MAPPING COGNITIVE AND NEUROPSYCHIATRIC SYMPTOM CLUSTERS IN IDIOPATHIC PARKINSON'S DISEASE

A CROSS-SECTIONAL AND LONGITUDINAL DATA ANALYSIS

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Abstract

Introduction: The purpose of this study was to map subtypes in Parkinson's disease with respect to motor, cognitive and neuropsychiatric symptoms, assess the possible relation between these symptoms, and assess their longitudinal disease trajectory. **Methods:** Data from 341 idiopathic Parkinson's disease patients were used to perform a Hierarchical Cluster Analysis (HCA). We included measurements of motor, cognitive and neuropsychiatric symptoms. A Linear Discriminant Analysis (LDA) was performed to determine which constructs could best differentiate the clusters and a repeated measures ANOVA was used to assess the development of symptoms over a period of two years. **Results:** The HCA revealed six clusters: (A) a cluster with low motor symptoms and high REM sleep behavior disorder (age M: 61.6); (B) a neuropsychiatrically and cognitively impaired cluster with rapidly worsening REM sleep behavior disorder (age M: 66.3); (C) a cluster with severe motor dysfunction and below average but stable cognition and neuropsychiatry (age M: 68.1); (D) a cluster with overall average functioning without RBD symptoms (age M: 65.9); (E) a young aged overall unimpaired cluster (age M: 58.0); and (F) an old-aged cluster with severe overall impairments (age M: 68.6). The LDA revealed that cognitive symptoms could best discriminate the clusters. **Conclusion:** We differentiated six cluster (A-E). The mean age in clusters A and E were relatively similar, as is the case for clusters B, C, D, and F. We found a distinction between these two cluster groups based on disease onset and severity of symptoms. The clusters were further distinguishable on specific cognitive, motor and neuropsychiatric symptoms. Future research should focus on determining whether the distinction we found is based on different underlying neuropathology or other factors, like medication effectiveness.

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Introduction

In 'An Essay on the Shaking Palsy' (1817), James Parkinson first wrote about 'Paralysis Agitans,' a condition that is now more commonly known as Parkinson's disease (PD). PD ranks second on the list of most common neurodegenerative diseases (Wirdefeldt, Adami, Cole, Trichopoulos, & Mandel, 2011), and seems to affect approximately one percent of the population over the age of 65 (Bastide, et al., 2015; De Lau, & Breteler, 2006). The pathological features that characterize idiopathic PD (PD without a known cause) are mainly the degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) and the presence of intracellular inclusions known as Lewy Bodies (Braak, Ghebremedhin, Rüb, Bratzke, & Del Tredici, 2004; Mullin, & Schapira, 2015; Stuss, Winocur, & Robertson, 2008). For a long time, PD was considered to be manifested predominantly by motor symptoms including resting tremor, bradykinesia, gait disturbance, rigidity and postural instability (Jankovic, 2008; Stuss et al., 2008; Wirdefeldt et al., 2011). However, symptomatology of PD seems more extensive: non-motor symptoms (NMS) of PD have been found to consist of neuropsychiatric symptoms (NPS), cognitive dysfunction, autonomic dysfunctions, gastrointestinal symptoms, sensory disturbances, sleep disturbances and fatigue (Barone, 2010; Lee, & Koh, 2015; Williams-Gray, Foltynie, Lewis, & Barker, 2006). The motor symptoms negatively affect the quality of life in PD patients (Hechtner, 2014; Lyons, & Pahwa, 2011). However, NMS are of even greater interest in relation to the quality of life in PD patients: NPS and cognitive dysfunctions in PD have been reported as having a more severe impact on the patients' quality of life in comparison with motor symptoms only (Starkstein, Brockman, & Hayhow, 2012; Weintraub, Moberg, Duda, Katz, & Stern, 2004).

NPS and cognitive dysfunction are an upcoming topic in PD research. A multitude of NPS have been observed in PD, including depression disorders, anxiety disorders, apathy, REM sleep behavior disorder (RBD), psychosis and impulse control disorders (ICDs) (Gallagher, & Schrag, 2012; Weintraub et al., 2010). A large review on the cognitive impairments in PD revealed that almost all kinds of cognitive deficits are prevalent in PD (Cholerton et al., 2014; Ding, Ding, Li, Han, & Mu, 2015). The cognitive domains that are most commonly impaired in PD are executive functioning, attention, memory and visuospatial functioning (Cholerton et al., 2014; Ding et al., 2015). For a more detailed description of cognitive dysfunction and psychiatric symptoms see Box 1.

Box 1. Cognitive dysfunctions and neuropsychiatric symptoms in PD.

Cognitive dysfunctions

Executive dysfunctions: PD patients often have problems with abilities that enable goal-directed behavior, such as planning and executing a goal. This consists of problems with cognitive flexibility, inhibition of automated response, monitoring, implementation of strategies for problem solving, self-control, and the maintenance and manipulation of information in working memory (Aarsland, Brønnick, & Fladby, 2011; Ding et al., 2015; Jurado & Rosseli, 2007).
Memory Problems: PD patients regularly have trouble with consolidating and retrieving memories. More specifically, episodic memory deficits have been reported even early in the disease. This mostly causes problems with learning and encoding (Aarsland et al., 2011; Stuss et al., 2008).
Visuospatial functioning: The visuospatial functioning in PD patients declines during the disease. It becomes more difficult to process incoming visual stimuli. This makes it harder to understand spatial relationships between objects and visualize images and scenarios (Aarsland et al., 2011; Montse, Pere, Carme, Francesc, & Eduardo, 2001).

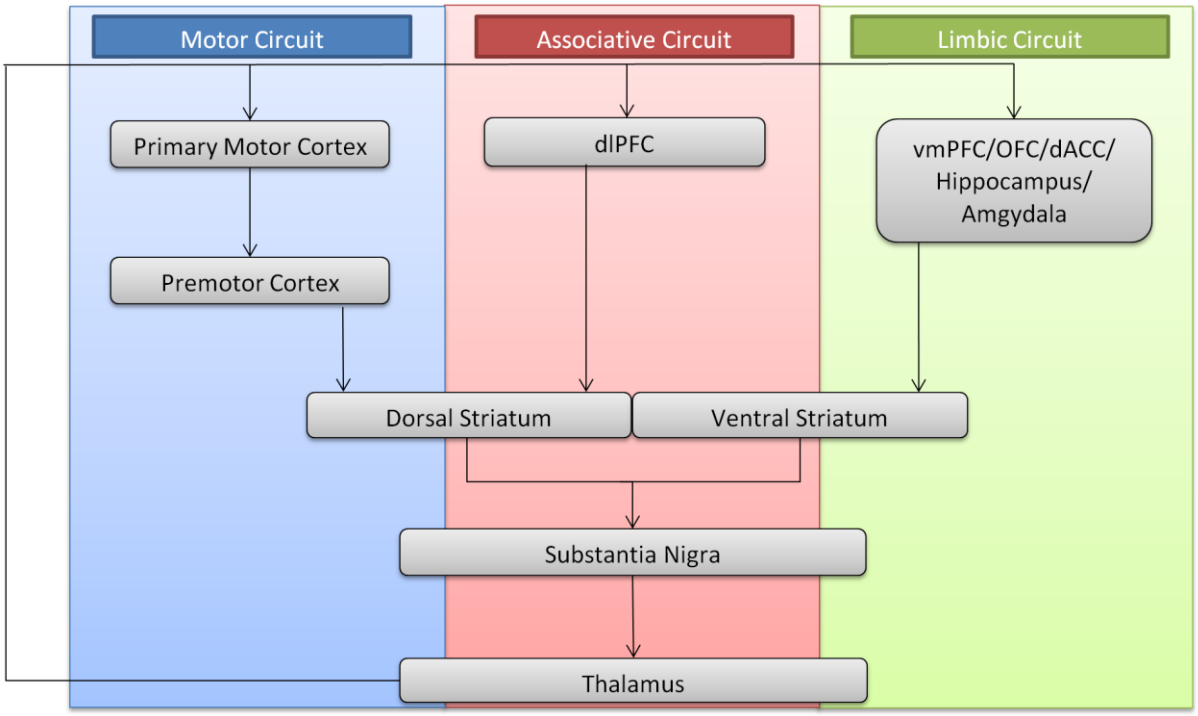
Neuropsychiatric symptoms

Depression: During the disease patients can experience a persistent feeling of sadness and loss of interest (Gray, 2010; Kummer & Teixeira).
Anxiety: PD patients often experience anxiety. Anxiety is an emotion characterized by feelings of tension, worried thoughts and physical changes like increased blood pressure. People with anxiety disorders usually have recurring intrusive thoughts or concerns. They may avoid certain situations out of worry. They may also have physical symptoms such as sweating, trembling, dizziness or a rapid heartbeat (Gray, 2010; Kummer & Teixeira, 2009)
Psychosis: Psychosis is sometimes associated with PD. It refers to an abnormal condition of the mind, involving a loss of contact with reality. People might experience hallucination, personality changes and thought disorders when having a psychosis. This may be accompanied by unusual behavior and difficulty with social interactions (Gray, 2010; Kummer & Teixeira, 2009).
Rem Sleep Behavior Disorder (RBD): The paralysis that normally occurs during REM sleep is incomplete or absent in a person with RBD. This causes people to act out their dreams, which are vivid, intense and violent. Dream-enacting behaviors include yelling, punching, talking, kicking, jumping, sitting, grabbing and arm flailing. This disorder is often present in PD patients (Boeve, 2010; Kummer & Teixeira, 2009).
Impulse Control Disorders: ICDs are a group of psychiatric disorders in which the person cannot control oneself: impulsivity. Commonly this consists of a failure to resist temptation, urge or impulse that may harm oneself or others. In PD these disorders are commonly reported (Gray, 2010; Kummer & Teixeira, 2009).

In PD, certain cognitive dysfunctions and NPS seem to co-occur (Trojano, Santagelo, Conson, & Grossi, 2013). This might be the result of some overlap in the underlying pathology of cognitive dysfunctions and NPS (Beyer, Janvin, Larsen, & Aarsland, 2007; Mak, Bergsland, Dwyer, Zivadinov, & Kandiah, 2014; Weintraub et al., 2005a). The cortico-striatal-thalamo-cortical circuit (CSTC) model

describes this underlying pathology and the overlapping mechanisms for motor, cognitive and psychiatric dysfunctions in PD (see Figure 1) (Groenewegen & Uylings, 2010).

Figure 1. Cortico-Striatal-Thalamo-Cortical Circuit (CSTC) Model



Derived from Alexander, Delong, & Strick,1986; Ballanger, Jahanshahi, Broussolle, & Thobios ,2009; Groenewegen & Uylings, 2010. dlPFC: dorsal lateral Prefrontal Cortex, vmPFC: ventral medial Prefrontal Cortex, OFC: orbitofrontal Cortex, dACC: dorsal Anterior Cingulate Cortex.

This circuit consists of specific connections between the dopaminergic neurons in the brainstem, basal ganglia and (pre)frontal cortex (Alexander et al., 1986; Groenewegen & Uylings 2010). In PD, degeneration of dopamine neurons in the substantia nigra and striatum cause a decreased signaling to all areas connected in the CSTC circuit (DeLong, & Wichmann, 2007). This, in turn, causes decreased activation in the CSTC circuit resulting in the motor, cognitive and psychiatric dysfunctions commonly found in PD, e.g. depression, anxiety, and executive dysfunction. For a more detailed description of the CSTC circuit model and the mechanisms behind specific symptoms see Box 2. This dopaminergic effect in CSTC circuit explains the co-occurrence of certain psychiatric and cognitive symptoms in PD. However, also other anatomical and neurotransmitter alterations have been found to play a role in emotional and cognitive dysfunction in PD, such as a loss of cholinergic, adrenergic and serotonergic neurons (Chaudhuri, Healy, & Schapira, 2006; Prediger, Matheus, Schwarzbold, Lima, & Vital, 2012). Further research is necessary to better understand the interaction between these different anatomical and neurotransmitter alterations and the various PD symptoms.

Box 2. Cortico-Striatal-Thalamo-Cortical Circuit and PD symptoms

Mechanism

The CSTC circuit can be divided in three semi-distinct circuits: a motor circuit, an associative circuit and a limbic circuit (Groenewegen & Uylings, 2010; Haber & Knutson, 2010). The associative circuit is thought to play a role in cognition (Alexander et al.,1986; Chudasama & Robbins, 2006; Leh, Petrides, & Strafella, 2010; Yuan & Raz, 2014) while the limbic circuit might be important in emotion and motivation (O'Callaghan, Bertoux, & Hornberger, 2014a; O'Callaghan, Shine, Lewis, & Hornberger, 2014b). Within each of the CSTC circuits different pathways lead to inhibition and excitation (Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo, 2014). It is presumed that degeneration of the dopamine neurons in the substantia nigra and striatum can either induce increased activity of the inhibitory pathways or cause a decreased activity of the excitatory pathways (DeLong & Wichmann, 2007). This will, in turn, result in a decreased activity of the cortical areas connected to the CSTC circuit, resulting in motor, cognitive and psychiatric dysfunction.

Cognitive dysfunction

The main cortical area of the associative CSTC circuit is the dorsolateral prefrontal cortex (dlPFC). This area is thought to play a role in cognitive flexibility, working memory and planning (Aupperle et al., 2012; Leh et al., 2010). Degeneration of the dopamine neurons in the substantia nigra and striatum cause hypo-excitation of the thalamus and dlPFC (Grahn et al., 2009; Owen, 2004), resulting in cognitive dysfunction (Ekman et al., 2012).

Psychiatric symptoms

Depression. Dopamine reduction in the ventral striatal areas induce an overactivity of the inhibiting pathway of the limbic CSTC circuit (Shen, Flajolet, Greengard, & Surmeier, 2008; Surmeijer, Ding, Day, Wang, & Shen, 2007). This causes a decreased stimulation of the cortical areas in the limbic system. Motivation and reward are then influenced which leads to the expression of depressive symptoms (Remy, Doder, Lees, Turjanski, & Brooks, 2005; Surmeier et al., 2007; Shen et al., 2008; Voon, Mehta, & Hallat, 2011b). Reduced dopamine transporter (DaT) availability in presynaptic striatal dopamine neurons can also be associated with depressive symptoms (Hesse et al., 2009; Rektorova, Srovnalova, Hubikove, & Prasek, 2008; Remy et al., 2005; Vriend et al., 2014b; Weintraub et al., 2005b). DaT causes the reuptake of dopamine from the synaptic cleft. Vriend et al. (2014) found that the severity of depressive symptoms in PD is correlated negatively with DaT availability in the caudate nucleus.

ICDs. It seems that ICDs in PD mostly appear when patients are medicated with dopamine agonists (Bastiaens, Dorfman, Christos, & Nirenberg, 2013; Bostwick, Hecksel, Stevens, Bower, & Ahlskog, 2009; Frank, Seeberger, & O'Reilly, 2004; Joutsa, Martikainen, Vahlberg, Voon, & Kaasinen, 2012). Treatment with dopamine agonists leads to an increased ventral striatal dopaminergic signaling, which alters reward-based learning (Bódi et al., 2009; Van Eimeren, 2009; Voon et al., 2011a). Not all PD patients develop ICDs. It could be possible that certain neurobiological substrates, like DaT availability (Vriend et al., 2014b), interact with the changing dopamine levels. This, in turn, could alter the normal processing in reward and motivation-related brain circuits (Bódi et al., 2009; Van Eimeren, 2009; Voon et al., 2011a).

Anxiety. The limbic CSTC circuit is connected to the amygdala (Groenewegen & Uylings, 2010), which is the key structure involved in the regulation and production of anxiety (Prediger et al., 2012). Both increases (Ceravolo et al., 2013; Moriyama et al., 2011) and decreases (Erro et al., 2012; Weintraub et al., 2005a) of DaT availability in the striatum have been associated with anxiety symptoms. Furthermore, some anxiety symptoms can be alleviated with PD medication in some patients (Kulisevsky et al., 2007; Tessitore et al., 2002). It seems that a dysfunctional amygdala accounts for anxiety symptoms in PD but the exact interaction between the dopaminergic system and anxiety should be further investigated (Dissanayaka et al., 2014).

To further understand the relationship between the various PD symptoms, research has focused on differences in the expression and (co-)occurrence of PD symptoms. An important question considers why some patients show certain symptoms while these remain absent in other patients. This heterogeneity has been assessed by studying symptom subtypes/subgroups in idiopathic PD patients. It is important to assess the heterogeneity in PD since homogeneous groups of patients are more likely to share genetic and pathological features. Identification of possible symptom profiles might lead to more tailored treatment strategies and earlier disease recognition. Possible subtypes have been identified. For example, Van Rooden et al. (2010) conducted a review on cluster analyses in PD. Although the results remained somewhat inconclusive, most studies found two distinctive cluster profiles, ‘‘old age-at-onset and rapid disease progression’’ and ‘‘young age-at-onset and slow disease progression.’’ Some motor symptom subtypes have also been identified. For instance, Reijnders, Ehrt, Lousberg, Aarsland, and Leentjens (2009) and Lewis et al. (2005) identified the motor subtypes: “tremor dominant (TD)” and “bradykinesia/rigidity and Postural Instability Gait Disturbance (PIGB) dominant.” These motor subtypes were also confirmed by Van Rooden et al. (2010). However, few studies included extensive cognitive function measurement and NPS in their analysis. One study that did include these variables found several subgroups: ‘young disease onset,’ ‘tremor dominant,’ ‘non-tremor dominant with significant levels of cognitive impairment and mild depression’ and ‘rapid disease progression but no cognitive impairment’ (Lewis et al., 2005). Unfortunately, specific domains of cognitive symptoms and NPS were not assessed in this study. Janvin, Larsen, Aarsland and Hugdahl (2006) conducted a study on the subtypes of mild cognitive impairment in PD. They found that an “amnestic type,” a “single non-memory domain” type and a “multiple domains slightly impaired” type could be distinguished in PD. Patients with the “single non-memory domain” type had either deficits in the executive domain or deficits in the visuospatial domain. Patients with the “multiple domain slightly impaired” type had either executive impairment and/or visuospatial impairment and/or memory impairment (Janvin et al., 2006). This study did not assess whether these subtypes of mild cognitive impairment could be linked to specific NPS.

