatment and prognosis.

In the past fifteen years, there has been increasing attention for subtype recognition in PD. Several data-driven studies have identified subtypes of PD, and heterogeneity in motor symptoms is a frequently described phenomenon. A systematic review by Van Rooden and colleagues (2010) of seven data-driven studies observed the (motor-)subtypes "old age-at-onset and rapid disease progression" and "young age-at-onset and slow disease progression". Furthermore, in two studies, the "Tremor dominant" and "Dominance of bradykinesia / rigidity, PIGD" subtypes were found. Table 2 shows the cognitive and neuropsychiatric features of these clusters. What stands out, is the fact that neuropsychiatry and cognition were not included in these analyses. One of the few studies that assessed heterogeneity in neuropsychiatry observed that clusters with higher prevalence of hallucinations had lower

Table 2 Overview of Cognitive and Neuropsychiatric Features of Previous Clusters Found. Derived from Van Rooden et al., 2010.

Old age-at-onset and rapid disease progression	No, mild or severe cognitive impairment No information on psychiatric symptoms
Young age-at-onset and slow disease progression	No or mild cognitive impairment Mild to severe depression
Tremor dominant	No cognitive impairment No depression
Dominance of bradykinesia/rigidity, PIGD	Cognitive impairment, specifically in EF Depression, hallucinations and apathy

Mini Mental State Examination (MMSE) scores (Bronnick et al., 2005). Dujardin and colleagues (2013) studied heterogeneity in cognitive disorders in PD. This study found five clusters, in which three clusters showed progressively increased cognitive dysfunction. Interestingly, the clusters with more cognitive dysfunction showed higher prevalences of hallucinations, depression and apathy compared with the cognitively intact clusters. However, no differences between clusters on specific cognitive domain dysfunction were reported. Heterogeneity in EF impairment was studied by Kudlicka and colleagues (2013) in patients with mild to moderate PD. Their cluster analysis resulted in two patient profiles of EF dysfunctions: patients with attentional control deficits and patients with abstract reasoning problems. Post-hoc profile comparisons showed no differences in anxiety or depression symptoms. Everything considered, there are two important limitations in previous data-driven studies. First of all, most studies on profiling PD have focused on motor symptoms and consequently neglect the cognitive and neuropsychiatric symptoms of PD. Secondly, within the studies using more broad neuropsychological assessments, the hypothetical relationship between cognition and neuropsychiatry was not assessed. In sum, the question remains if disparate profiles of neuropsychiatric disturbances relate to specific cognitive domain dysfunction in PD.

In conclusion, multi-domain cluster analyses containing specifically neuropsychiatry and cognition in PD are scarce. Since there is no "standard" cognitive and psychiatric symptom profile in PD patients, our aim is to identify profiles of psychiatric symptoms that are related to specific cognitive domain dysfunction, using a data-driven approach. This is important, given the fact that (i) these non-motor symptoms have significant influence on the HRQoL, (ii) no elaborate research has been done in finding this relation, although a common underlying pathology may be indicated, and (iii) insight in this relationship will improve diagnostics and treatment by improved 'staging and profiling', relevant profile-specific prognosis and treatment alternatives.

METHODS

Patients

Data from 344 consecutive patients were used from a database of PD patients who were referred to the movement disorders 'day screening' at the outpatient clinic of the VU University medical centre (VUmc) in Amsterdam. This screening, which was part of routine clinical practice, included a neurological examination, elaborate neuropsychological assessment and several neuropsychiatric and behavioral questionnaires. Data were obtained between May, 2008 and June, 2014. Patients were diagnosed clinically with idiopathic PD by an experienced movement disorders specialist (Prof. dr. H. Berendse and Dr. E. Foncke). Inclusion criteria for this study were 1) presence of idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank criteria (Hughes, Daniel, Kilford & Lees, 1992), 2) availability and written informed consent of the patient to use the data from the day screening for scientific purposes and 3) a complete set of neurological, neuropsychological and neuropsychiatric variables selected for cluster analysis (see *Statistical Analysis*).

Measurement Instruments

The measurement instruments assessed the following clinical features: motor symptoms, cognitive function, psychiatric symptoms, sleep disorders, autonomic symptoms and ADL functioning. All instruments were conducted by trained professionals or Master's students. An overview of the measurement instruments is given in Appendix I. Data analysis was performed using Statistical Package for the Social Sciences (SPSS) version 20 (IBM Corp., 2011).

Statistical Analysis

First of all, several cognitive measures were corrected for gender, age and education level, and transformed to *t*- or percentile scores (*p*-scores), using the Dutch norms by Schmand, Houx and De Koning (2012). *T*-scores have a mean of 50 and a standard deviation of 10. A summary of the corrected variables is shown in Table 3. An overview of the qualitative description of norm scores used is shown in Table 4. In the BAI and BDI questionnaires, data were imputed if 1/6 or less of the items were missing. In the SCOPA-SLEEP, data were imputed in the daytime sleepiness subscale (item D1-D6), with a maximum of one missing value (i.e. 1/6 of the items). Regarding the SCOPA-AUT, the sex-specific items (item 22-25) and the item concerning medication (item 26) were not included in the imputation due to different answer scales within these items. Item 1-21 were only imputed if three or less items

Table 3 Summary of Cognitive Measures that were Corrected for Age, Gender and/or Education Level. A '+'-sign Indicates Correction for this Variable.

Cognitive variable	Corrected for			Transformed measure
	Age	Gender	Education level	
Stroop card I	+		+	*t*-score
Stroop card II & III	+	+	+	*t*-score
Stroop III | II	+	+	+	*t*-score
TMT part A	+		+	*t*-score
TMT part B	+	+	+	*t*-score
TMT B | A	+	+	+	*t*-score
Digit span			+	*t*-score
Category fluency	+		+	*t*-score
Letter fluency			+	*t*-score
15WT recall	+	+	+	*t*-score
RCFT copy	+			*p*-score

Abbreviations: 15WT = 15 Woorden Taak; *RCFT* = Rey Complex Figure Task; *TMT* = Trail Making Task

were missing. Imputed data were computed using the average score of the participant on valid items in that questionnaire. Data were not imputed for the SCOPA-PC, since this questionnaire measures different constructs of psychiatric symptoms (psychotic symptoms, REM sleep behavioral disorder and impulse control), which are all assessed by three or less items. Total scores were computed for the psychiatric measures and motor scales. The variables were checked for normality. Because of skewed distributions in the BDI and BAI measures, these variables were transformed using a square root transformation. Outliers were identified using the interquartile range (IQR): measures 2.2 × IQR above the 75th percentile or 2.2 × IQR below the 25th percentile were marked as outliers.

The steps of the statistical analyses are shown in Figure 2. The first step included a hierarchical cluster analysis (HCA). Variables in the cluster analysis had to be mutually independent (i.e. $r < .90$; Mooi & Sarstedt, 2010) and measured on an interval- or ratio scale. Furthermore, variables were chosen which measure a variety of cognitive, psychiatric and motor symptoms, and had low percentage of missing values. Variables in the HCA were

Table 4 Qualitative Description of Frequently used Normscores, including *Z*-scores, *t*-scores and Percentile Scores.