Although previous research shows that there is evidence for specific cognitive symptom clusters, it remains unclear whether and how specific cognitive domains might be related to neuropsychiatric symptoms in PD. Van Balkom et al. (2015) performed a recent study on the cognitive and psychiatric heterogeneity in 226 PD patients. They conducted a cluster analysis and revealed four clusters: (1) a young-age, cognitively and neuropsychiatrically unimpaired cluster, (2) an old-age cluster with severe overall impairments, (3) a cluster with specifically executive dysfunction and anxiety and depression symptoms and (4) a cluster with motor symptoms, anxiety and depression symptoms and verbal memory impairment. Cluster 1 and 2 seem equivalent to the cluster profiles found in earlier studies (Rooden et al., 2010). These clusters are thought to represent the opposite sides of the PD disease trajectory. In their opinion, cluster 1 represented the early stages of the disease, while cluster 2 represented a later stage of the disease, with more severe symptoms. The patients in clusters 3 and 4 had different symptom profiles but same age and disease duration. Van Balkom et al. (2015) hypothesized that these clusters represent different pathways of disease progression, with presumably distinct underlying pathology.

In the study from Van Balkom et al. (2015), distinct neuropsychiatric profiles could not be differentiated because the neuropsychiatric measurements they used were sensitive to only depressive and anxiety symptoms. It remains unclear whether other neuropsychiatric domains are related to cognitive symptoms in PD. The present study will focus on the question: Can we distinguish specific motor, cognitive and neuropsychiatric symptom profiles within PD? The aim of the study is to validate the subtypes found by Van Balkom et al. (2015) in a separate cohort, using a broader and different set of measurements to assess cognitive dysfunctions and NPS. We hypothesize that the cluster solution found by Van Balkom et al. (2015) will also be observed in this study, and thus proposing a viable basis that the effects found are the product of the same underlying cognitive and neuropsychiatric constructs. We therefore expect to differentiate a cluster with young-age, cognitively and neuropsychiatrically unimpaired subjects, a cluster with severely impaired old-age subjects, a cluster with motor- and memory impaired subjects with anxiety and depression symptoms and, lastly, a cluster with subjects who display specific executive dysfunction, anxiety and depression. We also expect to find a cluster with ICD symptoms and executive dysfunctions (similar to cluster 3 found by Van Balkom et al., 2015), because in healthy populations ICDs and executive dysfunctions frequently co-occur (Forbush et al., 2008; Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2008; Kertzman et al., 2008).

Methods

To accomplish a more conclusive image of the different symptom profiles in PD, we investigated cognitive and psychiatric heterogeneity in PD using data from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). PPMI is an observational clinical study initiated to comprehensively evaluate cohorts of significant interest using advanced imaging, biologic sampling and clinical and behavioral assessments to identify biomarkers of Parkinson's disease progression. Up-to-date information about the study can be found on the PPMI study website (www.ppmi-info.org).

Participants

Data from 449 idiopathic PD patients and 210 healthy controls were used. Data were obtained between 2010 and 2015. Inclusion criteria were: 1) a diagnosis of idiopathic PD, 2) data from cognitive, neuropsychiatric and motor symptom measurements, assessed at baseline, one year and two years after baseline and 3) written consent to use all acquired PPMI data for scientific purposes. For a complete list of inclusion and exclusion criteria, see appendix I.

Measurements

Table 1 describes the measurements used in the cluster analysis. Table 2 displays the measurements used to further describe the cluster found in our analysis.

Table 1 Measurement instruments included in cluster analysis

Instrument with construct measured	Author
Motor function	
MDS-UPDRS part III (UPDRS)	Goetz et al., 2007
Cognitive function	
Global Cognition	
The Montreal Cognitive Assessment (MoCA)	Nasreddine et al., 2005
Memory	
Hopkins Verbal Learning Test (HVLT)	Brandt, 1991
Executive Function	
WMS-III Letter-Number Sequencing (LNS)	Psychological Corporation, 1997
Processing speed	
Symbol Digit Modalities Test (SDMT)	Smith, 1982
Visuospatial Function	
Benton Judgment of Line Orientation Test (BJLOT)	Benton, Varney, & Hamsher, 1978
Language	Goodglass & Kaplan, 1972
Semantic Fluency/Verbal Learning Task (VLT)	
Neuropsychiatric function	
State-Trait Anxiety Inventory (STAI)	Spielberger, 1970
REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)	Stiasny-Kolster et al., 2007

Table 2 Measurement instruments not included in cluster analysis

Instrument with construct measured	Author
Disease Severity Stage	
Hoehn & Yahr Scale (H&Y Scale)	Hoehn, & Yahr, 1967
Neuropsychiatric function	
Geriatric Depression Scale (GDS15)	Sheikh, & Yesavage, 1986
Questionnaire for Impulsive-Compulsive Disorders (QUIP-S)	Weintraub et al., 2009
Autonomic function	
Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction (SCOPA-AUT)	Visser, Marinus, Stiggelbout, & van Hilten, 2004
Sleep function	
The Epworth Sleepiness Scale(ESS)	Johns, 1991
Activities of Daily living (ADL)	
Modified Schwab & England Activities of Daily (MSEADL)	Goetz et al., 2007

Motor symptoms were measured with the Unified Parkinson's Disease Rating Scale part III (UPDRS part III; Goetz et al., 2007). The UPDRS consist of four parts. Part I is concerned with non-motor experiences of daily living and consist of Part IA containing 6 questions assessed by the investigator and focuses on complex behaviors and part IB containing 7 questions that are part of the patient questionnaire completed by the subject. Part II contains 13 questions in the patient questionnaire that assess the motor experiences of daily living. Part III was administered by the investigator and assesses the motor signs of PD by means of tasks and observation. Part IV is completed at each visit once a subject has started PD medication, this part assesses motor complications using historical and objective information (The Parkinson Progression Marker Initiative, 2014).

Measurements focusing on specific cognitive domains were used in the analysis. The Hopkins Verbal Learning Test (HVLT; Brandt, 1991) measured verbal, short-term memory/new learning requiring rapid encoding of information (Benedict, Schretlen, Groninger & Brandt, 1998). The WMS-III Letter-Number Sequencing test (LNS; Psychological Corporation, 1997) measured executive functioning/working memory. The Symbol Digit Modalities Test (SDMT; Smith, 1982) measured attention, concentration and speed of information processing. The Benton Judgement of Line Orientation Test (BJLOT; Benton et al., 1978) measured spatial perception and orientation. Language will be assessed using the Semantic Fluency test (VLT; Goodglass & Kaplan, 1972). The Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005) consists of tasks measuring global cognitive functioning.

Neuropsychiatric functioning was assessed by means of questionnaires. The Geriatric Depression Scale (GDS15; Sheikh, & Yesavage, 1986), measured depression using 15, yes/no questions. A score ≥ 5 on the GDS15 indicates clinical significant depression symptoms (Weintraub, Oehlberg, Katz, & Stern, 2006). The State-Trait Anxiety Inventory (STAI; Spielberger, 1970) measured self-rated anxiety affect. The questionnaire consists of 40 items which are scored on a 4-point Likert scale. A score ≥ 54 on the STAI indicated clinical significant anxiety (Kvaal, Ulstein, Nordhus, & Engedal, 2005). ICDs and other compulsive behaviors were measured with the Questionnaire for Impulsive-Compulsive Disorders (QUIP-S; Weintraub et al., 2009). The questionnaire consists of 13, yes/no, self-administered items about gambling, sex, buying, eating, other behaviors and medication use. On the QUIP-S questionnaire a score ≥ 1 (Yes) for any item indicated presence of an ICD (Weintraub et al., 2009). The REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ; Stiasny-Kolster et al., 2007) measures sleep-wake disturbances. It is a 10-item, yes/no, self-rated questionnaire. A score ≥ 6 indicated presence of RBD (Nomura, Inoue, Kagimura, Uemura & Nakashima, 2011).

We also analyzed the following measurements to define their contribution to the clusters. The Hoehn & Yarh (H&Y) Scale (Hoehn, & Yahr, 1967) described how symptoms of PD progress, using stages from 0 to 5 indicating the relative level of disability. The Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction (SCOPA-AUT; Visser et al., 2004) consisted of a 26 self-administered items scored on a 4-point Likert scale to assess whether autonomic dysfunctions increase as the disease severity progresses. The Epworth Sleepiness Scale (ESS; Johns, 1991) is a self-administered questionnaire about the tendency to fall asleep in eight different situations rated on a 4-point Likert scale (The Parkinson Progression Marker Initiative, 2014). Lastly, activities of daily living (ADL) were assessed using the Modified Schwab & England Activities of Daily Living (MSEADL; Fahn, & Elton, 1987), assessing the ease at which daily activities can be performed (The Parkinson Progression Marker Initiative, 2014).

Procedure

The data collecting for the PPMI study has been performed in 24 different clinical sites, located in The United States, Germany, Norway, Australia, France, Greece, Spain, Israel, Austria and Italy (For a complete overview see PPMI study website: http://www.ppmi-info.org/about-ppmi/ppmi-clinical-sites/). Idiopathic PD patients and healthy controls were followed during a five-year period. After an extensive baseline assessment, subjects were assessed every three to six months for a minimum of three years. Data is collected by each site under uniformly established protocols and stored and analyzed at designated core facilities (The Parkinson Progression Marker

Initiative, 2014). We used data from the assessments at baseline, one year after baseline and two years after baseline. The assessment took about three hours to complete. After giving informed consent subjects underwent a neurological examination and height, weight, vital signs, blood and urine measures were taken. Hereafter, a complete set of cognitive and neuropsychiatric measures is assessed, consisting of: The Physical Activity Scale for the Elderly (Washburn, Smith, Jette, & Janney, 1993), the ESS, the RBDSQ, the GDS15, the STAI, the QUIP-S, the SCOPA-AUT, the MoCA, the LNS, the HVLT, the SMDT, the BJLOT, and the VLT. After this the UPDRS part I to III was administered, part IV might also be conducted if the subject has started on PD medication. The MSEADL is administered. The UPDRS part III and H&Y Scale is administered again one hour following dosing in clinic for subjects who have started on levodopa or a dopamine agonist. Following these assessments subjects continue with a lumbar puncture for collection of cerebrospinal fluid. Different imaging techniques are used, i.e. SPECT, VMAT-2 PET, florbetaben PET imaging, MRI DTI and resting state MRI. The current medical condition and concomitant medications of subjects is questioned. The measurements for the control condition are the same as the PD condition, with the exception of the UPDRS. Subjects were not compensated for their participation in this study (The Parkinson Progression Marker Initiative, 2014).

Statistical analysis

A hierarchical cluster analysis was conducted on the data. Variables included in the cluster analysis were: the UPDRS total score of part III, The HVLT total score of the delay condition. The LNS total score, the SMDT total score, the BJLOT total score, the VLT total score of the animal category, the MoCA total score, the STAI total score and the RBDSQ total score. During the computing of total scores for the UPDRS part III we discovered some discrepancy between the “on” and “off” scores in the PPMI sample. We concluded that it was not possible to distinguish the “on” and “off” score for each participant correctly. We dealt with this problem by taking the average of the “on” and “off” score for each participant and using this average in our analysis. To get a sense of the different motor symptoms in each cluster, we also computed mean scores for the following symptoms: tremor, postural instability/gait, rigidity and hypokinesia, based on a method that is frequently used (Lewis et al., 2005; Liu, Feng, Wang, Zhang, & Chen, 2011; Stebbins et al., 2013). An overall non tremor dominant (NTD) score was also computed. See table 3 for the items used to compose these mean scores. Patients were then marked as “tremor dominant (TD),” “postural instability/gait difficulty (PIGD)” or “mixed,” based on the ratio score of the total tremor score to the total PIGD score. A ratio score of ≤ 0.9 was marked as “PIGD”, a score ≥ 1.15 was marked as “TD” and a score ≥ 0.90 and ≤ 1.15 was marked as “mixed” (Lewis et al., 2005; Liu et al., 2011; Stebbins et al., 2013). We performed

a chi-square test to analyze the association between the clusters and the percentage of patients with the specific subtypes.

Table 3. UPDRS part III items used to compute mean symptoms scores

Tremor	Hypokinesia	PIGD	Rigidity	Non-Tremor
3.15 postural tremor	3.4 Finger Tapping	3.9 Arising from chair	3.3 Rigidity	3.1 Speech
3.16 kinetic tremor	3.5 Hand movements	3.10 Gait		3.2 Facial expression
3.17 rest tremor amplitude	3.6 Pronation-Supination	3.11 Freezing of gait		3.3 Rigidity
3.18 constancy of rest tremor	3.7 Toe tapping	3.12 Postural stability		3.4 Finger tapping
	3.8 Leg agility	3.13 Posture		3.5 Hand movements
	3.14 Bradykinesia			3.6 Pronation – Supination
				3.7 Toe tapping
				3.8 Leg agility
				3.9 Arising from chair
				3.10 Gait
				3.11 Freezing of gait
				3.12 Postural stablility
				3.13 Posture
				3.14 Bradykinesia

Cognitive measures were standardized to *z*-scores using the mean and standard deviations of the healthy control population to control for age effects. Cases were excluded from the cluster analysis if there were missing values on the variables described above. Data from all questionnaires were imputed by using the average score of the participant on valid items if no more than 1/6 of the items were missing. Outliers were marked using the Mahalanobis D square measure, a multivariate assessment of each observation across a set of variables. The Mahalanobis D square measure is distributed as a Chi-square statistic with degrees of freedom equal to the number of variables in the analysis. This makes it possible to compute the probability value per case. A small probability value indicated cases which were more distant from the other cases in the sample (Hair, Black, Babin, Anderson, & Tatham, 2010). Outliers were marked ($p < 0.001$) and excluded from analysis. Collinearity among the variables was assessed. Variables were excluded from the cluster analysis if they were highly correlated ($r > 0.7$). A recent study concluded that a correlation coefficient between predictor variable of $|r| > 0.7$ was an appropriate indicator for when collinearity begins to severely distort model estimation and subsequent prediction (Dormann et al., 2013). The total score of the HVLT recall condition was excluded from analysis, because of high collinearity with HVLT delay condition ($r = 0.808$). The GDS15 total score was also excluded from analysis because of high collinearity with the STAI total score ($r = 0.718$). The Squared Euclidean distance measure was applied, in combination with Ward's clustering method of minimal variance (Ward Jr., 1963). We compared the 'best cut' dendogram output with the 'elbow' in the scree plot, to determine the appropriate number of clusters to select. All variables were standardized to *z*-scores and checked for

normality. With non-normality in variables was dealt by transforming the data, using a square root or log transformation.

Linear discriminant analysis (LDA) was performed to evaluate which variables in the cluster analysis could discriminate the clusters the best. A second LDA was performed to asses which variables not included in the cluster analysis could also discriminate between the clusters. All variables were also analyzed to determine the best way to describe the clusters, e.g. by means of analyses of variance (ANOVAs), Kruskal-Wallis tests or Chi-square tests. If the assumption of equal variances for ANOVA was not met, we computed a Welch's ANOVA. In addition, we examined the distribution of medication use, gender, education years and disease duration per cluster. A value of $\alpha < 0.05$ was considered significant. A correction for multiple comparisons was computed, following ANOVA, Hochberg's GT2 procedure for unequal sample sizes was applied. Following Welch's ANOVA, Games-Howell procedure for unequal variances was applied. Lastly, the Bonferroni method was apllied following, Kruskal-Wallis and Chi-square test.

To formulate a better understanding of the symptom progression of the clusters, we compared the cluster means with baseline scores and the scores from one year after baseline. The following variables were included: the UPDRS total score of part III, the HVLT total score of the delay and recall condition, the LNS total score, the SDMT total score, the BJLOT total score, the VLT total score of animal category, the MoCA total score, the STAI total score and the RSBDQ total score, the GDS15 total score, the SCOPA-AUT total score, the ESS total score, the MSEADL total score. Cognitive measures on baseline and one year after baseline were standardized into *z*-scores using the mean and standard deviations of the healthy control population at that time point, to control for age effects. All variables were then standardized to *z*-scores. For each cluster we calculated the percentage of change between baseline and two years after baseline score for each variable. A one-way repeated measures ANOVA was performed for each cluster on all individual variables, to reveal if there was a significant change in scores between baseline, one year and two years after baseline. A value of $\alpha < 0.05$ was considered significant. All assumptions were checked. When the assumption of sphericity was violated we corrected the degrees of freedom with the Greenhouse-Geisser correction or the Huynh-Feldt correction to gain a more conservative test for the within subject effect of our variables. For the anxiety and depression measures we also performed separate one-way repeated measures ANOVA's using only the score from baseline and two years after baseline, because of the excessive amount of missing values on these variables at one year after baseline. All variables at baseline were also analyzed to determine the best way to describe the differences between the cluster at that time, e.g. by means of ANOVAs, Kruskal-Wallis tests or Chi-square tests. This gave us

information about the significant differences between the clusters for each variable seperatly. If the assumption of equal variances for ANOVA was not met, we computed a Welch's ANOVA. A value of $\alpha < 0.05$ was considered significant. A correction for multiple comparisons was computed. Following ANOVA, Hochberg's GT2 procedure for unequal sample sizes was applied. Following Welch's ANOVA, Games-Howell procedure for unequal variances was applied. The Bonferroni method was applied following, Kruskal-Wallis and Chi-square test. Lastly, we labeled and named each cluster and characterize each cluster by means of observable variables. All statistical analyzes were performed using SPSS 21.0 (IBM Inc., Armonk, NY).

Results

Demographics

Our starting sample consisted of 449 Parkinson patients. We had to exclude 102 cases from this sample due to missing values on the variables selected for the cluster analysis. We also excluded six cases that were marked as outliers. Thus, our final sample used in analysis consisted of data from 341 Parkinson patients with 65.4 % males (age M=63.91; SD=9.98) and 34.6 % females (age M=61.85, SD=9.43). For an overview of the demographics and characteristics of this sample see table 4. Additionally, to compute *z*-scores corrected for age effects on cognitive variables in our Parkinson sample we used data from 210 healthy controls, 64.3 % males (age M=62.95, SD=10.97) and 35.7 % females (age M=61.30, SD=11.79), see table 4.