Classification	*Z*-scores	*t*-normscore	Percentile Scores
Very High	≥ 2.0	≥ 70	≥ 98
High	1.4 – 1.9	64 – 69	91 – 97
Above Average	0.7 – 1.3	57 – 63	75 – 90
Average	-0.6 – 0.6	44 – 56	25 – 73
Below Average	-1.3 – -0.7	37 – 43	9 – 23
Low	-2.0 – -1.4	30 – 36	2 – 8
Very Low	≤ -2.1	≤ 29	< 2

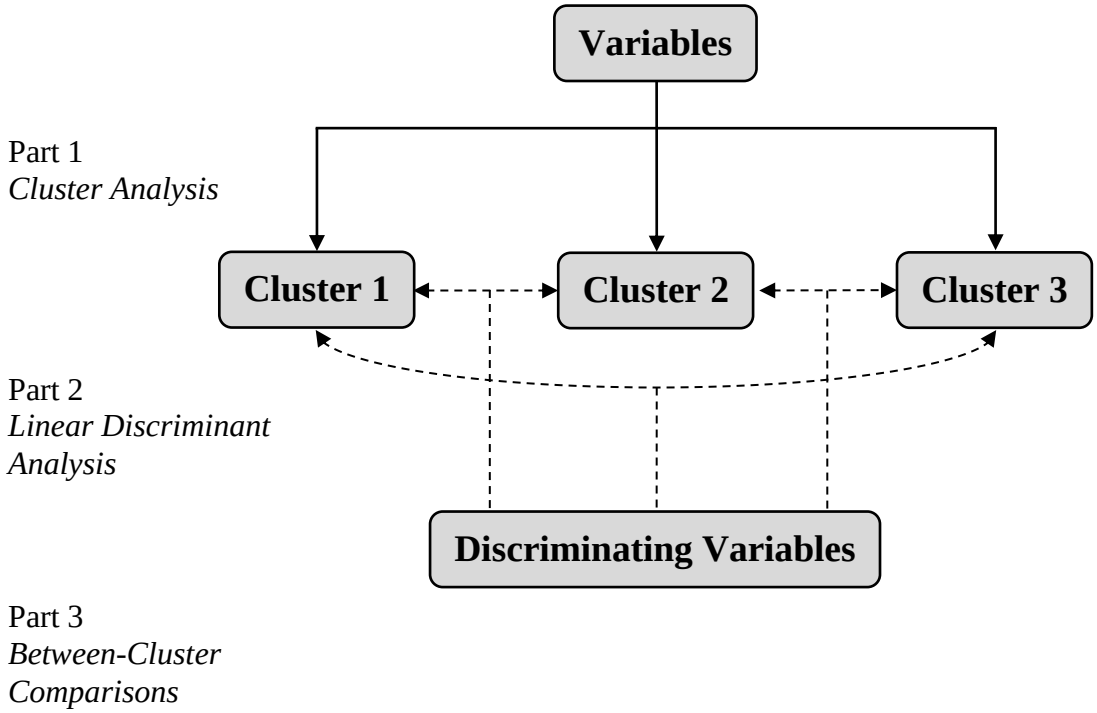


Figure 2 Outline of the Statistical Analyses.

standardized to *z*-scores – after standardization of the cognitive measures – to equalize the unit of measurement. We used the squared Euclidean distance measure, with Ward's clustering method of minimal variance (Ward Jr., 1963). This combination of distance measure with clustering method seems to have good clustering qualities (Everitt, Landau, Leese & Stahl, 2011). The number of clusters identified were determined by 1) the dendrogram output and 2) the ecological value of the cluster solutions. The visual output – i.e. the 'best cut' in the dendrogram – indicates which cluster solution fits best in the dataset. This depends on how similar features the clusters have and, consequently, how far the clusters are apart in this plot. The more horizontal distance between two 'nodes', the more dissimilar two clusters are. An example is shown in Figure 3.

In the cluster analysis, we included several measures of cognitive function (i.e. Stroop III | II, TMT B | A; Digit span backwards, 15WT delayed recall, MMSE), a motor symptom measure (UPDRS-III) and one neuropsychiatric measure (BAI). We could include just one measure of neuropsychiatry due to the mutual independency and interval- or ratio scale assumptions (see Table 5 for an overview of the variables included in the HCA). For the BAI, we used a threshold of 12-13 for clinically relevant anxiety symptoms (Leentjens et al., 2011) and for the BDI a threshold of 14-15 (Visser, Leentjens, Marinus, Stiggelbout & Van Hilten,

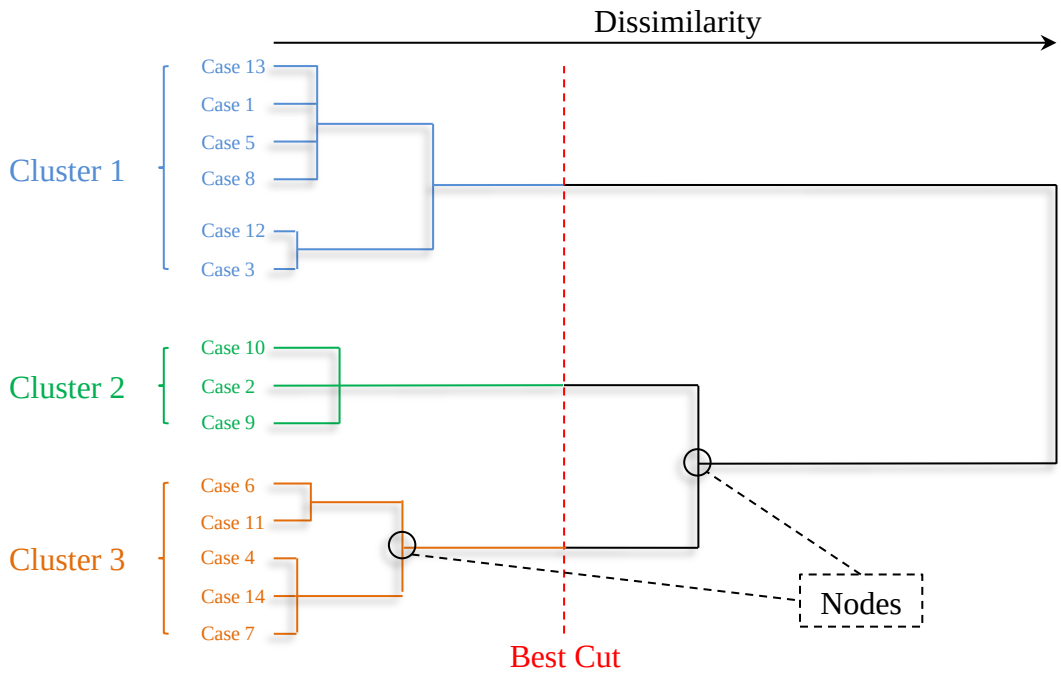


Figure 3 Determining the Number of Clusters using the Dendrogram. Different Colors Indicate Different Clusters. The Horizontal Distance between two Nodes Indicates the Dissimilarity between Clusters. The Best Cut Indicates a Three-Cluster Solution.

2006). A MMSE lower than 24 was used as indicative of cognitive impairment (Hoops et al., 2009).

Following the cluster analysis, a linear discriminant analysis (LDA) was conducted in order to assess which variables could discriminate the clusters, and how much variability these variables explained in differences between clusters. Moreover, a second LDA was used to analyze which variables that were not in the HCA could predict cluster membership as well. Finally, comparison of means and medians (Analysis of variance (ANOVA), Mann-Whitney U-test and Kruskall-Wallis test) or Chi-square tests were used to describe differences between the clusters on demographic and non-normally distributed variables. Differences

Table 5 Measures of Motor Sympoms, Cognition and Neuropsychiatry Included in the HCA.