Table 4. Sample characteristics PD sample

	Mean/percentage (Standard deviation)	
Characteristics	***PD Sample***	***Healthy Controls***
N	341	210
Age	63. 2 (9.83)	62.33 (11.28)
Gender (male %)	64.3%	64.3%
Education years	15.51 (2.89)	16.00 (2.95)
Disease duration in years	3.93 (1.44)	-
Percentage of medication use	87.3%	-
	0 = 0.3%	-
	1 = 24.9%	
Hoehn & Yahr Scale	2 = 69.8%	
	3 = 3.8%	
	4 = 1.2%	

Cluster Analysis

The hierarchical clustering results indicated a three or six cluster solutions based on de 'best cut' dendogram and the elbow in the scree plot, see figure 2 and 3. However, after inspection of variables means per cluster, we decided that a six cluster solution would render the best clustering solution. Figure 4 and 5 show a radar graph of the mean *z*-score of each cluster on specific variables.

Figure 2. Dissimilarity dendogram with the red line showing the best cut at six clusters.

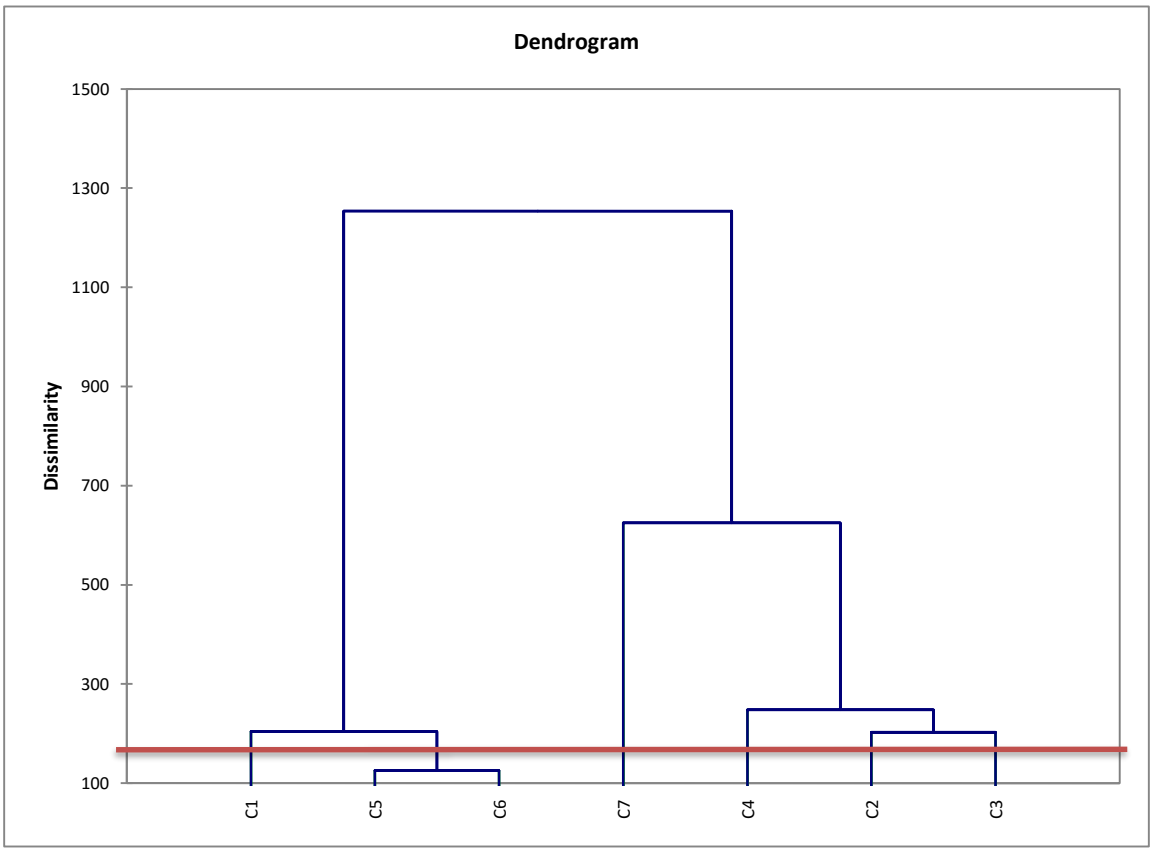
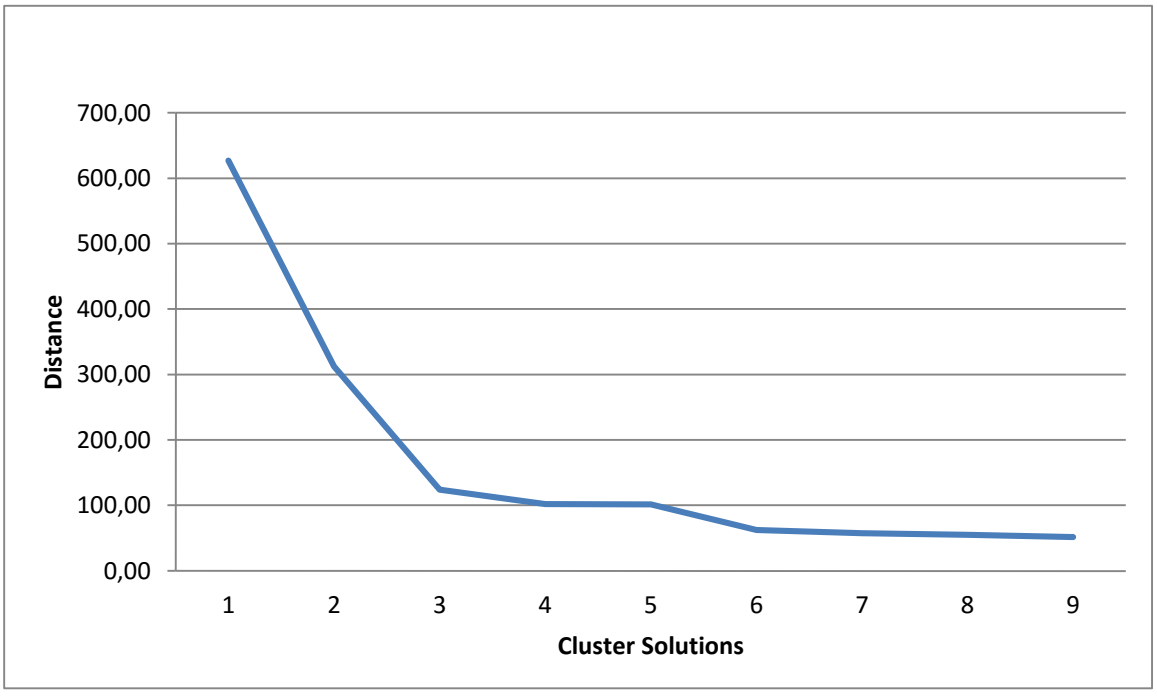
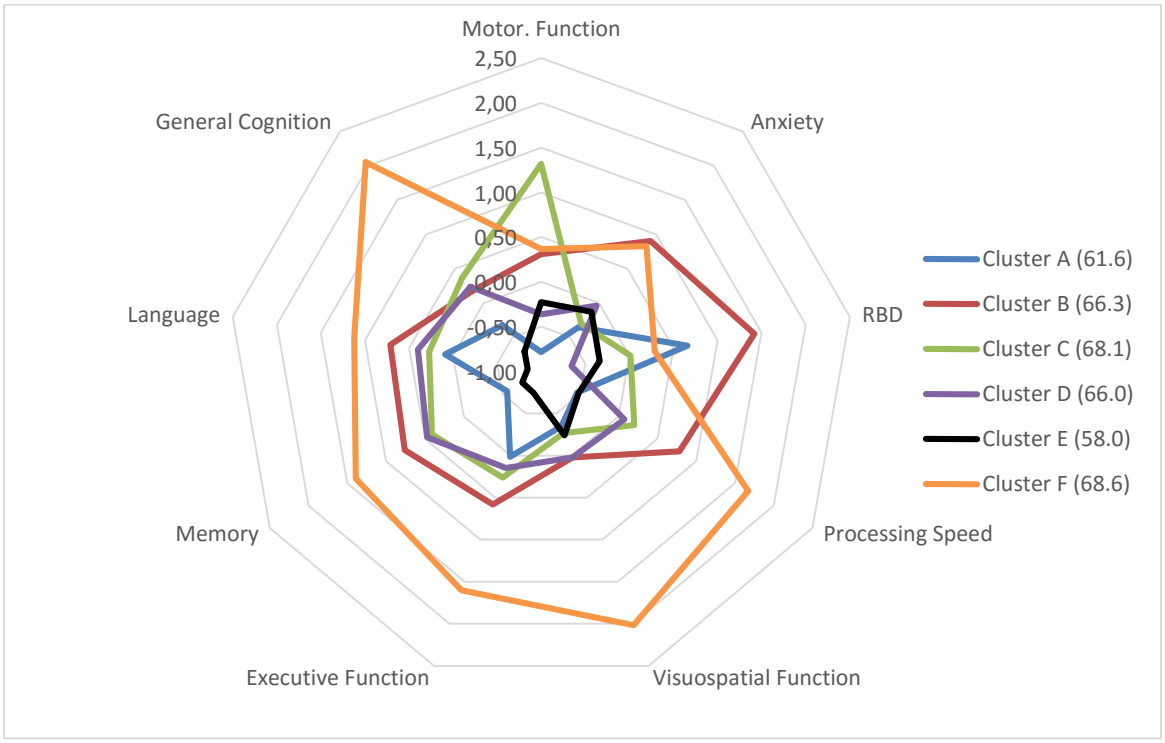


Figure 3. Scree plot of the distance between each possible clusters solution.



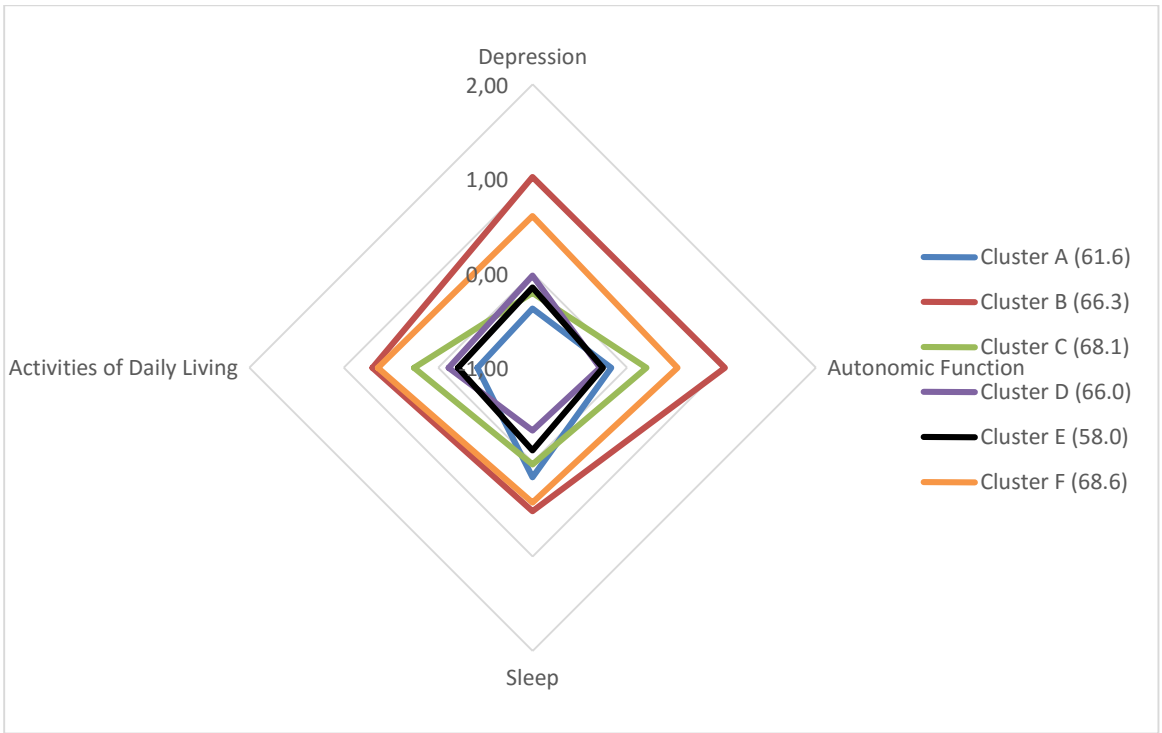
The elbow at three and six clusters indicates the most distance between these and the following cluster solutions.

Figure 4. Radar Graph of variables included in cluster analysis for each of the six clusters.



The chart displays mean *z*-score of each cluster on specific variables. For each cluster the mean age of each cluster is displayed in parentheses. Higher *z*-scores indicate more symptoms on that specific symptom cluster. The symptom clusters are composed by the following total scores: Motor Function: UPDRS part III; Anxiety: STAI; RBD: RBDSQ; processing speed: SDMT, Visuospatial Function: BJLOT; Executive function: LNS, Memory: HVLT delay condition; Language: VLT animal condition.

Figure 5. Radar Graph of variables not included in cluster analysis for each of the six clusters.



The chart displays mean *z*-score of each cluster on specific variables. For each cluster the mean age of each cluster is displayed in parentheses. Higher *z*-scores indicate more symptoms on that specific symptom cluster. The symptom clusters are composed by the following total scores: Motor Function: UPDRS part III; Anxiety: STAI; RBD: RBDSQ; processing speed: SDMT, Visuospatial Function: BJLOT; Executive function: LNS, Memory: HVLT delay condition; Language: VLT animal condition.

Discriminant Analysis

A six-group discriminant analysis was performed on variables between the six clusters. In the first discriminant analysis the variables included in the cluster analysis were used as discriminating (predictor) variables. The obtained discriminant functions in combination accounted for a statistically significant percentage of the between-group differences, *Wilks' Λ*= 0.052, χ^2 (45, n = 341) = 982,362, $p < 0.001$, overall R_c^2 = 0.948, in this model 85.6% of the cases were correctly classified. For an overview of the percentage of explained variance for each statistically significant function see table 6. All five function were statistically significant ($p < 0.001$). However, function 1 was dominant, accounting for approximately 78.1% of the explained variance.

Table 5. Variance explained by each function

Function	Percentage variance explained
Function 1	78.1%
Function 2	10.8%
Function 3	4.4%
Function 4	1.5 %
Function 5	0.7 %

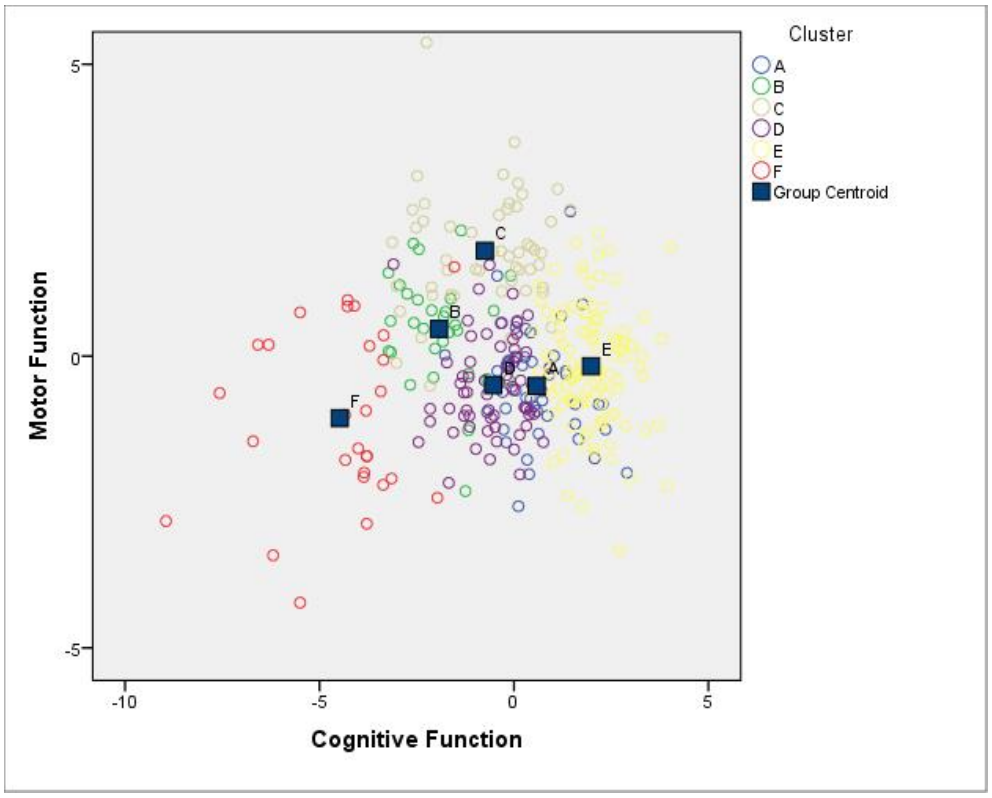
The latent construct represented by the discriminant functions can be interpreted with respect to the structure coefficients, which are shown in table 7. For the first function, higher levels of the latent variable are indicated primarily by higher levels on global cognitive functioning, executive functioning and processing speed; this construct appears to represent cognitive functioning. The latent construct for the second function is indicated primarily by lower motor functioning; this construct appears to represents motor symptomatology. The latent construct for the third function is indicated by higher levels of RBD. The fourth construct appears to represents better language functioning and decreased visuospatial functioning, while the fifth function seems to present a state of anxiety and decreased memory functioning. Figure 6 displays the distribution of the cluster on the first two functions, since these contributed the most to the model. If a cluster displays a higher score on the cognitive function that cluster is relatively more cognitively impaired than the cluster that score lower on the cognitive function. Higher scores on the motor function represent increased motor impairment.

Table 6. Structure Matrix

	Function				
Variable	**1**	**2**	**3**	**4**	**5**
MoCA	.585*	.059	.311	.007	.411
LNS	.472*	.030	-.074	.091	.248
SDMT	.438*	-.006	.111	-.361	-.216
UPDRS part III	-.193	.828*	-.284	.351	-.107
RBDSQ	-.161	.129	.803*	.423	-.197
BJLOT	.328	.379	.287	-.484*	.296
VLT-animal	.442	-.020	-.164	.461*	-.088
HVLT-delay	.528	-.123	.170	.197	-.530*
STAI	-.166	-.128	.082	.429	.461*

*. Largest absolute correlation between each variable and any discriminant function
UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDM: Symbol Digits Modalities Test, LNS: Letter Number Sequencing (WMS-III), BJLO: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment.

Figure 6. Cluster distribution on the first two functions.



In the second discriminant analysis the variables not included in the cluster analysis were used as discriminating (predictor) variables. The obtained discriminant functions in combination accounted for a statistically significant percentage of the between-group differences, *Wilks' Λ*= 0.308, χ^2 (20, n = 341) = 307,967, $p < 0.001$, overall R_c^2 = 0.62, in this model 50.8% of the cases were correctly classified. For an overview of the percentage of explained variance for each statistically significant function see Appendix II. The functions one through three were statistically significant ($p < 0.001$). A fourth function was created however this function was not statistically significant ($p = 0.177$). Function 1 was dominant, accounting for approximately 54.8% of the explained variance. The first function appears to represent better short term memory functioning. While the second function seems to represent increased autonomic dysfunction and increased depressive symptoms. The third function seems similar, representing increased depression. Appendix II. displays the structure coefficients and the distribution of the clusters on the first two functions.

Post hoc tests

After performing the LDA, we conducted either an One-Way ANOVA, a Welch's ANOVA, a Kruskal-Wallis H Test or a Chi-square test to determine the best way to describe the clusters. Post hoc testing was used to determine which clusters were significantly different from each other on the specific measurements. See table 10 for an overview of these results.

Table 7. Variable means for each cluster

				Demographics			
Variable	**Total**	**Cluster A**	**Cluster B**	**Cluster C**	**Cluster D**	**Cluster E**	**Cluster F**
Age[3]	63.20	61.58[cf]	66.27[e]	68.06[ae]	65.91[e]	58.02[bcdf]	68.61[ae]
Education years [4]	15.51	15.44	14.83	16.12	14.90	16.03	14.54
Disease duration in years[1]	3.93	3.97	3.93	4.21	3.93	3.87	3.64
Gender[2°]	65.4%	60.4%	80.0%	80.8%[e]	68.7%	56.9%[c]	57.1%
Medication Use[2x]	86.8%	91.7%	93.3%	78.0%	86.6%	87.9%	89.3%
				Variables in cluster analysis			

	Total	Cluster A	Cluster B	Cluster C	Cluster D	Cluster E	Cluster F
UPDRS-III [4]	24.87	16.04^{bcdef}	28.37^{acde}	39.71^{abdef}	20.80^{abc}	22.30^{abc}	29.02^{ac}
STAI[3]	64.98	58.48^{bf}	81.60^{acde}	59.35^{bf}	64.24^{bf}	62.62^{bf}	80.29^{acde}
RBDSQ [4]	5.43	7.40^{bcde}	9.67^{acdef}	5.46^{abd}	3.46^{abcef}	4.42^{abcdf}	6.29^{bde}
SDMT[3]	39.84	45.88^{bcdf}	30.97^{acdef}	37.56^{abef}	39.01^{abef}	45.72^{bcdf}	20.93^{abcde}
BJLOT[1]	25.71	27.25^{f}	25.60^{f}	26.88^{f}	25.61^{f}	26.78^{f}	16.79^{abcde}
LNS [4]	10.32	10.27^{bef}	8.67^{adef}	9.58^{ef}	9.90^{bef}	12.43^{abcdf}	5.79^{abcde}
HVLT-delay [4]	8.15	9.83^{bcdf}	5.87^{ae}	6.92^{aef}	6.73^{aef}	10.42^{bcdf}	3.96^{acde}
VLT-animal[3]	21.00	20.48^{bf}	16.90^{ae}	19.42^{ef}	18.70^{ef}	25.87^{abcdf}	14.54^{acde}
MoCA [4]	26.16	27.21^{bcdef}	25.57^{aef}	24.96^{aef}	25.40^{aef}	28.45^{abcdf}	19.54^{abcde}

Variables not in cluster analysis

	Total	Cluster A	Cluster B	Cluster C	Cluster D	Cluster E	Cluster F
HVLT-recall [4]	23.56	26.52^{bcdf}	18.97^{ae}	21.17^{aef}	21.19^{aef}	27.65^{bcdf}	16.54^{ace}
SCOPA-AUT[3]	11.60	10.48^{bf}	18.53^{acde}	12.98^{be}	9.69^{bf}	9.90^{bcf}	15.18^{ade}
ESS[3]	6.67	7.33	8.80^{de}	6.77	5.30^{bf}	6.16^{b}	8.43^{d}
MSEADL [4]	88.62	91.96^{bcf}	83.00^{ade}	86.56^{a}	89.52^{b}	90.31^{bf}	83.46^{ae}
GDS15[1]	2.56	1.52^{bf}	5.40^{acde}	1.98^{bf}	2.49^{b}	2.15^{bf}	4.25^{ace}
QUIP-S[2]*	37%	29.2%	50.0%	42.3%	34.3%	36.2%	35.7%
	0=0.3%	0=0%	0=0%	0=1.9%	0=0%	0=0%	0=0%
	1=24.9%	1=33.3%	1=6.7%	1=9.6%	1=25.4%	1=34.5%	1=17.9%
H&Y Scale	2=69.8%	2=66.7%	2=80%	2=71.2%	2=73.1%	2=64.7%	2=75%
	3=3.8%	3=0%	3=13.3%	3=9.6%	3=1.5%	3=0.9%	3=7.1%
	4=1.2%	4=0%	4=0%	4=7.7%	4=0%	4=0%	4=0%
N	341	48	30	52	67	116	28

[a]Significantly ($p < 0.05$) different from cluster A, [b]Significantly ($p < 0.05$) different from cluster B, [c]Significantly ($p < 0.05$) different from cluster C, [d]Significantly ($p < 0.05$) different from cluster D, [e] Significantly ($p < 0.05$) different from cluster E, [f]Significantly ($p < 0.05$) different from cluster F.

[1]Kruskal-Wallis H-Test, [2]Chi Square Test, [3]One Way ANOVA, [4]Welch's ANOVA

* Percentage of participants with impulse control disorder(s)

° Percentage of male participants

ˣ Percentage participants using medication

UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDMT: Symbol Digits Modalities Test, LNS: Letter Number Sequencing (WMS-III), BJLOT: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment, HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADL: Modified Schwab & England Activities of Daily Living, QUIP-S: Questionnaire for Impulsive-Compulsive Disorders, H&Y Scale: Hoehn & Yahr Scale.

Using the mean score of UPDRS part III items, we analyzed our clusters based on the TD to PIGD ratio score, See figure 7. Table 8 displays the mean scores of the clusters on the other motor symptom mean scores. There seems to be a higher percentage of patients with PIGD in cluster B, but overall there is no significant association between the specific motor symptoms and the different clusters, χ^2 (10) = 6.127, p = 0.804.

Figure 7. Percentage of patients marked as TD, PIGD or mixed subtype

TD: tremor dominant. PIGD: postural instability/gait. Mix: mixed motor subtype TD/PIGD.

Table 8. Cluster means (standard deviation) on motor symptoms

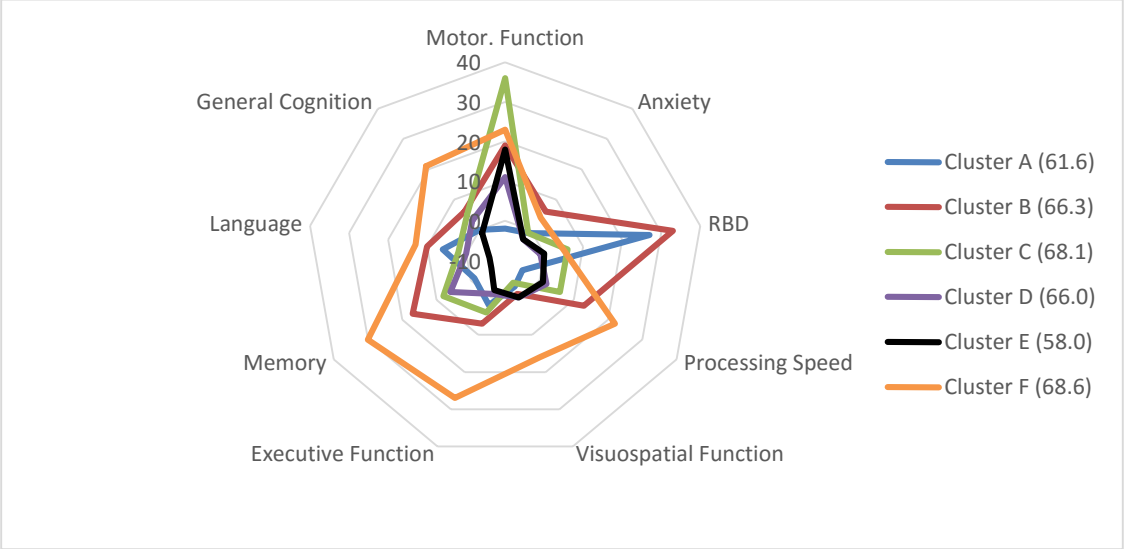
	Cluster A	Cluster B	Cluster C	Cluster D	Cluster E	Cluster F
Tremor dominant	0.35(0.24)	0.45(0.31)	0.56(0.40)	0.44(0.32)	0.38(0.27)	0.55(0.41)
PIGD	0.23(0.26)	0.43(0.28)	0.44(0.26)	0.29(0.23)	0.24(0.26)	0.35(0.28)
Hypokinesia	0.67(0.36)	0.99(0.53)	1.23(0.45)	0.74(0.45)	0.79(0.43)	0.92(0.56)
Rigidity	0.58(0.40)	0.84(0.50)	1.12(0.64)	0.66(0.44)	0.73(0.51)	0.85(0.60)
Tremor dominant/non tremor dominant ratio score	0.76(0.67)	0.78(0.99)	0.64(0.59)	1.07(1.83)	0.73(0.70)	1.26(2.07)

Longitudinal course analysis

For this analysis we compared the 2-year follow-up data with baseline and 1-year follow-up. Appendix III displays the z-scores for each cluster at baseline. First of all, we calculated the percentage of change between the mean scores at baseline and two years after baseline on all

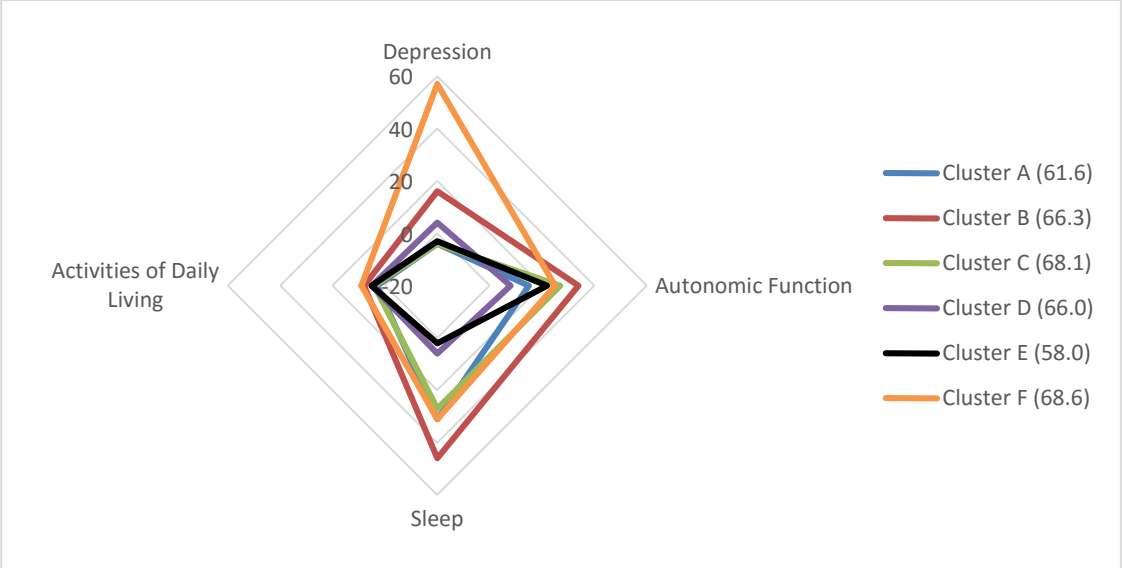
variables. The results are shown in Figure 8 and 9. Positive percentages indicate an increased symptom severity at two years after baseline compared with the baseline score. For all variable the change on each cluster is displayed by means of line graphs in Appendix IV. Appendix V displays the change in medication use over the years. We also analyzed the differences between the cluster means at baseline on all measures, by means of ANOVA's, Kruskal-Wallis tests or Chi-square tests. The results of this analysis is shown in appendix VI.

Figure 8. Percentage of change between two years and baseline on variables in cluster analysis



The chart displays percentage of change between baseline and two years after baseline of each cluster on specific variables for each cluster (mean age). Higher percentages indicate symptom deterioration on that specific symptom cluster as compared to baseline. The symptom clusters are composed by the following total scores: Motor Function: UPDRS part III; Anxiety: STAI; RBD: RBDSQ; processing speed: SDMT, Visuospatial Function: BJLOT; Executive function: LNS, Memory: HVLT delay condition; Language: VLT animal condition.

Figure 9. Percentage of change between two years and baseline on variables not in cluster analysis



The chart displays percentage of change between baseline and two years after baseline of each cluster on specific variables for each cluster (mean age). Higher percentages indicate symptom deterioration on that specific symptom cluster as compared to baseline. The symptom clusters are composed by the following total scores: Depression: GDS15; Autonomic Function: SCOPA-Autonomic; Sleep: ESS; Activities of Daily Living: MSEALD; General Cognition: MoCA.

For each cluster we conducted a one-way Repeated Measures ANOVA on all individual variables, comparing the score at baseline, one year after baseline and two years after baseline, see table 9 for the results. The detailed results of the within-subject effects comparison are shown in appendix VII.

Table 9. Repeated measures results between baseline, one year and two years after baseline

	Variables in cluster analysis					
Variable	**Cluster A**	**Cluster B**	**Cluster C**	**Cluster D**	**Cluster E**	**Cluster F**
UPDRS-III		-	-	-	-	
STAI						
RBDSQ	-	-				
SDMT	+	-		-		-
BJLOT			+			-
LNS					+	-
HVLT-delay					+	
VLT-animal					+	-
MoCA	-		-	-	+	
	Variables not included in the cluster analysis					
Variable	**Cluster A**	**Cluster B**	**Cluster C**	**Cluster D**	**Cluster E**	**Cluster F**
HVLT-recall		-				
SCOPA-AUT		-	-		-	
ESS	-	-				
MSEADL	-	-	-	-	-	-
GDS15						-

+ significant difference between baseline, one year and two years after baseline, indicating an improvement on that measurement.
- significant difference between baseline, one year and two years after baseline, indicating a deterioration on that measurement.
UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDMT: Symbol Digits Modalities Test, LNS: Letter Number Sequencing (WMS-III), BJLOT: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment, HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADL: Modified Schwab & England Activities of Daily Living.

Cluster descriptions and labeling

Overall there were no significant differences between the clusters on education years, medication use, disease duration and ICDs reported.

Cluster A. "Relatively young-age, with low motor symptoms and high RBD symptoms."

This cluster was characterized by relatively young-aged patients. The severity of motor symptoms in this group was relatively low compared to the other clusters and seems stable over a period of two years. However, the severity of RBD symptoms in this group was relatively high and has increased rapidly in the last two years compared to the other clusters. On all other neuropsychological and neuropsychiatric measures this cluster was comparable to the healthy population. This has been the case over a period of two years. Lastly, the activities of daily living seemed relatively high in this group in comparison with the other clusters and comparable to the healthy controls.

Cluster B. Neuropsychiatrically and cognitively impaired cluster with rapidly worsening RBD."

Patients in this cluster had a mean age of 65 years. They displayed substantial motor dysfunction and were neuropsychiatrically impaired. The scores on questionnaires measuring anxiety, depression and RBD exceeded the clinical cut-off score for these disorders. However, the course of these symptoms seemed to be different. Anxiety and depression remained relatively stable, albeit impaired. The RBD symptoms seemed to increase substantially in the last two years. Cognitive dysfunction was found in specifically the executive function/mental processing speed and memory function, which seemed to decline rapidly over the course of two years. Other symptoms that seemed to increase in this period were the autonomic function and sleep function. The ADL functioning of these patients was relatively impaired.

Cluster C. "Old age with severe motor dysfunction and lower than average but stable cognition and neuropsychiatry."

Patients in this cluster were characterized by older age in comparison with the other clusters. These patients scored higher on motor symptoms compared to the other clusters. These symptoms seemed to increase quickly in a period of two years, from mildly pronounced to impaired. Cognitive function seemed below average but relatively stable over time. Visuospatial function seemed to improve over the course of two years. The neuropsychiatry in this group was higher than average but not substantially. There are some signs of RBD and patients seemed to have other sleep problems. Autonomic symptoms were mild compared to the other clusters. Overall, patients in cluster C were impaired in their ADL functioning.

Cluster D. "Overall average functioning without RBD and sleep problems."

These patients had an overall average functioning and had mean age of 65 years. They seemed to have mild motor symptoms compared to the other clusters, which increased over time. Anxiety was prevalent but stable in this cluster. However, depression and RBD seemed almost absent. Cognitive functioning was comparable to healthy controls and stable over time. This group had relatively good ADL function.

Cluster E. "A young-age, motor, cognitively and neuropsychiatrically unimpaired cluster."

Patient in this cluster were of relatively young-age. Overall this young cluster seemed relatively unimpaired. This cluster had moderate motor symptoms which slowly increased over time. They had a stable but normal neuropsychiatric profile compared to the healthy controls. Cognitively this cluster seemed to function better than average. Patients in this cluster improved on cognitive measures as compared to baseline. ADL functioning, autonomic functioning and sleep functioning all appeared within the same range as the healthy controls.

Cluster F. "An old-age cluster with severe overall impairments."