Motor symptoms	UPDRS-III	Fahn & Elton, 1987
Cognition	MMSE	Folstein, Folstein & McHugh, 1975
	Stroop card III compared to card II	Hammes, 1971
	TMT part B compared to part A	Reitan & Wolfson, 1985
	Digit span backwards (WAIS-III)	Wechsler, 2000
	RAVLT (Dutch version – 15WT) delayed recall subtask	Saan & Deelman, 1986
Neuropsychiatry	BAI	Beck, Brown, Epstein & Steer, 1988

Abbreviations: 15WT = "15 Woorden Taak"; BAI = Beck Anxiety Inventory; MMSE = Mini-mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; TMT = Trail Making Task; WAIS = Wechsler Adult Intelligence Scale; UPDRS = Unified Parkinson's Disease Rating Scale.

were considered significant using the $\alpha = .05$ level. Furthermore, post-hoc tests were corrected for multiple comparisons. Following ANOVA tests, we used Hochberg's GT2 procedure to correct for multiple comparisons, which has greater power when sample sizes are different (Field, 2013). Post-hoc tests following the Kruskall-Wallis test and the Chi-square test were computed using the Bonferroni correction, as built-in in SPSS.

RESULTS

Demographic and descriptive characteristics

The final sample (N = 226) consisted of 145 male patients (age M = 62.8, SD = 10.5) and 81 female patients (age M = 64.5, SD = 9.8). In 75 patients, one or more items were imputed in the questionnaires. 128 patients were excluded from the analyses due to an incomplete dataset for the cluster analysis (see Figure 4). The demographic characteristics of the final sample are shown in Table 6.

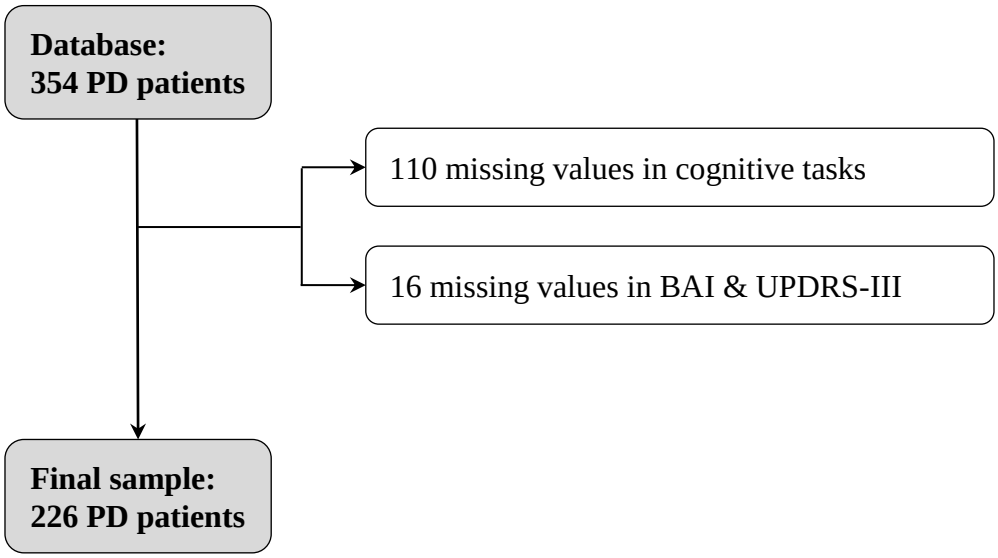


Figure 4 Flowchart of the Sample Used in the Analyses.

Table 6 Demographic Characteristics of the PD Patients. Means or Frequencies are Followed by Standard Deviations (SD) or Percentages Between Brackets.

Female, N (*%*)	81	(35.8)
Age, mean years (*SD*)	63.4	(*10.2*)
Subjective age at disease onset, mean years (*SD*)	58.0	(*11.2*)
Hoehn &Yahr disease stage, median (*range*) (Hoehn & Yahr, 1967)	2	(*0-4*)
Education level according to the Dutch Verhage classification, N (*%*) (Verhage, 1964)		
Elementary school or lower (less than six years)	2	(*0.9*)
Elementary/middle school finished (six years)	8	(*3.5*)
Junior high school (seven-eight years)	13	(*5.8*)
Senior middle/high school (nine years)	34	(*15.0*)
First year high school (ten years)	55	(*24.3*)
Second year high school/high school finished/applied sciences (eleven-twelve years)	55	(*24.3*)
University level	59	(*26.1*)

Part 1 – Cluster Analysis

The hierarchical cluster analysis identified four clusters. The demographic variables of these clusters are shown in Table 7. The behavioural characteristics of the four clusters have been illustrated in Figure 5. In this radar chart, various measurements are shown on four axes as standardized *Z*-scores. The EF and working memory measurements are taken together in the top axis, the direct and delayed verbal memory recall are shown on the right axis, the BDI and BAI scores are merged into a psychiatry score on the lower axis and lastly the UPDRS-III motor symptom severity is shown on the left axis. The *Z*-scores in this chart are transformed as such, that a lower *Z*-score represents lower symptom severity, whereas higher *Z*-scores indicate higher symptom severity.

Table 7 Descriptive Variables of the Four Clusters. In the Right Column, the Statistical Significance of the Group Comparisons are Shown.

Variable		**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**	***p***
Female	%	34.9	20.0	54.3[d]	29.1[c]	**.018**[3]
Age	M ± SD	59.9 ± 10.2[b-d]	72.3 ± 9.8[a,d]	64.7 ± 9.2[a]	64.8 ± 9.5[a,b]	**.000**[1]
Age at onset	M ± SD	54.9 ± 11.4[b]	66.3 ± 11.9[a]	58.9 ± 10.5	59.2 ± 10.3	**.001**[1]
Disease length	median	2.0	6.0	2.0	3.0	.107
Education	median	Applied Sciences	Lower Vocational Education	Lower Vocational Education	Applied Sciences	.069[2]
H&Y	M ± SD	1.8 ± .6[b,d]	2.3 ± .5[a]	2.0 ± .5[d]	2.3 ± .5[a,c]	**.000**[1]
Stage 0	N	1	0	0	0	
Stage 1	N	19	0	5	0	
Stage 1.5	N	9	1	5	2	
Stage 2	N	39	7	18	40	
Stage 2.5	N	12	3	12	24	
Stage 3	N	5	4	2	9	
Stage 4	N	0	0	0	3	
Unmedicated LEDD†	%	54.7	46.7	54.3	62.0	.620[3]
total	median	450	460	330	330	.312[2]
non-LD	median	200	240	225	213	.872[2]
LD	median	375	400	300	338	.902[2]
COMT	median	600	900	1200	800	.405[2]
MAOB	median	1.00	3.00	1.00	1.00	.504[2]

[1]Univariate ANOVA; [2]Non-parametric Kruskal-Wallis H Test; [3]Pearson's Chi-Square Test. †Of medicated patients.
Significant differences on the α = .05 level are shown in bold. Post-hoc testing: [a]Significantly different from Cluster 1 on the α = .05 level; [b]Significantly different from Cluster 2 on the α = .05 level; [c]Significantly different from Cluster 3 on the α = .05 level; [d]Significantly different from Cluster 4 on the α = .05 level.
Abbreviations: H&Y = Hoehn & Yahr; LEDD = Levodopa Equivalent Daily Dosage.