This old age cluster, had a short disease onset, with overall impairment. They experienced substantial motor impairments. Anxiety, depression and RBD were all clinically significant in this cluster. These patients were impaired on all cognitive domains. The motor, neuropsychiatric and cognitive symptoms in this cluster were prevalent and seemed to rapidly increase over time. This cluster had a low ADL functioning compared to the other clusters.

Discussion

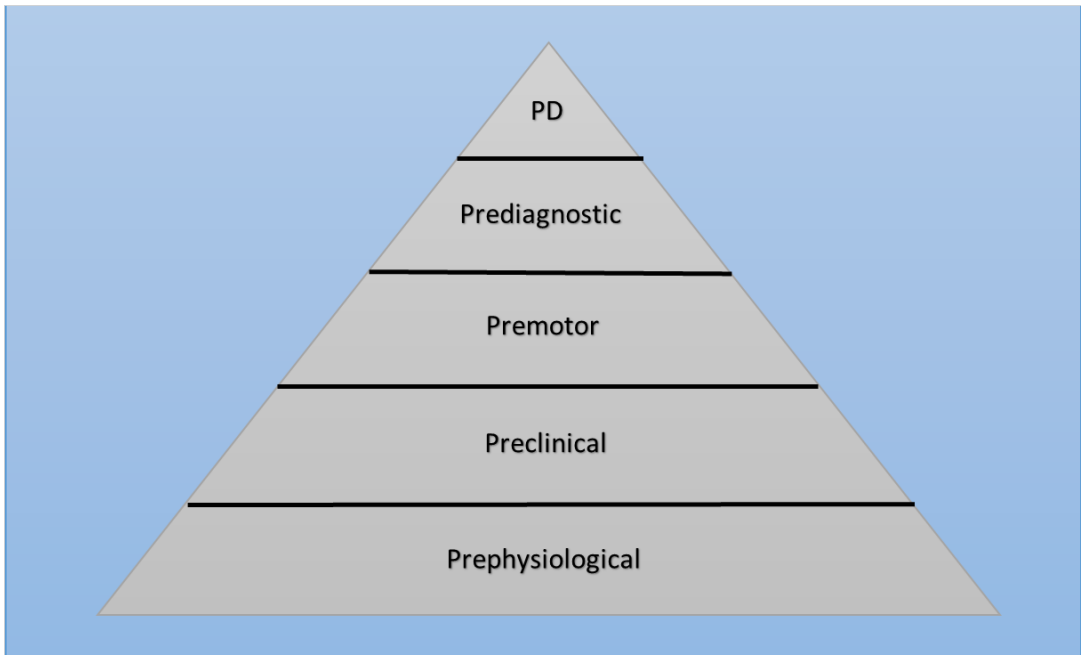
In this study we attempted to map symptom clusters in patients with idiopathic PD. The immense variability in patients with PD raises the question of how and why certain patients develop specific symptoms while others do not develop these symptoms. Since it is possible that homogeneous groups of patients are more likely to share genetic and pathological features, it is important to assess the heterogeneity in PD. Studies in symptom profiling may contribute to the future development of tailored treatments strategies and earlier disease recognition.

Data from 341 idiopathic PD patients were used to perform a hierarchical cluster analysis, resulting in six clusters. Patients in cluster A were of relatively young-age (mean age: 61 years) and had low motor symptoms with high RBD symptoms. The mean age in cluster B was 65 years. These patients were neuropsychiatrically and cognitively impaired and had RBD symptoms that increased significantly over time. Patients in cluster C were relatively old (mean age: 68 years) and had severe motor dysfunction. Their cognitive and neuropsychiatry scores were lower than average but stable over a period of two years. Patients in cluster D had a mean age of 65 years with overall average functioning. RBD and sleep problems in this cluster seemed almost absent. Cluster E was a relatively young cluster (mean age: 58 years) and seemed overall unimpaired, while cluster F was an old age cluster (mean age: 68 years) with severe overall impairment. The discriminant analysis revealed that the clusters are best distinguished by the cognitive measures. However, motor symptoms and RBD symptoms could also be used to distinguish the clusters. Neuropsychiatric symptoms, like depression and anxiety, were not useful in distinguishing the clusters. Lastly, we looked at the development of the symptoms over a period of two years. The everyday functioning decreased significantly in each cluster – which was to be expected, considering the progressive course of the disease and the impact of the symptoms on everyday life (Starkstein, et al., 2012; Weintraub et al., 2004). Concerning the neuropsychiatric symptoms, only depression symptoms increased significantly for cluster F. The cognitive constructs that changed significantly over time were different for each cluster. Each cluster displayed a specific symptom profile. There seemed to be a distinction between two relatively young clusters with an earlier onset, A and E, and four older-aged clusters with later onset, B, C, D and F. We will discuss the specific symptoms profiles of these cluster and compare them with the same-aged clusters.

All clusters were comparable on gender, disease duration and medication use. Cluster A and E were relatively young clusters. In cluster A, the motor symptoms were the lowest compared to the other clusters. This group seemed relatively unimpaired with respect to motor function, while the RBD symptoms are the second highest of all clusters. All other symptoms were below the average of

the other clusters. This cluster could represent a preclinical fase, before the onset of PD symptoms (Siderowf, & Stern, 2006). Siderowf and Stern (2006) propose the term "Parkinson's Disease at Risk Syndrome" (PARS) to refer to individuals who do not yet have a disorder that could be diagnosed as PD but do show markers that place them at a high risk for developing PD. In figure 10 a hierarchical taxonomy for PARS is displayed. Siderowf and Stern (2006), thought PARS consisted of four distinct levels: prediagnostic, premotor, preclinical and prephysiological. Patients in the prediagnostic fase have motor features that are typical of PD, but have not yet reached the strict diagnostic criteria. In the premotor fase there are no motor features that characterize PD, but some of the non-motor features that are often seen in PD are present, like depression or olfactory loss. In the preclincal fase, patients do not have any clinical features of PD, but there are abnormalities on neuroimaging measures. Lastly, the prephysiologic fase, describes patients who have a genetic risk of developing PD, but they do not show any symptoms at this stage (Siderowf & Stern, 2006).

Figure 10. Parkinson's Disease at Risk Syndrome (PARS) pyramid



Derived from Siderowf and Stern (2006).

Individuals at risk have a predisposition to develop PD (Siderowf & Stern, 2006). Not every individual who is at risk will succeed to each individual level in the pyramid. According to Siderowf and Stern (2006) only a small portion of the persons at risk will, in the end, develop PD. These individuals who do not progress to PD, may go on to develop other parkinsonian disorders or they will remain in the at risk group (Siderowf & Stern, 2006). Based on this taxonomy we could say that patients in cluster A might still be in the transition between the premotor fase and PD. These patients were diagnosed with PD, but the motor symptoms were relatively low compared to the

other clusters. Other non-motor features of PD are not present in this cluster. Only RBD seemed present in this cluster and because RBD is a NMS that is often present before the onset of motor symptoms, we hypothesize that this cluster is in a transitioning stage between the premotor fase and PD.

Cluster E seemed relatively similar in age with respect to cluster A. However, the motor symptoms in cluster E were relatively higher than in cluster A, while the RBD symptoms were lower than in cluster A. Also the cognitive functioning in cluster E seemed better than in cluster A. At baseline, cluster E scored better on executive functioning and language, in comparison with cluster A. They scored relatively similar on memory, visuospatial and processing speed. In two years' time cluster E scored relatively higher on all cognitive measures in comparison with the baseline score. Cluster A, in contrast, scored lower on all cognitive measures, indicating a deterioration of cognition. It is possible that cluster E represents patients transitioning from the prediagnostic fase to PD in the PARS pyramid. They are diagnosed with PD but they only display motor symptoms, while the NMS are relatively absent. They have cognitive scores that are comparable to the healthy population. It seems that this cluster is relatively unimpaired, only motor symptoms are prevalent, which are an indicator of the prediagnostic fase in the PARS pyramid. Another explanation for the distinction between cluster A and C could be that in one of the cluster the medication was more effective or one cluster had a better tailored medication schema, rendering a better effect of the medication. We can speculate about the exact cause of this distinction. Both clusters appeared to have the same percentage of medication use at baseline and two years after baseline. No data were available about the dosages of the medication and what sort of medication is used. It could be that cluster A, has a different kind of medication than cluster E, rendering a different response and symptom profile. Cluster E, could probably benefit from dopaminergic treatments to lower the motor symptoms (Perez-Lloret, & Rascol, 2010), while cluster A could benefit from cholinergic treatments for the RBD symptoms (Aurora et al., 2010). These different kind of drugs also have a different effect on the other symptoms (Leroi, Collins, & Marsh, 2006). It could also be that cluster A is well treated, which is why the motor symptoms are low, while cluster E is still being under treated, which is why the motor symptoms are higher and still increasing. However, this is speculative and more information about the medication is needed in order to make a more conclusive statement. We can conclude that cluster A and E can be distinguished based on the motor, cognitive and RBD symptoms. The patients in these clusters had a mean disease duration of approximately four years. We also compared the cluster at baseline, when they had a mean disease duration of two years. The distinction based on the same symptoms at two years after baseline were also prevalent at baseline, indicating a distinction that is present shortly after onset of the disease. This makes it highly likely that these

cluster represent patients that had different symptom profiles at the beginning of the disease and these patients possibly develop a different symptom profile during the course of the disease.

We also found four cluster with an older mean age. The mean age of patients in cluster B, C, D and F lied between 66 and 68 years old. These patients had a disease duration of 4 years. Compared to cluster A and E these clusters had moderately impaired cognition. This has been associated with a later disease onset, in cross-sectional and longitudinal studies (Katzen, Levin, & Llabre, 1998; Locascio, Corkin, & Growdon, 2003; Muslimović, Post, Speelman, & Schmand, 2005). A later disease onset has also been linked to higher overall severity of the disease (Muslimović et al., 2005). These are features that can also be observed in clusters B, C, D and F. However, there are differences between these clusters. For instance, earlier studies indicated that the severity of motor impairment can be positively correlated to cognitive impairment on all cognitive constructs (Locascio et al., 2003). This can be noticed in our sample. Cluster C, represents a cluster with severe motor impairment and had relatively good cognitive scores compared to cluster B and F. Cluster B and F, in turn, had severe cognitive impairment with relatively low motor impairment. Furthermore, these cluster were each characterized by specific symptoms. Cluster C and D scored relatively the same on all symptoms, except for motor function. This remained stable over a period of two years. In theory, these two patient groups might have belonged to the same cluster. However, the patients in cluster C might have been non-responders to medication, causing the motor symptoms to increase rapidly. The motor symptoms in cluster D could have been managed better using medication. As mentioned before, we didn't have detailed information about the medication use, rendering it impossible to make conclusions about the difference between these two clusters.

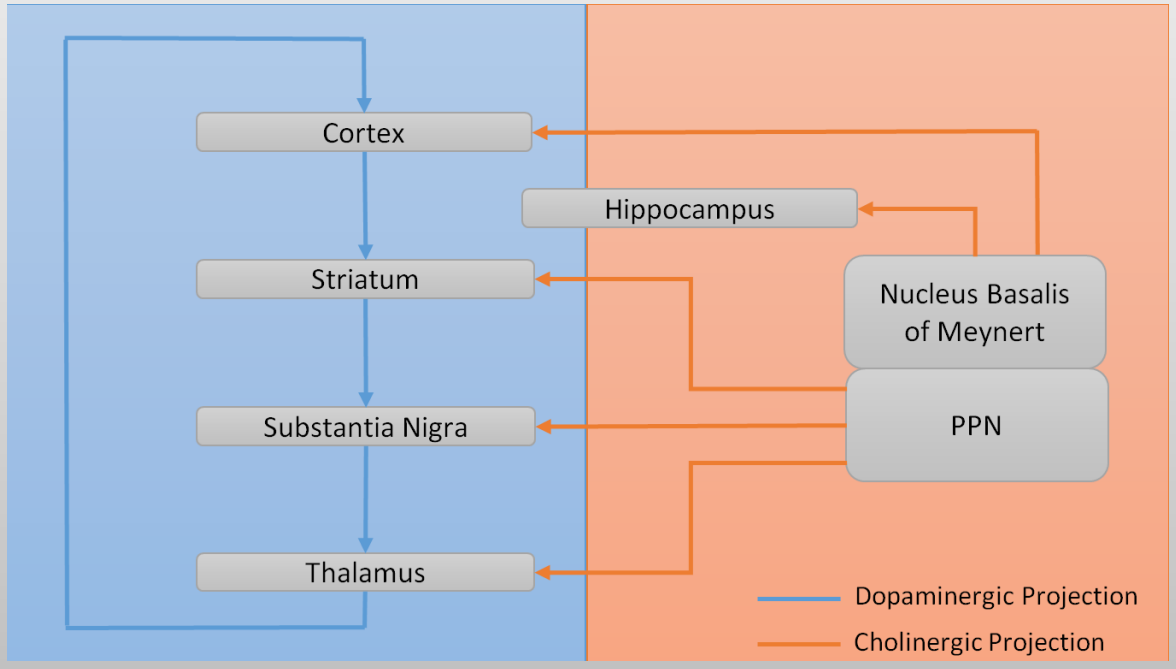
Cluster B showed an interesting symptom profile, different from cluster C and D. The motor symptoms are mild in comparison with the total population. In addition, we also analysed the distribution of patients with a TD subtype or PIGD subtype. In our sample there is no significant difference between the specific motor symptoms in each individual cluster, however, the PIGB subtype seems somewhat more prevalent in cluster B. Furthermore, the scores on questionnaires measuring anxiety, depression and RBD exceeded the clinical cut-off score for these disorders. The cognitive profile of this cluster in characterized by impaired executive functioning and processing speed. The memory scores for this cluster are lower than average but they remain in the same range as cluster C and D. This cluster had the highest autonomic dysfunction and a lower ADL functioning of all clusters. This profile is very distinctive and might be associated with dysfunction of non-dopaminergic neurotransmitters. PD is associated with a degeneration of dopamine neurons but other non-dopaminergic neurotransmitters can also be affected, e.g. GABA, glutamate, serotonin, noradrenaline and acetylcholine (Bonnet, 2000). It is possible that a disbalance between these

neurotransmitters can cause heterogeneity in PD symptoms (Calabresi, Picconi, Parnetti & Di Fillippo, 2006). All neurotransmitters are interacting with each other and dysfunction in one neurotransmitter system has consequences for another system. This in turn affects the functioning of the body and the brain, resulting in a different symptoms profile for each individual patient (Calabresi et al., 2006). In certain neurotransmitters there appears to be a degeneration of neurons, similar to the dopamine neurons, while in others there is no deterioration. For instance, glutamate neurons do not degenerate in PD. However, the loss of dopamine in the brain causes a loss of inhibition of glutamate, in turn causing an increase in glutamate in the brain (Leroi et al., 2006). This example briefly illustrates the interaction role of the neurotransmitters in PD. Covering all neurotransmitter dysfunction in PD, lies outside the scope of this thesis, but to explain the symptoms found in cluster B and F we will further focus on the symptoms associated with an imbalance between dopamine and acetylcholine. Acetylcholine neurons degenerate in PD. However, less substantial than dopamine neurons (Bonnet, 2000). For an illustration of the interacting effect of dopaminergic and cholinergic pathways, see box 3.

Box 3. Cholinergic and Dopaminergic pathways in PD.

In PD, cholinergic degeneration can be associated with certain motor and non-motor features. Cholinergic degeneration is often associated with impaired cognition (Bohnen et al. 2006), falls (Yarnall, Rochester, & Burn, 2011), slower gait speed (Bohnen et al., 2013), RBD (Kotagal et al., 2012) and impaired olfaction (Bohnen, & Müller, 2013). Cholinergic system degeneration affects the basal forebrain, specifically the nucleus basalis of Meynert and the Pendunculopontine nucleus (PPN) (Bohnen et al., 2012). These areas, in turn, influence the cortex, striatum, SNc and thalamus, which are also affected by dopaminergic denervation (Calabresi et al, 2006; Mena-Segovia, Bolam, & Magill, 2004). Acetylcholine and dopamine interact on the same areas in the brain, and thus can influence the expression of certain symptoms. See figure 11 for a simplified illustration of the interaction between dopaminergic and cholinergic systems in PD.

Figure 11. Simplified illustration of dopaminergic and cholinergic pathways in PD



Derived from Calabresi et al., 2006

Cluster B displayed symptoms that could have been associated with both dopaminergic and cholinergic dysfunctions. For instance, research has shown that patients with cholinergic dysfunction often display a PIGB subtype of motor symptoms, while patients with a TD subtype are characterized by low cholinergic dysfunction (Karachi et al., 2010). Cluster B, seemed to have a relatively higher percentage of patients with a PIGB motor subtype. However, this was not a significant difference. Müller et al. (2015) reported that RBD is often more prevalent in patients with distinct cholinergic dysfunction. In cluster B the RBD score is the highest among all our clusters. In addition, Marion et al. (2008) reported that RBD is often associated with a PIGB motor subtype. Research also revealed that RBD symptoms are associated with increased anxiety (Mahlknecht et al., 2015) and depression symptoms (Tandberg, Larsen, & Karlsen, 1998) a feature that was also present in cluster B. Interestingly, the cognitive profile found in cluster B could be linked to both cholinergic dysfunction and dopaminergic dysfunction (Bohnen et al., 2006; Leh et al., 2010). Cluster B seemed to have both executive dysfunction and memory dysfunction. The dopaminergic degeneration in the associative CSTC circuit is thought to play a role in executive dysfunction (Aupperle et al., 2012; Leh et al., 2010), while cholinergic dysfunction can be linked to memory dysfunction (Dubois, 1987; Sadeh, Braham, & Modan, 1982). However, executive function can also be influenced by cholinergic dysfunction. Bedard, Lemay, Gagnon, Masson and Paquet (1998) showed that anti-cholinergic drugs can cause executive dysfunction in PD patients but not in healthy controls, which makes it plausible that there is some cognitive cholinergic vulnerability in PD. It is possible that cholinergic dysfunction

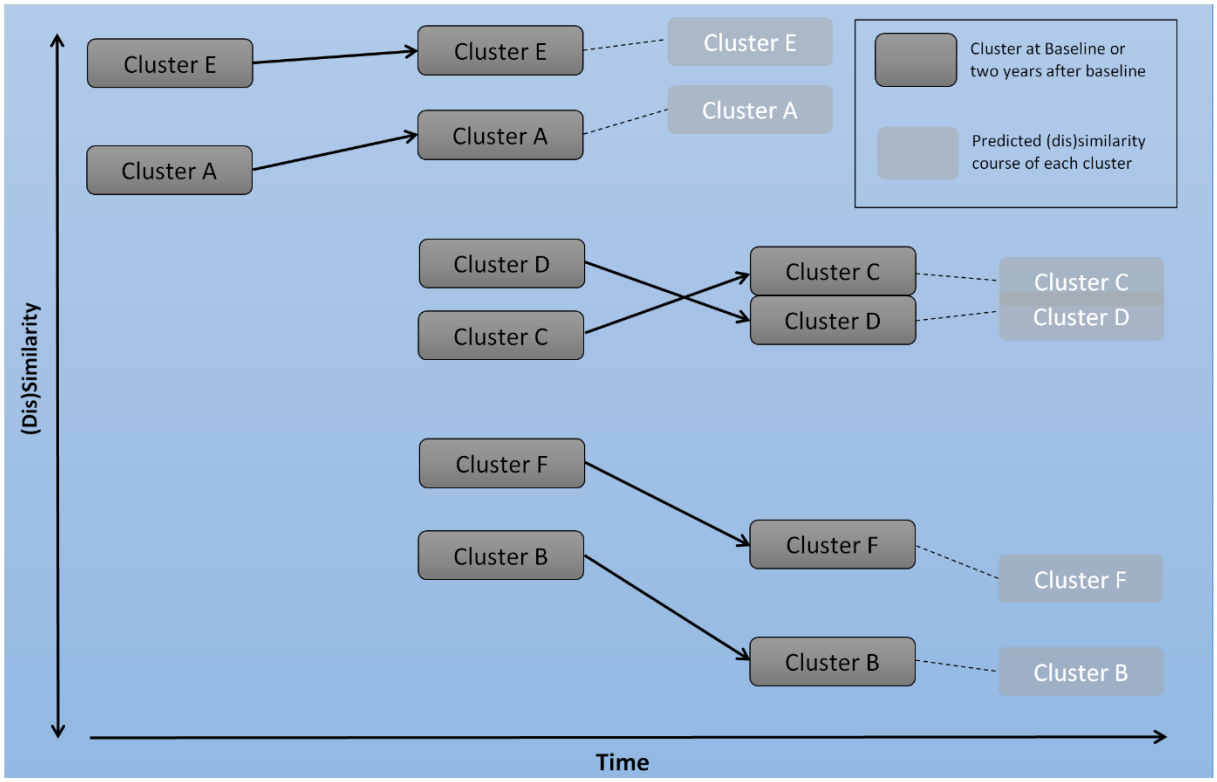
further increases the cognitive deficits caused by striatal dopaminergic changes in PD (Williams-Gray et al., 2009). Conclusively, cluster B seemed to represent patients that are affect by both dopaminergic and cholinergic dysfunctions.

Cluster F, was the most impaired cluster compared with the other clusters. There was no significant difference between the disease duration of each cluster. However, the disease duration in cluster F was relatively the shortest. Cluster F was characterized by motor impaired, which remained stable for over two years. The neuropsychiatry in cluster F was clinically relevant and stable for over a period of two years. The cognitive profile of cluster F is characterized by an overall severe impairment. Over a period of two years we encountered a significant decline in visuospatial functioning, executive functioning, language functioning and processing speed. However, the memory impairment stayed relatively stable over two years. Cluster F could possibly consist of patients who had developed, or had a high risk for developing Parkinson's disease dementia (PDD), because of the low cognitive score compared to the other clusters. Even over a period of two years we see a rapid decline in cognition for this cluster. Other symptoms remain relatively stable over a period of two years, albeit impaired. However, depression is an exception. The depression symptoms increased over two years, to a subclinical level. Interestingly, Giladi et al. (2000) discovered a positive relation between depression and the change to develop PDD. A positive relation with PDD has also been reported with the PIGD motor subtype (Alves et al., 2006) and RBD (Marion et al., 2008). Overall, we see features that can be associated with PDD. However, based on our data we can only speculate about the correct clinical diagnosis. Another possible theory could be that these patients display a form of dementia what was previously known as Dementie with Lewy Bodies (DLB). DLB used to be diagnosed when the motor symptoms and cognitive decline/dementia occur within one year after onset of the disease (McKeith et al., 2005). In our cluster, we saw that an overall severe impairment was present at baseline. At this point the disease duration for this cluster was one and a half years. Because the high level of impairment and the relatively short disease duration, it may well be possible that this cluster was already impaired at the onset of the disease. Again, this is also speculative, because we cannot conclude this based on our data. We can ascertain that this cluster probably had a very fast disease progression, with rapidly increasing symptoms.

Overall, the clusters we found were distinguishable from each other on a large amount of specific constructs. Each cluster had a different symptom profile. However, there also was overlap between the clusters. For instance, cluster C and D were almost identical, except for motor function. Cluster A and E were also somewhat similar, as was the case for clusters B and F. Over a period of two years we saw a change in symptoms for each cluster, mainly indicating an increasing level of dysfunction. Figure 12 displays the relative similarity and dissimilarity between the clusters,

measured at baseline and two years after baseline. This image illustrates the change between the clusters in this period. The dashed lines indicate a possible (dis)similarity trajectory for each cluster based on previous change. We notice an increase in dissimilarity between the opposite ends of the figure, between cluster A/E and cluster B/F. It seems that these cluster change in time, making them better distinguishable from the other cluster pair. However, cluster D and C, become more similar over time. It is possible that, in the end, these clusters will merge in to one cluster. This could be the result of a better tailored medication schedule, as was proposed earlier.

Figure 12. (Dis)similarity between the cluster over time



This study aimed to validate and replicate the finding by Van Balkom et al. (2015). However, our cluster analysis could not replicate the four clusters described in said study. Cluster E and F were characterized by relatively healthy and young patients and older overall severely impaired patients, respectively. This distinction between relatively young healthy patients and older impaired patients has also been reported in earlier data-driven studies (Van Balkom, 2015; see for a review Van Rooden et al., 2010). Cluster B was characterized by high anxiety and depression scores and executive dysfunction which is comparable to cluster 3 in the study by Van Balkom et al. (2015). However, this cluster also showed impaired memory function and impaired language functioning, which was not specifically assessed in the study by Van Balkom et al., (2015). Some similarities between cluster 4 in Van Balkom's et al. (2015) study and cluster C in our study could be reported. This cluster showed severe motor symptoms. In contrast to Van Balkom's et al. (2015) results,

anxiety and depression scores were relatively low in comparison with the total score of our PD population. This cluster did display lower levels of (verbal) memory functioning, similar to Van Balkom et al. (2015).

Our study had several strengths compared to earlier studies. We included a large sample and a broad spectrum of PD symptoms in our cluster analysis. We included measures of RBD and ICDs in our analysis, making it possible to gain a more complete image of the dissociation between the broad range of symptoms in PD. We also included a longitudinal analysis, in which we looked at the way the symptoms changed over a period of two years, giving us information over possible difference between the cluster in the way they progress. Our cluster didn't differ on disease duration, gender distribution and medication use, rendering it possible to exclude these variables from having a significant influence on our cluster analysis. This was also done for possible age effects in our results, by correcting the cognitive measures.

Our study did have some limitations. We had to exclude a large amount of data because of missing values. Additionally, on the UPDRS part III we had problems determining which score was the "on" of "off" score. We dealt with this problem by taking the mean of the both scores. This could have possibly caused our data set to be different from the normal PD population. As a result of the first LDA we preformed it was determined that our cluster could be best distinguished based on the cognitive measures. However, in our cluster analysis we had a high number of cognitive measures as compared with neuropsychiatric and motor measures. The cognitive measure might have weighted more in the cluster result than the other measures, possibly leading to a slightly distorted cluster solution. However, after analyzing the specific symptoms by means discriminant analysis and ANOVAs, Kruskal-Wallis test and Chi-square tests, it became clear that the cluster were distinguishable also by other constructs like RBD, motor symptoms and neuropsychiatry. In this cohort, no measures of psychosis and apathy were taken, rendering us unable to profile these symptoms. These symptoms are often reported in association with PD (Chaudhuri et al., 2006; Gallagher, & Schrag, 2012). We would have expected to find a higher rate of psychosis in the cluster B and F because psychosis is often associated with memory dysfunction, working memory dysfunction and PD dementia (Ramírez-Ruiz, Junqué, Martí, Valldeoriola, & Tolosa, 2006). To form a complete and more detailed description of the possible symptom profiles in PD, future research should include psychosis and apathy measures. The ICD measure that we used, unfortunately only described ICD on a dichotomic scale. In future research, it may be advisable to use a more detailed measurement of ICDs, to gain a more complete view of the ICD symptoms.

All in all, we attempted to define cluster of symptoms in patients with idiopathic PD. Our research yielded an interesting result, indicating a distinction between two clusters with an earlier disease onset and relatively mild symptoms and four impaired clusters with a later disease onset. Further research should focus on determining what could cause the distinction between the earlier and later onset. However, it might be more profitable to look at the distinction between the clusters individually. For instance, comparing the four clusters with later onset, and determining why the patients with the same age at onset and disease duration develop different symptoms. There could be a neuropathological basis for this distinction. Information about this could be revealed using neuroimaging techniques. Medication effectiveness could also be important in explaining our results. It could be interesting, in the future, to collect more data over a longer period of time to assess the heterogeneity in PD. Research should, furthermore, include different measurement to assess an even larger set of symptoms often seen in PD, including psychosis, apathy and ICDs. Ideally, further research will continue mapping and assessing the heterogeneity in PD symptoms, making it possible to gain a more conclusive image about different symptoms profile in PD. Even though, studies might render different clustering solutions we might encounter specific characteristics that are more commonly associated with other symptoms and specific disease courses. In clinical practice this might provide a possibility to predict the disease progression and symptom expression in PD patients. Hopefully, this will in the end lead to more tailored treatment options and earlier disease recognition.

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Appendix I. PPMI Inclusion/Exclusion Criteria (The Parkinson Progression Marker Initiative, 2014)

Inclusion Criteria-Parkinson Disease Subjects

- Patients must have at least two of the following: resting tremor, bradykinesia, rigidity (must have either resting tremor or bradykinesia); OR either asymmetric resting tremor or asymmetric bradykinesia
- A diagnosis of Parkinson disease for 2 years or less at Screening.
- Hoehn and Yahr stage I or II at Baseline
- Not expected to require PD medication within at least 6 months from Baseline.
- Male or female age 30 years or older at time of PD diagnosis
- Confirmation from imaging core that screening dopamine transporter SPECT scan is consistent with dopamine transporter deficit (or for sites where DaTSCANTM is not available that VMAT-2 PET scan is consistent with VMAT deficit)
- Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations
- Willing and able to comply with scheduled visits, required study procedures and laboratory tests
- Women may not be pregnant, lactating or planning pregnancy during the course of the study;
    - Includes a negative urine pregnancy test on day of Screening scan prior to injection (DaTSCANTM and/or 18F-AV-133)
    - Includes a negative serum pregnancy test prior to Screening scan injection (18F-AV-133 only)
- Women participating in VMAT-2 PET imaging must be of non-childbearing potential **or** be using a highly effective method of birth control 14 days prior to until at least 24 hours after injection of 18F-AV-133)
    - Non-child bearing potential is defined as a female that must be either postmenopausal (no menses for at least 12 months prior to Screening) or surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy).
    - Highly effective method of birth control is defined as practicing at least one of the following: A birth control method that results in a less than 1% per year failure rate when used consistently and correctly, such as oral contraceptives for at least 3 months prior to injection, an intrauterine device (IUD) for at least 2 months prior to injection, or barrier methods, e.g., diaphragm or combination condom and spermicide. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) is not acceptable

Exclusion Criteria-Parkinson Disease Subjects

- Atypical PD syndromes due to either drugs (e.g., metoclopramide, flunarizine, neuroleptics) or metabolic disorders (e.g., Wilson's disease), encephalitis, or degenerative diseases (e.g., progressive supranuclear palsy)
- Currently taking levodopa, dopamine agonists, MAO-B inhibitors (e.g., selegiline, rasagiline), amantadine or other PD medication
- Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of Baseline
- Has taken levodopa or dopamine agonists prior to Baseline for more than a total of 60 days
- A clinical diagnosis of dementia63 as determined by the investigator (Appendix 1)
- Received any of the following drugs that might interfere with dopamine transporter SPECT imaging: Neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative, within 6 months of Screening
- Subjects participating in VMAT-2 PET imaging have received any of the following medications that might interfere with 18F-AV-133 PET imaging: neuroleptics, metoclopramide, alpha methyldopa, methylphenidate, reserpine, or amphetamine derivative, within 2 weeks prior to the Screening 18F-AV-133 injection
- Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture
- Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia
- Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation
- Use of investigational drugs or devices within 60 days prior to Baseline (dietary supplements taken outside of a clinical trial are not exclusionary, e.g., coenzyme Q10)
- Previously obtained MRI scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).

Appendix II. Discriminant analysis results, variables not in cluster analysis

Table 10. Variance explained by each function

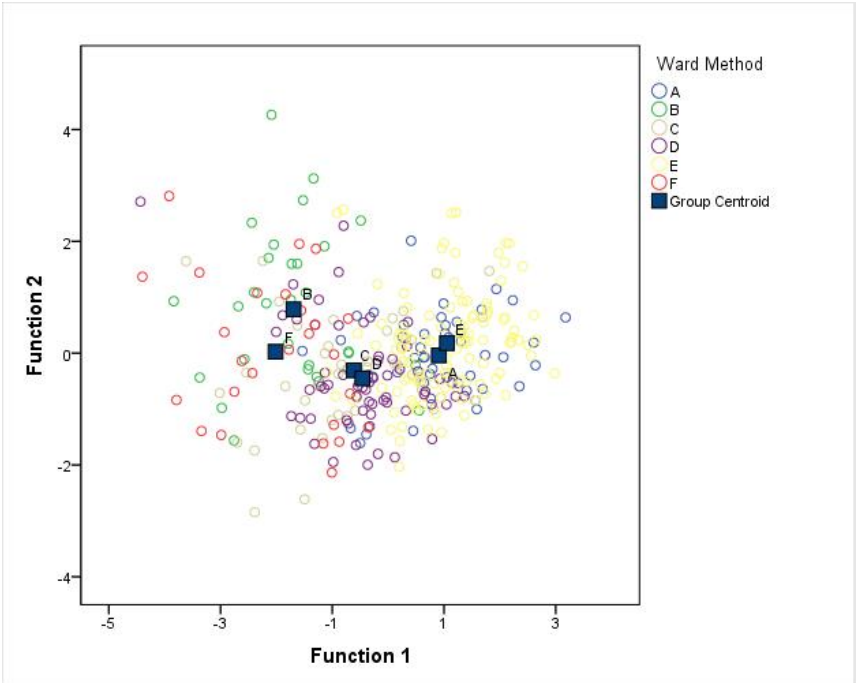
Function	Percentage variance explained
Function 1	54.8%
Function 2	5.0%
Function 3	2.3%

Table 11. Structure Matrix

	Function			
Variable	**1**	**2**	**3**	**4**
HVLT-recall	.877*	.426	-.124	-.185
SCOPA-AUT	-.317	.715*	-.497	.376
GDS15	-.319	.714*	.623	-.029
ESS[b]	-.092	.325*	-.078	.061
MSEADL	.318	-.344	.277	.839*

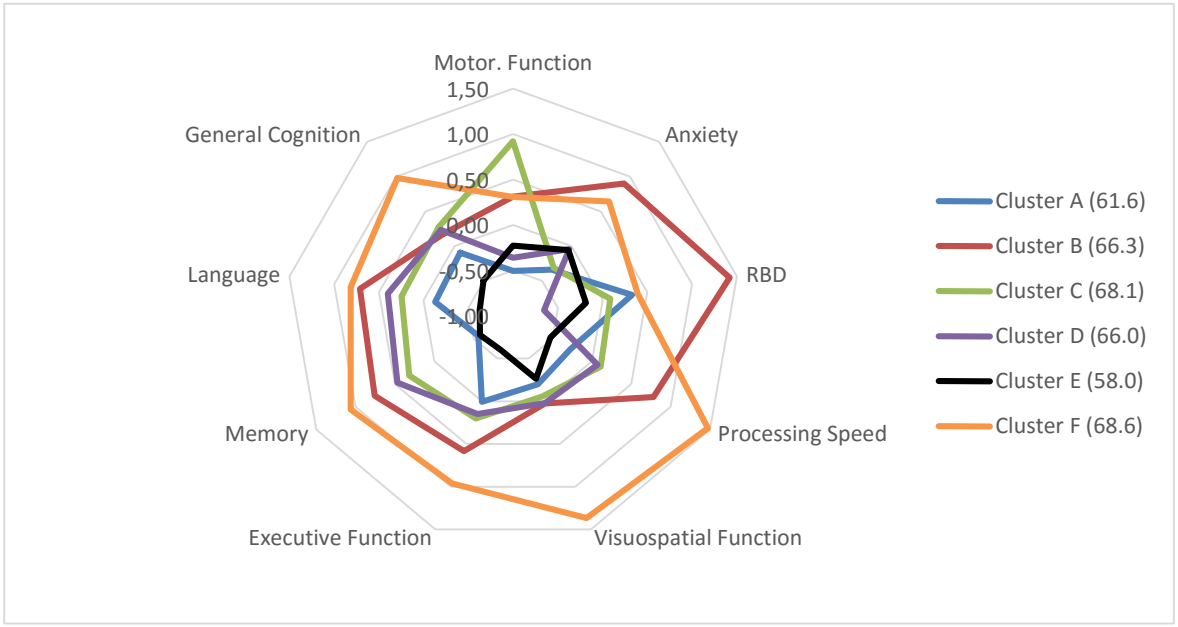
b. This variable not used in the analysis
*. Largest absolute correlation between each variable and any discriminant function
HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADL: Modified Schwab & England Activities of Daily Living.