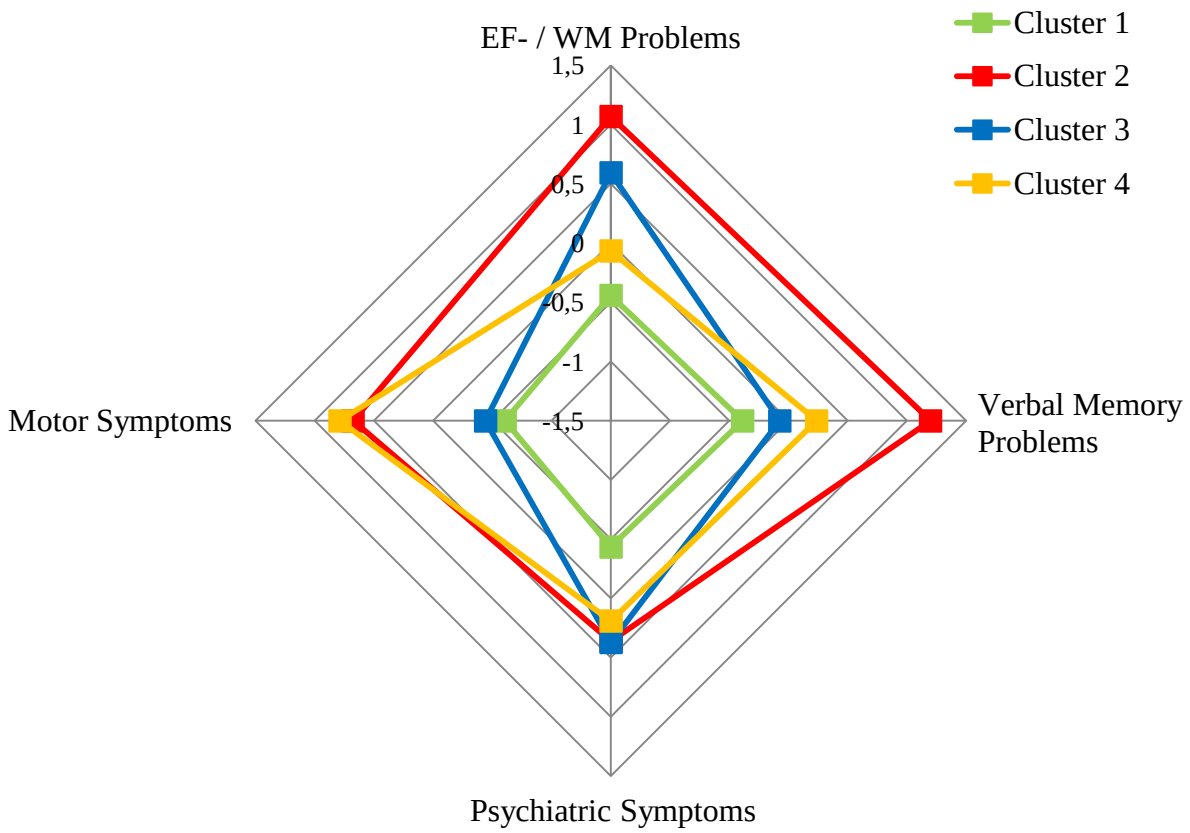


Figure 5 Radar Chart containing Four Domains of Neuro(psycho)logical and Neuropsychiatric Symptoms. Data Points indicate the Mean *Z*-score of the Cluster on the Four Domains. *Z*-scores are Transformated as such, that Lower *Z*-scores indicate less Symptom Severity, whereas high *Z*-scores indicate more severe Symptoms. The Four Axes: *EF- / WM Problems:* Stroop card III | II, Trail Making Task part B | A, Digit Span Backwards*; Verbal Memory Problems:* 15Words Test Direct and Delayed Recall subtests*; Psychiatric Symptoms:* Beck Anxiety Inventory, Beck Depression Inventory*; Motor Symptoms:* Unified Parkinson's Disease Rating Scale-III.

Part 2 – Linear Discriminant Analysis

Following the HCA, we conducted a LDA in order to assess which variables in the HCA could explain the differences between the clusters. Due to the low sample size of cluster 2, this cluster had to be eliminated from the LDA. Furthermore, the MMSE was eliminated from this analysis due to violation of the normality assumption in the LDA. The LDA with cluster 1, 3 and 4 (*N = 211*) resulted in two discriminant functions.

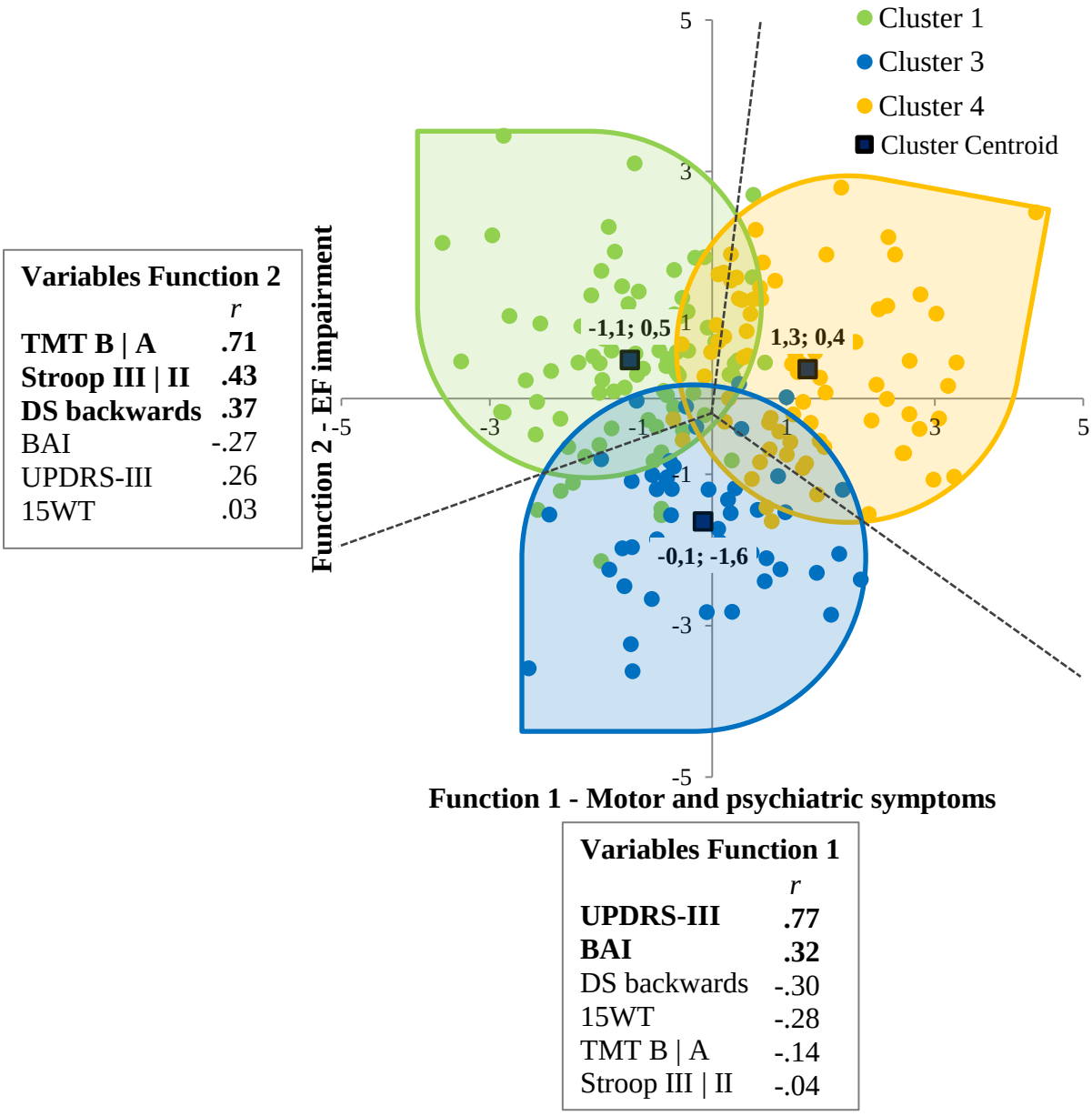
As illustrated in Figure 6, function 1 (*x*-axis) discriminated cluster 1 from cluster 4. Cluster 3 had a low mean *Z*-score on this function. The most important discriminating variable within this function was the UPDRS-III (r = .77). Furthermore, the BAI also discriminated these clusters (r = .32). Function 2 (*y*-axis) discriminated cluster 1 and 4 from