Figure 13. Distribution of clusters on the first two functions in LDA



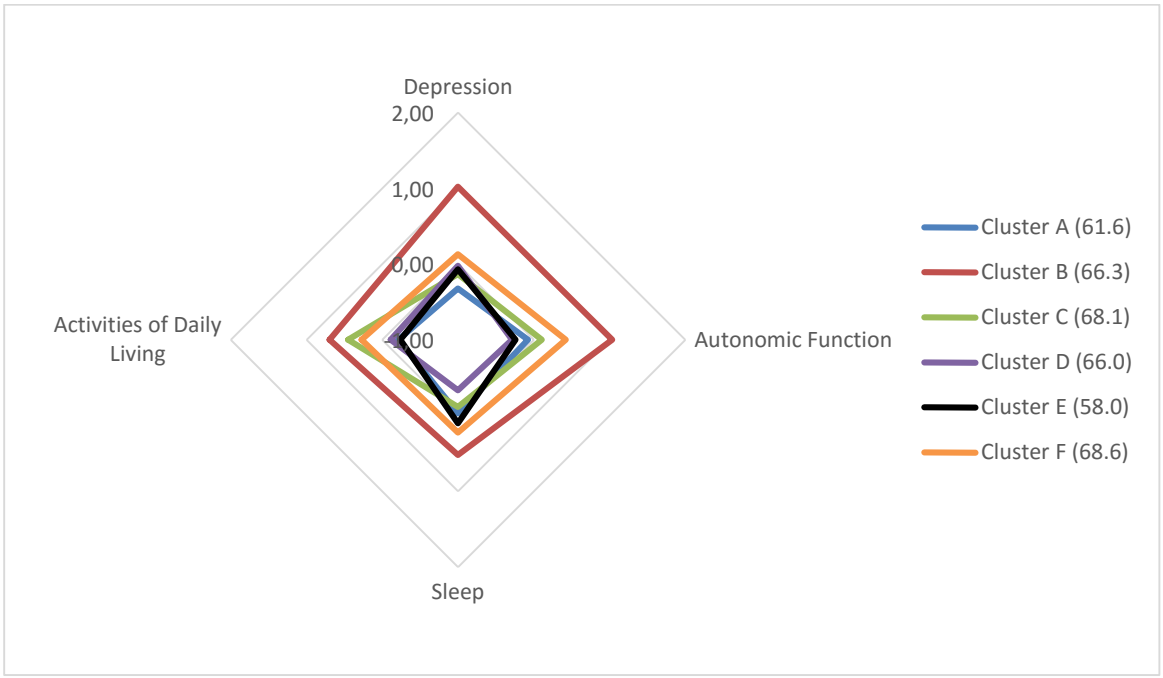
Appendix III. Radar Graphs of variables at baseline for each cluster

Figure 14. Radar Graph of variables included in cluster analysis for each of the six clusters (mean age) at baseline



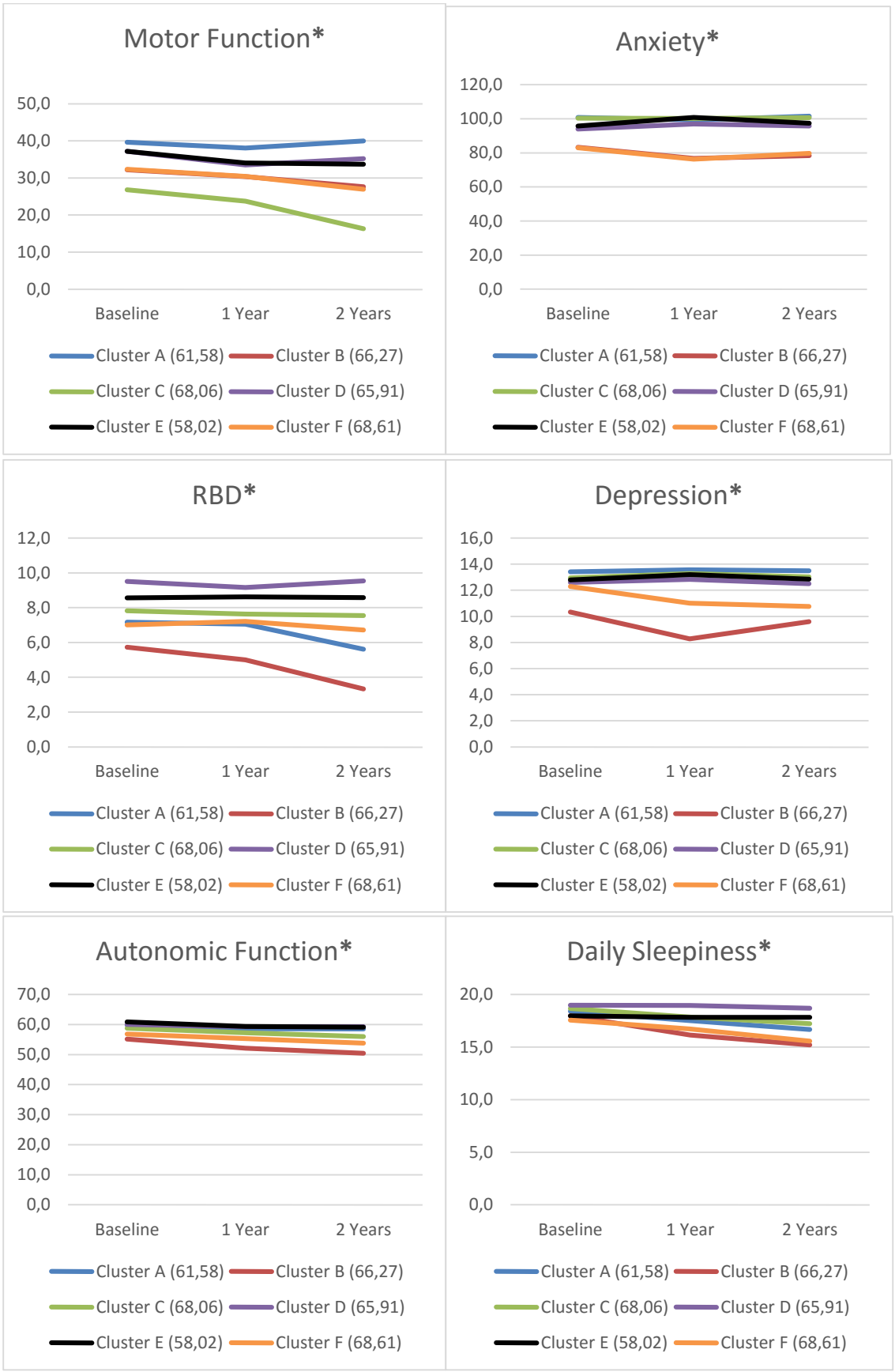
The chart displays mean z-score of each cluster on specific variables. For each cluster the mean age of each cluster is displayed in parentheses. Higher z-scores indicate more symptoms on that specific symptom cluster. The symptom clusters are composed by the following total scores: Motor Function: UPDRS part III; Anxiety: STAI; RBD: RBDSQ; processing speed: SDMT, Visuospatial Function: BJLOT; Executive function: LNS, Memory: HVLT delay condition; Language: VLT animal condition.

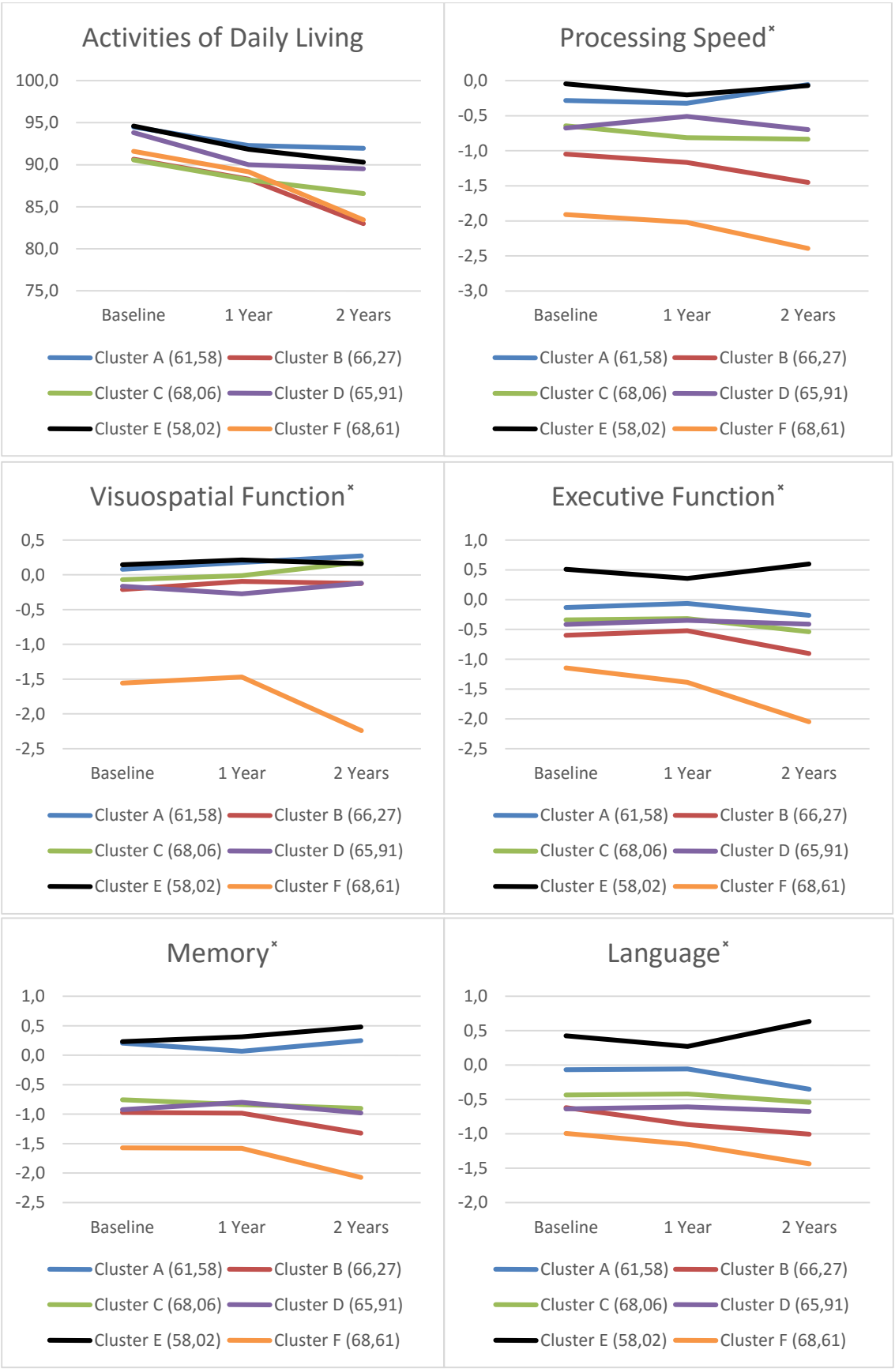
Figure 15. Radar Graph of variables not included in cluster analysis for each of the six clusters at baseline

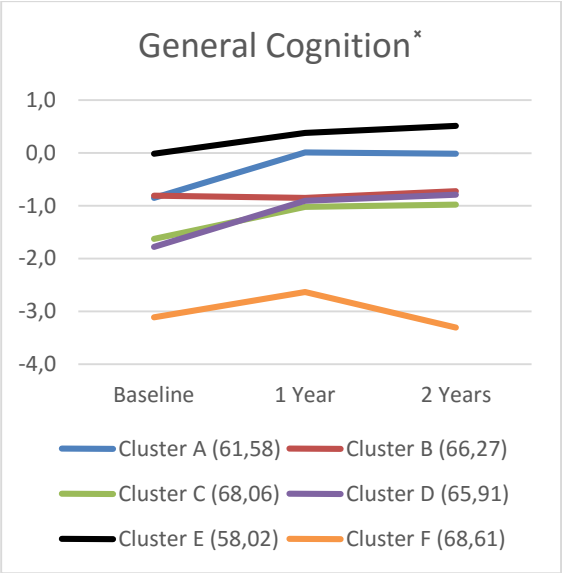


The chart displays mean z-score of each cluster on specific variables. For each cluster the mean age of each cluster is displayed in parentheses. Higher z-scores indicate more symptoms on that specific symptom cluster. The symptom clusters are composed by the following total scores: Motor Function: UPDRS part III; Anxiety: STAI; RBD: RBDSQ; processing speed: SDMT, Visuospatial Function: BJLOT; Executive function: LNS, Memory: HVLT delay condition; Language: VLT animal condition.

Appendix IV. Line graphs displaying change of each variable over a period of two years for each cluster (Mean Age)




Activities of Daily Living
100,0
95,0
90,0
85,0
80,0
75,0
Baseline
1 Year
2 Years
Cluster A (61,58)
Cluster B (66,27)
Cluster C (68,06)
Cluster D (65,91)
Cluster E (58,02)
Cluster F (68,61)
Processing Speed*
0,0
-0,5
-1,0
-1,5
-2,0
-2,5
-3,0
Baseline
1 Year
2 Years
Cluster A (61,58)
Cluster B (66,27)
Cluster C (68,06)
Cluster D (65,91)
Cluster E (58,02)
Cluster F (68,61)
Visuospatial Function*
0,5
0,0
-0,5
-1,0
-1,5
-2,0
-2,5
Baseline
1 Year
2 Years
Cluster A (61,58)
Cluster B (66,27)
Cluster C (68,06)
Cluster D (65,91)
Cluster E (58,02)
Cluster F (68,61)
Executive Function*
1,0
0,5
0,0
-0,5
-1,0
-1,5
-2,0
-2,5
Baseline
1 Year
2 Years
Cluster A (61,58)
Cluster B (66,27)
Cluster C (68,06)
Cluster D (65,91)
Cluster E (58,02)
Cluster F (68,61)
Memory*
1,0
0,5
0,0
-0,5
-1,0
-1,5
-2,0
-2,5
Baseline
1 Year
2 Years
Cluster A (61,58)
Cluster B (66,27)
Cluster C (68,06)
Cluster D (65,91)
Cluster E (58,02)
Cluster F (68,61)
Language*
1,0
0,5
0,0
-0,5
-1,0
-1,5
-2,0
Baseline
1 Year
2 Years
Cluster A (61,58)
Cluster B (66,27)
Cluster C (68,06)
Cluster D (65,91)
Cluster E (58,02)
Cluster F (68,61)



*rescaled to make higher scores correspond with better functioning on the construct.

˟Scores were corrected to *z*-scores using the mean and standard deviation of the healthy controls on that measure.

Appendix V: Medication use at baseline, one year and two years after baseline

Figure 16. Percentage medication use at baseline

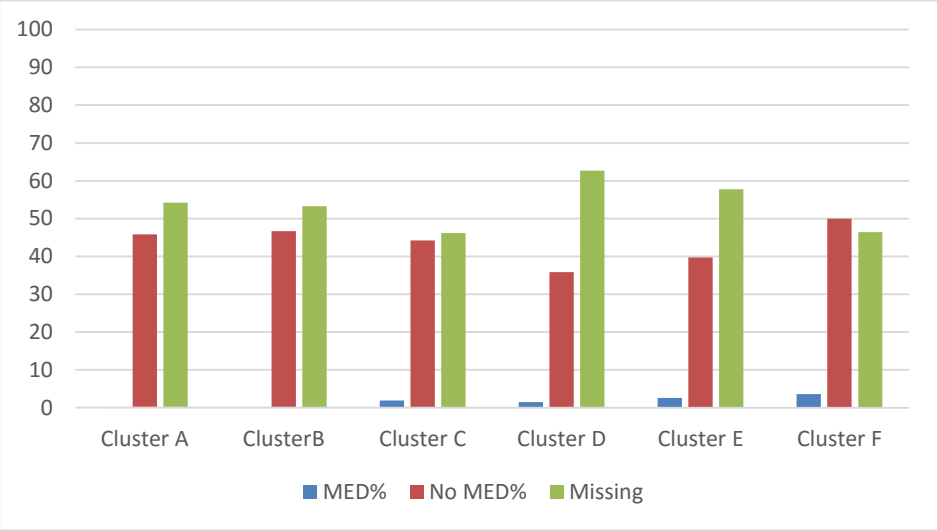


Figure 17. Percentage medication use at one year after baseline

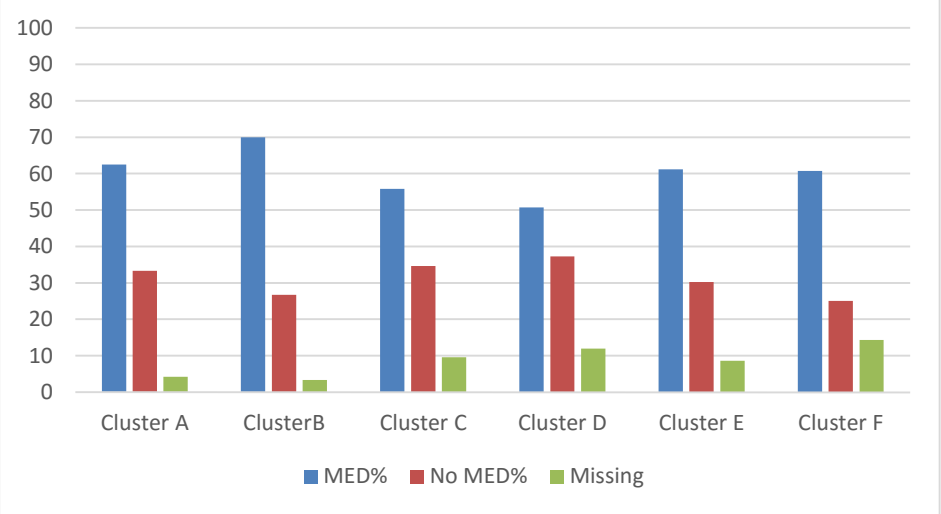
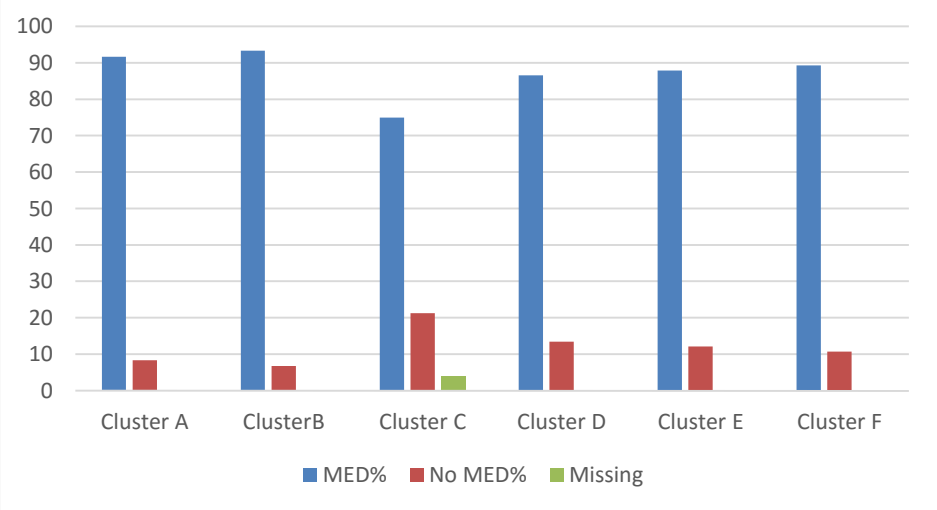