cluster 3. Within this function, the TMT part B | A was the most important discriminating variable (r = .71). Furthermore, the Stroop card III | II measure (r = .43) and the Digit span backwards (r = .37) were important discriminating variables. In the LDA, only the 15WT delayed recall did not contribute to the analysis according to the rule of thumb, $r > .3$.

The two discriminant functions combined explained 74% of the variance in the clusters. This combination of functions differentiated significantly between clusters: $\Lambda = .267$, $\chi^2(12) = 271.1$, $p < .001$. The first function explained 53% of the variance in the dependent variable (R^2; explained variance model = 60.4%; canonical R = .73). The second function explained 21% of the variance in the dependent variable (explained variance model = 39.6%; canonical R = .654). When eliminating the first function from analysis, the second function alone could also differentiate significantly between clusters: $\Lambda = .572$, $\chi^2(5) = 114.6$, $p < .001$. Using the two discriminating functions, 83.9% of the cases could be classified correctly and significantly higher than chance: Press's Q = 242.7, $p < .01$.[1]

To explore which variables that were not used in the HCA could discriminate between cluster 1, 3 and 4, we conducted a second LDA. The variables included in this analysis are shown in Appendix II, Table 10, including the canonical correlations. The LDA resulted in two discriminating functions that explained 29% of the variance in the dependent variable. In this, the first function explained 27% of the variance, and the second function explained 2% of the variance. The two functions together discriminated significantly between groups: $\Lambda = .672$, $\chi^2(10) = 62.4$, $p < .001$. Eliminating the first function from analysis, the second function alone could still discriminate significantly between groups: $\Lambda = .923$, $\chi^2(4) = 12.6$, $p < .05$. Using the discriminant functions derived from this analysis, 64.2% of the cases could be classified correctly, significantly higher than classification through chance: Press's Q = 81.5, $p < .01$. In the first function, mental speed, disease stage, verbal memory, nighttime sleep and depressive and autonomic symptoms were important discriminating variables. In de second function, only an executive function measure was an important discriminating variable. The discrimination between clusters by the two functions in the second LDA are illustrated in Figure 8 (Appendix II).

[1] Press's Q statistic has a chi-square distribution with df = 1. If Q exceeds 6.63, the statistic is significant for the $\alpha = 0.01$ level.



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

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

Figure 6 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.

Part 3 – Post-hoc comparisons and cluster characterization

The four clusters were labeled, according to the characteristics of patients in the clusters, and the differences between clusters. The cluster scores on the variety of clinical measures are shown in Table 8.

Cluster 1 (*N = 86*) - "Young, young-onset and low symptom severity"

This cluster was characterized by young patients, with a young age at onset in an early disease stage. Patients in this cluster were characterized clinically by a relatively intact functioning on the neuropsychological tasks. Functioning on these tasks lied within the 'average' range of the healthy population. That is, the PD patients were cognitively well functioning. Furthermore, the mean anxiety and depression scores of these patients were below the thresholds, indicating no clinically relevant anxiety or depressive symptoms. The mean motor symptom severity of the patients was low, and patients in this cluster experienced low daytime sleepiness and autonomic symptoms. Finally, ADL functioning was relatively high.

Table 8 Cluster Means on the Variables of the Four Clusters.

Variables in HCA				
Variable	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**
Stroop card III | II*	52.8[b,c]	44.6[a,d]	45.2[a,d]	51.7[b,c]
TMT part B | A*	52.0[b-d]	27.8[a,c,d]	38.1[a,b,d]	48.5[a-c]
Digit span backward*	58.0[b-d]	42.1[a,d]	47.0[a]	50.4[a,b]
15 WT delayed recall*	47.5[b,d]	31.2[a,c,d]	44.0[b]	40.5[a,b]
MMSE†	28.8[b]	23.7[a,c,d]	28.2[b]	28.2[b]
BAI†,‡	9.5[c,d]	16.9	17.6[a]	15.4[a]
UPDRS-III‡	18.1[b,d]	31.9[a,c]	19.9[b,d]	33.1[a,c]
Variables not included in HCA				
Variable	**Cluster 1**	**Cluster 2**	**Cluster 3**	**Cluster 4**
Stroop card I*	48.1[b,c,d]	29.7[a,c]	43.0[a,b]	42.6[a,b]
Stroop card II*	46.9[b,c,d]	28.7[a]	42.3[a]	42.0[a]
TMT part A*	49.4[b,c,d]	36.7[a,c,d]	44.4[a,b]	48.2[a,b]
COWAT*	52.0[b]	32.8[a,c,d]	50.3[b]	47.3[b]
Category fluency*	51.5[b]	36.3[a,d]	49.7	48.8[b]
Digit span forward*	55.5[c]	47.0	48.9[a]	51.3
15WT direct recall*	46.4[b,d]	25.5[a,c,d]	43.7[b]	39.4[a,b]
RCFT copy total†	34.4[b,c]	29.9[a]	33.0[a]	33.0
RCFT delayed recall total	21.0[c]	17.9	16.7[a]	19.0
BADS rule shift cards (time) ‡	40.2[b,c]	56.2[a,d]	48.7[a]	41.1[b]
BADS key search†,‡	12.1[b]	8.0[a,d]	10.6	12.0[b]
BDI†,‡	7.7[c,d]	14.0	13.5[a]	12.5[a]
SCOPA-psychiatric complications†,‡	.7[b]	2.2[a]	1.2	1.2
SCOPA-daytime sleepiness†,‡	8.7[b-d]	12.9[a]	10.6[a]	10.7[a]
SCOPA-AUT‡	31.3[b-d]	38.3[a]	36.2[a]	35.8[a]
UPDRS-II ADL‡	7.7[b,d]	11.8[a]	9.1	11.2[a]
Schwab & England scale†	92.7[b,d]	82.3[a]	86.9[d]	83.3[a,c]

* *t*-scores.

†non-parametric Kruskall-Wallis H-test. Unless otherwise specified, differences are tested using ANOVA.

‡Lower score indicates less symptom severity.

Post-hoc testing: [a]Significantly different from Cluster 1 on the α = .05 level; [b]Significantly different from Cluster 2 on the α = .05 level; [c]Significantly different from Cluster 3 on the α = .05 level; [d]Significantly different from Cluster 4 on the α = .05 level.

Abbreviations: 15 WT = 15 Words Test; ADL = Activities of Daily Living; BADS = Behavioural Assessment for the Dysexecutive Syndrome; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; COWAT = Controlled Oral Word Association Test; MMSE = Mini Mental State Examination; RCFT = Rey Complex Figure Test; SCOPA = Scales for Outcomes in Parkinson's Disease; TMT = Trail Making Task; UPDRS-III = Unified Parkinson's Disease Rating Scale – III.

Cluster 2 (*N = 15*) – "High age, high age at onset and high symptom severity"

Patients in cluster 2 had a high age and high age at onset. These patients were in a later disease stage compared to the other clusters. Overall, patients in cluster 2 had high symptoms severity. Clinically, the Stroop III | II measure and the digit span backwards measure were on the lower edge of the 'average' score of the healthy population. However, the TMT and 15WT scores were well below this average, and can clinically be classified as deviating, indicating disorders in multiple cognitive domains. Furthermore, the mean MMSE score fell below the cut-off score of 24 that is indicative of cognitive impairments. Patients in this cluster had a mean anxiety and depression score well above the respective thresholds, indicating clinically relevant symptoms of anxiety and depression. The mean motor symptom severity was high, and comparable to that of cluster 4. It should be noted that the cluster size was relatively small.

Cluster 3 (*N = 46*) – "Decreased executive function and psychiatric symptoms"

Cluster 3 contained a relatively high proportion of female patients. The mean age and AO of the patients in this cluster were around the mean of the study population. Patients in cluster 3 had a relatively low disease stage, and low motor symptom severity. The EF measures, i.e. TMT B|A, Stroop III|II, BADS Rule Shift Cards, relatively low. Clinically, the TMT B|A score fell within the 'below average' category, whereas the Stroop measure still was in the 'average' category. Furthermore, symptoms of depression (i.e. BDI) and anxiety were clinically above the respective cut-off values. Finally, the ADL functioning as measured by the S&E scale was higher, compared to cluster 4.

Cluster 4 (*N = 79*) – "Motor and psychiatric symptoms, and decreased verbal memory"

Cluster 4 contained a relatively low proportion of female patients, and patients' age and AO were comparable those of the study population. Furthermore, the disease stage was relatively high. Patients in this cluster had more severe motor symptoms compared to cluster 1 and 3. On cognitive level, measures of verbal memory were 'below average'. In contrast, measures of EF, language and some measures of attention and mental speed were clinically in the 'average' category. The anxiety and depression measures exceeded the respective cut-off scores. Lastly, the ADL functioning (S&E scale) was low, compared with cluster 3.

DISCUSSION

Heterogeneity in the clinical manifestation of PD is a phenomenon that has been studied extensively. While previous studies have focused primarily on heterogeneity of motor symptoms (Van Rooden et al., 2010), NMS seem to have a higher negative impact on the health-related quality of life (Martínez-Martín et al., 2011). In our study, the objective was to map heterogeneity in the neuropsychiatric and cognitive symptoms existing in PD, and assess a relationship – if present – between these neuropsychiatric symptoms and specific cognitive domain impairment. To our knowledge, only one study by Dujardin and colleagues (2012) has assessed cognitive heterogeneity in PD by using cluster analysis, but this study did not find different profiles of specific cognitive domain impairment. Furthermore, the cognitive profiles were not relatable to psychiatric symptoms.

Our data-driven, cross-sectional study of 226 PD patients resulted in four clusters. The clusters had distinct clinical profiles, suggesting either various stages of the disease, or different subtypes of PD. In short, patients in cluster 1 were young, had a young AO and were characterized by an overall low motor as well as non-motor symptom severity. In contrast, patients in cluster 2 were of older age, had a high AO and overall high severity of motor and non-motor symptoms. Patients in cluster 3 had predominantly 'frontal' cognitive impairments and depression and anxiety symptoms. The patients in cluster 4 had a similar disease duration and age compared with cluster 3, but this cluster had high motor and psychiatric symptom severity, and cognitive impairments were more posterior cortical. Subsequent linear discriminant analyses resulted in two discriminating functions. The clusters were discriminated by EF, and motor and psychiatric symptoms.

This cluster solution might be a reflection of the progressive stages of PD. Since in the HCA not all variables were corrected for disease stage, age or disease duration, the differences could be the result of differences in these disease characteristics. However, cluster 3 and 4 have similar age and disease duration, so these clusters might be different subtypes of clinical PD manifestation. We hypothesize that cluster 3 and 4 may be representations of disparate pathways of disease progression. That is, patients in cluster 1 may represent the early-stages of PD, while cluster 2 represents patients who are in a later, more severe stadium of PD. The differences in subjective disease duration of these clusters confirm this. Cluster 3 and 4 are placed in the chronological 'middle' of this model, within which patients in cluster 1 can progress to either cluster 3 or 4. Finally, cluster 2 is a later, more

severe stage of the disease, characterized by high motor and non-motor symptom severity. Patients in this cluster might have PDD, given the cognitive impairments in multiple domains.

Since a proportion of PD patients does not develop PDD over time – cumulative prevalences of PDD range from 75% to 90% (Kehagia, Barker & Robbins, 2010) – cluster 2 is not likely to be a stadium all PD patients will progress in to. So, differences in pathologies may be present between patients who do, and patients who do not develop PDD. As stated in the introduction, the clinical manifestation of PD is an interaction between various factors rather than simply a disruption of the dopaminergic circuits (Robin & Cools, 2014). Also, genetic predisposition seems to play a role. For example, the enzyme catechol-O-methyltransferase (COMT), which mediates cortical dopamine levels, is in its turn dependent on the COMT Val158Met genotype (Lewis & Barker, 2009). Thus, differences in interaction between pathology and (genetic) predispositions could explain differences in the route of PD progression. When comparing the cognitive profile of cluster 3 and 4, marked differences can be found that seem to be complementary. Like mentioned above, patients in cluster 4 have predominantly 'frontal' cognitive impairments. Thus, the CSTC circuits may play a large role in their symptom manifestation (Owen, 2004). In contrast, cluster 4 shows more posterior cognitive impairments. These, in turn, can be related to hippocampal atrophy, something frequently described in PD (Brück, Kurki, Kaasinen, Vahlberg & Rinne, 2004; Camicioli et al., 2003; Riekkinen et al., 1998). In sum, patients in cluster 3 may have different pathological mechanisms underlying their PD manifestation, compared to patients in cluster 4.

This division of frontal versus posterior cortical cognitive profiles within PD is reported earlier (Williams-Gray et al., 2009; Williams-Gray, Foltynie, Brayne, Robbins & Barker, 2007). They examined high predictive value of two posterior cortical tasks and the MAPT H1/H2 gene for early dementia risk, while they did not find this in frontostriatally based tasks (Williams-Gray et al., 2009). Furthermore, more severe motor symptoms in early PD stages are identified as a risk factor for PDD (Pagonabarraga & Kulisevsky, 2012). Translating this theory to our results, patients in cluster 4 may be at larger risk for developing – at least early – PDD, compared to patients in cluster 3. As mentioned earlier, patients in cluster 2 may well have PDD, given the high motor and non-motor symptoms, in combination with the higher age and disease duration, although this remains speculation. Using this, patients in cluster 4 may be expected at later age to progress to characteristics found in patients in cluster 2. This process is illustrated in Figure 7.