Figure 18. Percentage medication use at two years after baseline



Appendix VI. Variable means for each cluster at baseline

	Variables in cluster analysis						
	Total	**Cluster A**	**Cluster B**	**Cluster C**	**Cluster D**	**Cluster E**	**Cluster F**
UPDRS-III[3]	20.89	16.33[bcf]	23.77[ae]	29.15[ade]	18.80[c]	18.84[bc]	23.64[a]
STAI[3]	65.30	59.17[bf]	76.73[abe]	59.69[bf]	65.97	64.26[bf]	76.96[abe]
RBDSQ [4]	4.94	5.83[de]	7.27[de]	5.17[d]	3.50[abcf]	4.44[ab]	6.00[d]
SDMT[3]	41.14	43.81[bf]	35.73[aef]	40.02[ef]	39.66[ef]	46.31[bcdf]	26.68[abcde]
BJLOT[1]	25.72	26.55[f]	25.40[ef]	25.96[f]	25.58[ef]	26.81[bdf]	20.07[abcde]
LNS[3]	10.55	10.53[ef]	9.33[e]	10.00[ef]	9.81[ef]	12.18[abcdf]	7.93[acde]
HVLT-delay [4]	8.35	9.77[bcdf]	7.03[ae]	7.54[aef]	7.15[ae]	9.82[bcdf]	5.64[ace]
VLT-animal[3]	21.05	21.72[def]	18.77[e]	19.75[e]	18.66[ae]	24.36[abcdf]	16.75[ae]
MoCA [4]	27.03	27.25[ef]	27.30[f]	26.38[e]	26.21[e]	28.19[acdf]	24.71[abe]
	Variables not in cluster analysis						
	Total	**Cluster A**	**Cluster B**	**Cluster C**	**Cluster D**	**Cluster E**	**Cluster F**
HVLT-recall[3]	24.35	26.55[bdef]	21.63[ae]	22.56[aef]	22.19[aef]	27.44[bcdf]	19.29[acde]
SCOPA-AUT [4]	9.60	9.13[b]	13.83[ade]	10.23	9.00[b]	8.15[b]	12.18
ESS [4]	5.70	5.60	6.03	5.33	5.01	6.03	6.44
MSEADL[3]	93.23	94.48[c]	90.67[e]	90.58[ade]	93.81[c]	94.61[bc]	91.61
GDS15[1]	2.40	1.58[bf]	4.67[acdef]	2.06[b]	2.39[b]	2.22[b]	2.71[ab]
N	341	48	30	52	67	116	28

[a]Significantly ($p < 0.05$) different from cluster A, [b]Significantly ($p < 0.05$) different from cluster B, [c]Significantly ($p < 0.05$) different from cluster C, [d]Significantly ($p < 0.05$) different from cluster D, [e] Significantly ($p < 0.05$) different from cluster E, [f]Significantly ($p < 0.05$) different from cluster F.

[1]Kruskal-Wallis H-Test, [2]Chi Square Test, [3]One Way ANOVA, [4]Welch's ANOVA

* Percentage of participants with impulse control disorder(s)

° Percentage of female participants

ˣ Percentage participants using medication

UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDMT: Symbol Digits Modalities Test, LNS: Letter Number Sequencing (WMS-III), BJLOT: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment, HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for Outcomes in Parkinson's

Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADL: Modified Schwab & England Activities of Daily Living, QUIP-S: Questionnaire for Impulsive-Compulsive Disorders, H&Y Scale: Hoehn & Yahr Scale.

Appendix VII. Repeated Measures ANOVA results comparing baseline, one year and two years

Cluster A:

- RBDSQ: F (2, 88) = 0.305, $p < .0001$, $\eta 2 = .159$
- SDMT: F (2, 88) = 4.527, $p = .013$, $\eta 2 = .093$
- MoCA: assumption of sphericity was violated
    - Mauchly's W = .308, $\chi 2$ (2, n = 46) = 51.78, $p < .0001$
    - Greenhouse-Geisser adjusted F (1.182, 53.200) = 10.232, $p = .001$, $\eta 2 = .185$
- ESS: F (2, 56) = 5.670, $p = .006$, $\eta 2 = .168$
- HVLT recall condition: F (2, 88) = 3.467, $p = .036$, $\eta 2 = .073$
- MSEADL, F (2, 86) = 4.899, $p = .010$, $\eta 2 = .102$

Clusters B:

- UPDRS part III: F (2, 50) = 3.901, $p = .027$, $\eta 2 = .135$
- RBDSQ: F (2, 56) = 9.074, $p < .0001$, $\eta 2 = .245$
- SDMT: F (2, 56) = 9.254, $p < .0001$, $\eta 2 = .248$
- LNS: F (2, 56) = 3.870, $p = .027$, $\eta 2 = .121$
- ESS: F (2, 56) = 5.670, $p = .006$, $\eta 2 = .168$
- SCOPA-AUT: F (2, 56) = 8.210, $p = .001$, $\eta 2 = .227$
- MSEADL: F (2, 56) = 18.409, $p < .0001$, $\eta 2 = .397$
- HVLT recall condition: F (2, 56) = 5.641, $p = .006$, $\eta 2 = .168$

Cluster C

- UPDRS: F (2, 74) = 34.846, $p < .0001$, $\eta 2 = .485$
- BJLOT: F (2, 92) = 3.402, $p = .0385$, $\eta 2 = .069$
- SCOPA-AUT: F (2, 92) = 8.421, $p < .0001$, $\eta 2 = .155$
- MoCA: assumption of sphericity was violated
    - Mauchly's W = .648, $\chi 2$ (2, n = 47) = 19.51, $p < .0001$
    - Greenhouse-Geisser adjusted F (1.479, 68.055) = 5.271, $p = .014$, $\eta 2 = .103$
- MSEADL: assumption of sphericity was violated
    - Mauchly's W = .776, $\chi 2$ (2, n = 44) = 10.64, $p = .005$.
    - Huynh-Feldt adjusted F (1.690, 72.670) = 5.271, $p = .010$, $\eta 2 = .109$.

Cluster D

- UPDRS: F (2, 104) = 4.254, p = .017, $\eta 2$ = .076
- SDMT: F (2, 116) = 4.010, p = .021, $\eta 2$ = .065
- MoCA: assumption of sphericity was violated
    - Mauchly's W = .573, χ 2 (2, n = 59) = 31.77, p < .0001
    - Greenhouse-Geisser adjusted F (1.401, 81.276) = 14.293, p < .0001, $\eta 2$ = .198
- MSEADL, F (2, 108) = 14.202, p < .0001, $\eta 2$ = .208

Cluster E

- UPDRS: F (2, 172) = 10.629, p < .0001, $\eta 2$ = .110
- LNS: F (2, 210) = 4.637, p = .011, $\eta 2$ = .042
- HVLT delay condition: F (2, 210) = 5.675, p = .004, $\eta 2$ = .051
- VLT animal condition: F (2, 210) = 8.593, p < .0001, $\eta 2$ = .076
- MoCA: assumption of sphericity was violated
    - Mauchly's W = .659, χ 2 (2, n = 106) = 43.32, p < .0001
    - Greenhouse-Geisser adjusted F (1.492, 31.075) = 156.638, p < .0001, $\eta 2$ = .089
- SCOPA-AUT: F (2, 210) = 11.944, p < .0001, $\eta 2$ = .102
- MSEADL: F (2, 204) = 23.466, p < .0001, $\eta 2$ = .187

Cluster F

- SDMT: F (2, 46) = 6.066, p = .005, $\eta 2$ = .209
- HVLT delay condition: F (2, 46) = 3.761, p = .031, $\eta 2$ = .141
- BJLOT: assumption of sphericity was violated
    - Mauchly's W = .520, χ 2 (2, n = 24) = 14.40, p = .001
    - Greenhouse-Geisser adjusted F (1.351, 31.075) = 3.933, p = .045, $\eta 2$ = .146
- LNS: F (2, 46) = 15.371, p < .0001, $\eta 2$ = .401
- VLT animal condition: F (2, 46) = 3.915, p = .027, $\eta 2$ = .145
- GDS15: F (1, 27) = 5.661, p = .025, $\eta 2$ = .173
- MSEADL: assumption of sphericity was violated
    - Mauchly's W = .600, χ 2 (2, n = 22) = 10.21, p = .006
    - Greenhouse-Geisser adjusted F (1.429, 30.003) = 7.488, p = .005, $\eta 2$ = .263

Table 12. Mean scores of Cluster A at baseline, one year and two years after baseline

	Variables included in cluster analysis		
	Baseline	**One year**	**Two years**
UPDRS-III	16.33	17.95	16.04
STAI	59.17	60.63	58.48
RBDSQ	5.83[c]	5.96[c]	7.40[ab]
SDMT	43.81	43.93[c]	45.88[b]
BJLOT	26.55	26.17	27.25
LNS	10.53	10.74	10.27
HVLT-delay	9.77	9.28	9.83
VLT-animal	21.72	22.17	20.48
MoCA	27.25[bc]	27.30[a]	27.21[a]
	Variables not included in cluster analysis		
	Baseline	**One year**	**Two years**
GDS15	1.58	1.44	1.52
SCOPA-AUT	9.13	10.41	10.48
ESS	5.60[c]	6.48	7.33[a]
MSEADL	94.48[c]	92.28	91.96[a]
HVLT-recall	26.55	25.33	26.52

[a]Significantly ($p < 0.05$) different from cluster baseline, [b]Significantly ($p < 0.05$) different from one year after baseline, [c]Significantly ($p < 0.05$) different from two years after baseline

UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDMT: Symbol Digits Modalities Test, LNS: Letter Number Sequencing (WMS-III), BJLOT: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment, HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADL: Modified Schwab & England Activities of Daily Living.

Table 13. Mean scores of Cluster B at baseline, one year and two years after baseline

	Variables included in cluster analysis		
	Baseline	**One year**	**Two years**
UPDRS-III	23.77[c]	25.63	28.37[a]
STAI	76.73	83.20	81.60
RBDSQ	7.27[c]	8.00[c]	9.67[ab]
SDMT	35.73[c]	34.66[c]	30.97[ab]
BJLOT	25.40	24.83	25.60
LNS	9.33	9.52	8.67
HVLT-delay	7.03	6.66	5.87
VLT-animal	18.77	18.00	16.90
MoCA	27.30	25.41	25.57

	Variables not included in cluster analysis		
	Baseline	**One year**	**Two years**
GDS15	4.67	6.73	5.40
SCOPA-AUT	13.83[bc]	16.90[a]	18.53[a]
ESS	6.03[c]	7.86	8.80[a]
MSEADL	90.67[c]	88.28[c]	83.00[ab]
HVLT-recall	21.63[bc]	19.76[a]	18.97[a]

[a]Significantly ($p < 0.05$) different from cluster baseline, [b]Significantly ($p < 0.05$) different from one year after baseline, [c]Significantly ($p < 0.05$) different from two years after baseline

UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDMT: Symbol Digits Modalities Test, LNS: Letter Number Sequencing (WMS-III), BJLOT: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment, HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADL: Modified Schwab & England Activities of Daily Living.

Table 14. Mean scores of Cluster C at baseline, one year and two years after baseline

	Variables included in cluster analysis		
	Baseline	**One year**	**Two years**
UPDRS-III	29.15[c]	32.26[c]	39.71[ab]
STAI	59.69	59.82	59.35
RBDSQ	5.17	5.36	5.46
SDMT	40.02	38.53	37.56
BJLOT	25.96[c]	25.23	26.88[a]
LNS	10.00	10.06	9.58
HVLT-delay	7.54	7.02	6.92
VLT-animal	19.75	20.30	19.42
MoCA	26.38[c]	25.04	24.96[a]
	Variables not included in cluster analysis		
	Baseline	**One year**	**Two years**
GDS15	2.06	1.73	1.98
SCOPA-AUT	10.23[bc]	11.77[a]	12.98[a]
ESS	5.33	6.15	6.77
MSEADL	90.58[c]	88.19	86.56[a]
HVLT-recall	22.56	21.68	21.17

[a]Significantly ($p < 0.05$) different from cluster baseline, [b]Significantly ($p < 0.05$) different from one year after baseline, [c]Significantly ($p < 0.05$) different from two years after baseline

UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDMT: Symbol Digits Modalities Test, LNS: Letter Number Sequencing (WMS-III), BJLOT: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment, HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for

Outcomes in Parkinson's Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADL: Modified Schwab & England Activities of Daily Living.

Table 15. Mean scores of Cluster D at baseline, one year and two years after baseline

	Variables included in cluster analysis		
	Baseline	**One year**	**Two years**
UPDRS-III	18.80[b]	22.51[a]	20.80
STAI	65.97	63.14	64.24
RBDSQ	3.50	3.85	3.46
SDMT	39.66[b]	41.86[a]	39.01
BJLOT	25.58	23.97	25.61
LNS	9.81	9.98	9.90
HVLT-delay	7.15	7.12	6.73
VLT-animal	18.66	19.32	18.70
MoCA	26.21[bc]	25.31[a]	25.40[a]
	Variables not included in cluster analysis		
	Baseline	**One year**	**Two years**
GDS15	2.39	2.17	2.49
SCOPA-AUT	9.00	9.71	9.69
ESS	5.01	5.05	5.30
MSEADL	93.81[bc]	90.00[a]	89.52[a]
HVLT-recall	22.19	22.68	21.19

[a]Significantly ($p < 0.05$) different from cluster baseline, [b]Significantly ($p < 0.05$) different from one year after baseline, [c]Significantly ($p < 0.05$) different from two years after baseline

UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDMT: Symbol Digits Modalities Test, LNS: Letter Number Sequencing (WMS-III), BJLOT: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment, HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADL: Modified Schwab & England Activities of Daily Living.

Table 16. Mean scores of Cluster E at baseline, one year and two years after baseline

	Variables included in cluster analysis		
	Baseline	**One year**	**Two years**
UPDRS-III	18.84[bc]	21.97[a]	22.30[a]
STAI	64.26	59.19	62.62
RBDSQ	4.44	4.38	4.42
SDMT	46.31	45.25	45.72
BJLOT	26.81	26.34	26.78
LNS	12.18	11.86[c]	12.43[b]
HVLT-delay	9.82[c]	9.90	10.42[a]

VLT-animal	24.36[c]	23.87[c]	25.87[ab]
MoCA	28.19[bc]	28.11[a]	28.45[a]
	Variables not included in cluster analysis		
	Baseline	**One year**	**Two years**
GDS15	2.22	1.81	2.15
SCOPA-AUT	8.15[bc]	9.66[a]	9.91[a]
ESS	6.03	6.167	6.16
MSEADL	94.61[bc]	91.84[ac]	90.31[ab]
HVLT-recall	27.44	27.37	27.65

[a]Significantly ($p < 0.05$) different from cluster baseline, [b]Significantly ($p < 0.05$) different from one year after baseline, [c]Significantly ($p < 0.05$) different from two years after baseline

UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDM: Symbol Digits Modalities Test, LNS: Letter Number Sequencing (WMS-III), BJLO: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment, HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADLG: Modified Schwab & England Activities of Daily Living.

Table 17. Mean scores of Cluster F at baseline, one year and two years after baseline

	Variables included in cluster analysis		
	Baseline	**One year**	**Two years**
UPDRS-III	23.64	25.59	29.02
STAI	76.96	83.67	80.29
RBDSQ	6.00	5.79	6.29
SDMT	26.68[c]	25.25	20.93[a]
BJLOT	20.07	18.08[c]	16.79[b]
LNS	7.93[c]	7.21[c]	5.79[ab]
HVLT-delay	5.64	5.17	3.96
VLT-animal	16.75[c]	16.50	14.54[a]
MoCA	24.71	21.52	19.54
	Variables not included in cluster analysis		
	Baseline	**One year**	**Two years**
GDS15	2.71[c]	4.00	4.25[a]
SCOPA-AUT	12.18	13.71	15.18
ESS	6.44	7.29	8.43
MSEADL	91.61[c]	89.17	83.46[a]
HVLT-recall	19.29	17.63	16.54

[a]Significantly ($p < 0.05$) different from cluster baseline, [b]Significantly ($p < 0.05$) different from one year after baseline, [c]Significantly ($p < 0.05$) different from two years after baseline

UPDRS-III: The Unified Parkinson's Disease Rating Scale part III, STAI: State-Trait Anxiety Inventory, RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire, SDMT: Symbol Digits Modalities Test, LNS:

Letter Number Sequencing (WMS-III), BJLOT: Benton Judgement of Line Orientation Test, HVLT-delay: Hopkins Verbal Learning Test delay condition, VLT-animal: Semantic Fluency animal category, MoCA: The Montreal Cognitive Assessment, HVLT-recall: Hopkins Verbal Learning Test recall condition, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease Assessment of autonomic dysfunction, ESS: Epworth Sleepiness Scale, GDS15: Geriatric Depression Scale, MSEADL: Modified Schwab & England Activities of Daily Living.