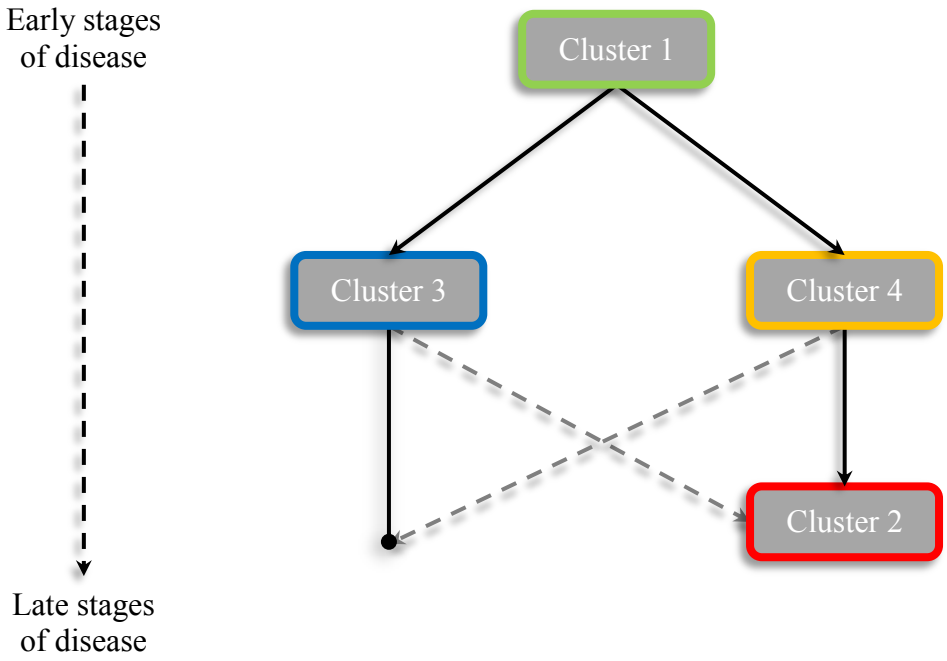


Figure 7 Illustration of the Hypothesis: Patients in Cluster 1 are in the Early Stages of PD and Develop to have Characteristics Seen in Cluster 3 or Cluster 4. Patients in Cluster 4 have more Posterior Cognitive Deficit, and Might Therefore have Larger Risk for Developing Early PDD. Moreover, Patients in Cluster 3 have Frontal Impairments, and might be Less Likely to Develop PDD.

While we did observe differences in the neuropsychological profile between the four clusters, this was not the case for the neuropsychiatric symptoms. The measurement level and high correlations between some of the neuropsychiatric measures limited our possibilities to include multiple neuropsychiatric variables in the HCA. Furthermore, apart from depressive and anxiety symptoms we found few other symptoms like psychotic symptoms or ICDs. This could be due to the fact that our database did not use questionnaires sensitive enough to measure subclinical symptoms, or patients in our database were not yet progressed as far in the disease for the questionnaires to pick up neuropsychiatric symptoms. Nevertheless, previous studies provide hypotheses as to how neuropsychiatry may be present, or develop in the clusters. Psychotic symptoms are more frequent in patients with PDD, compared to non-demented PD patients (Bronnick et al., 2005; Fenelon & Alves, 2010). However, since PDD develops after approximately 10 years after diagnosis (Hughes et al., 2000), and assuming the hypothesis stated above, it could well be that patients in cluster 2, and even in cluster 4 will develop PDD in the future. But, hallucinations are a risk factor for developing PDD (Fenelon, Mahieux, Huon & Ziégler, 2000). Consequently, psychotic symptoms might be found in patients in cluster 2 and 4. In contrast, PD patients with ICDs are frequently associated with

impaired EF (e.g. Vitale et al., 2011). Cluster 3 patients may for that reason have, or develop, more symptoms of ICDs compared to the other three clusters. Nevertheless, this remains highly speculative. Questionnaires like the Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS; Weintraub et al., 2012) and the Questionnaire for Psychotic Experiences (QPE) may provide more sensitive measure to differentiate clusters on these symptoms.

Our study has several strengths. First off, the differences found between the four clusters are likely due to differences in pathology or genetic predisposition, rather than solely a result from demographics or distinct disease stages. Furthermore, our cluster solution is comparable to clusters found in previous studies. In comparison with the meta-analysis by Van Rooden and colleagues (2010), cluster 1 and 2 resemble the "Young age-at-onset and slow disease progression" and the "Old age-at-onset and rapid disease progression" subtypes of PD, respectively. Additionally, our LDA resulted in cognitive, psychiatric and motor constructs which could well discriminate the three clusters. A second LDA confirmed the first LDA, with primarily motor symptoms and EF impairment as discriminating constructs between clusters. Moreover, we used a large sample of PD patients. Lastly, the PD patients were assessed with a variety of cognitive tasks. Using the described elaborate assessment, concerning all cognitive domains instead of a screening measure only, we were able to distinguish separate profiles of cognitive impairment in this population.

Nevertheless, there are also some limitations to our study. As stated above, only screening measures were available for establishing the presence of psychosis and ICDs. Secondly, since this study was cross-sectional, any theories stated as to how the different clusters may progress in PD could not be tested and thus remain hypotheses. Finally, cluster 2 had a small sample size, which impeded us from comparing this cluster statistically to the other clusters.

Given these limitations, there are possibilities for future research. Most importantly, future research should focus on relating the cognitive profiles found to neuropsychiatric symptoms. Whereas we provide theories on which neuropsychiatry can be found or can develop in the different clusters and how these clusters differ on the neuropsychiatric profile, future research using more elaborate questionnaires of a broad spectrum of neuropsychiatry can confirm or counter these. It should be noted that our study group has commenced a follow-up measurement of psychiatric symptoms on the same cohort used in this study.

Furthermore, the use of imaging techniques may shed light on possible differences in brain pathology. In a subgroup of this cohort, dopamine transporter (DaT) single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) were acquired for routine clinical practice, and will be analyzed in the context of these clusters. Finally, this cluster solution should be validated in an independent separate cohort. Longitudinal cohorts can provide information concerning disease progression, which can be used to confirm the described hypotheses.

In conclusion, we found four clusters of PD using a data-driven approach. We examined two demographically similar clusters with a distinct disease manifestation. 'Frontal' dysfunction one the one hand, versus more posterior cortical dysfunction on the other hand, with interaction from predisposition and pathology may well explain these results. This finding confirms the contemporary ideas of disparate profiles within PD, and may shed more light on distinct cognitive profiles in PD. Still, many questions remain unanswered, and these results call – once again – for large longitudinal cohort studies with elaborate motor *and* non-motor symptom measurements.

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APPENDIX I Measurement Instruments

Table 9 Measurement Instruments Used to Assess Disease Severity, Motor Symptoms, Cognitive Function, Neuropsychiatric Symptoms and Other Behavioural Symptoms.

Disease severity		Author	In HCA
Hoehn & Yahr scale		Hoehn & Yahr, 1967	
Motor symptoms			
UPDRS-III		Fahn & Elton, 1987	+
Cognitive function			
Cognitive screening			
Mini-Mental State Examination		Folstein, Folstein & McHugh, 1975	+
Executive function			
Stroop card III compared to card II		Hammes, 1971	+
TMT part B compared to part A		Reitan & Wolfson, 1985	+
BADS	Rule Shift Cards	Wilson, Alderman, Burgess, Emslie & Evans, 1996	
	Key Search		
Working memory			
WAIS digit span backwards		Wechsler, 2000	+
Attention			
WAIS digit span forwards		Wechsler, 2000	
Mental speed			
Stroop card I and II		Hammes, 1971	
TMT part A		Reitan & Wolfson, 1985	
Language			
COWAT (‘letter fluency’)		Schmand, Groenink, Van Den Dungen, 2008	
Category fluency (from GIT2)		Luteijn & Barelds, 2004	
Memory			
RAVLT (Dutch version – “15 Woorden Taak” (15WT))	direct recall subtask	Saan & Deelman, 1986	
	delayed recall subtask		+
	recognition subtask		
RCFT delayed recall subtask		Meyers & Meyers, 1995	
Visuoconstructive abilities			
RCFT copy subtask		Meyers & Meyers, 1995	
Neuropsychiatric symptoms			
BDI		Beck, Ward, Mendelson, Mock & Erbaugh, 1961	
BAI		Beck, Brown, Epstein & Steer, 1988	+
SCOPA-Psychiatric Complications		Visser et al., 2007	

APPENDIX I (continued)

Table (continued)

Sleep disorder symptoms	
SCOPA-SLEEP (nighttime & daytime sleepiness)	Marinus, Visser, Van Hilten, Lammers & Stiggelbout, 2003
Autonomic symptoms	
SCOPA-AUT	Visser, Marinus, Stiggelbout & Van Hilten, 2004
Activities of daily living	
UPDRS-II	Fahn & Elton, 1987
Schwab and England ADL scale	Schwab & England, 1969

Abbreviations: BADS = Behavioural Assessment of the Dysexecutive Syndrome; *BAI* = Beck Anxiety Inventory; *BDI* = Beck Depression Inventory; *COWAT* = Controlled Oral Word Association Test; *GIT2* = Groninger Intelligentie Test 2; *RAVLT* = Rey Auditory Verbal Learning Test, *RCFT* = Rey Complex Figure Test; *SCOPA* = Scales for Outcomes in Parkinson's Disease; *TMT* = Trail Making Task; *UPDRS* = Unified Parkinson's Disease Rating Scale; *WAIS* = Wechsler Adult Intelligence Scale

APPENDIX II Graphical representation, and table overview of the discriminating variables in the second LDA.

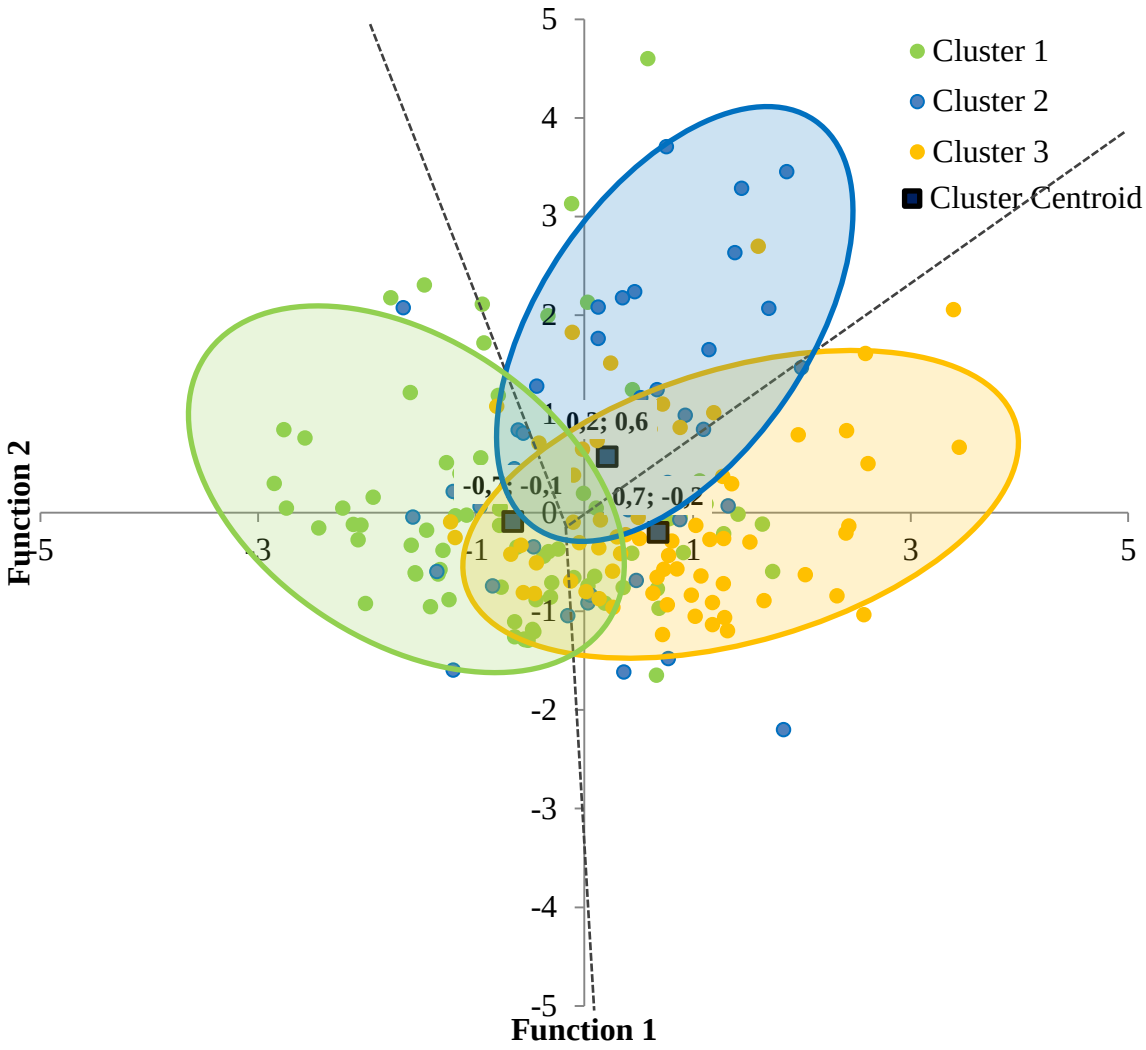

Figure 8 Discriminating Functions between the Three Clusters in the LDA. On the *X*-axis: Function 1; on the *Y*-axis: Function 2. The Coordinates of the Cluster Centroids represent Standardized Mean Scores of the Three Clusters on Function 1 and 2. Discriminant Variable Correlations per Function are Summarized in **Table** 10.

APPENDIX II (continued)

Table 10 Discriminant Variables in second LDA including Variable Correlations per Discriminant Function. Variables are Sorted by Importance per Function. In Bold: Important Discriminating Variables ($r > .3$).

	Function 1	Function 2
Stroop card I*	**- .577**	- .061
H&Y stage	**.540**	- .219
15WT direct recall*	**- .487**	.190
BDI	**.426**	.193
SCOPA-AUT†	**.379**	.011
SCOPA-SLEEP nighttime sleepiness†	**.300**	.046
UPDRS-II ADL†	.258	- .180
TMT part A*†	- .248	- .107
Category fluency*†	- .235	.099
Letter fluency*†	- .155	.097
Age†	.152	.149
Digit span forwards*†	- .060	- .053
BADS rule-shift task (time)	.154	**.907**
SCOPA-SLEEP daytime sleepiness†	.065	- .089

**t*-score; †Variable not included in model, due to too low F value for inclusion.

Abbreviations: H&Y = Hoehn & Yahr; 15WT = 15 Words Test; SCOPA = Scale for Outcomes of Parkinson's Disease; UPDRS = Unified Parkinson's Disease Rating Scale; TMT = Trail Making Task; BDI = Beck Depression Inventory; BADS = Behavioural Assessment of the Dysexecutive Syndrome.