Clinical Patterns in Parkinson's disease

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General introduction

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease, after Alzheimer's disease, with an estimated prevalence of 0.3% of the entire population in industrialised countries.[1] In the Rotterdam study, a prospective population based study of people aged 55 or more years in a suburb of Rotterdam, an incidence rate of 1.7 per 1000 person years was found , whereas in people over 85 years this number increased to 4.3 per 1000 person years.[2]

Even though it is nowadays recognized that many nonmotor domains are also involved in PD, the clinical diagnosis of PD is still based on motor symptoms only: The definition of probable PD according to The United Kingdom Parkinson's Disease Society Brain Bank Criteria requires the presence of bradykinesia and at least one of the following motor symptoms: resting tremor, rigidity, or postural instability.[3,4] The nonmotor symptoms that are involved in PD include, but are not limited to, olfactory dysfunction, cognitive impairment, depressive symptoms, sleep problems, daytime sleepiness, autonomic dysfunction, psychotic symptoms, and pain.[5] Olfactory dysfunction is one of the first PD features[6] to manifest and seems to be a feature unrelated to other impairment domains of PD.[7] Cognitive impairment, including executive dysfunction as well as memory, attention, and visuospatial problems, is frequently present, even in the early stages of the disease.[8] The point prevalence of dementia in PD in population based studies is approximately 30%, whereas the cumulative prevalence may rise to 75% in patients with long disease duration.[9] Depression is a common feature of PD, although the reported prevalence rates vary widely. Prevalence rates of 17% for major depressive disorder and 35% for depressive symptoms were estimated by meta-analyses.[10] The basis of depression is suggested to be related to the disease process, rather than being a secondary response to a chronic disease.[5] Sleeping problems mainly concern difficulties with maintaining sleep and often occur together with depressive symptoms. However, daytime sleepiness is more prevalent than nighttime sleeping problems and has an obvious impact on daily activities.[11] A wide range of autonomic symptoms is present in PD, including problems with cardiovascular, thermoregulatory, pupillomotor, sexual, urinary and gastrointestinal functioning, with the latter two domains showing the greatest difference in prevalence as compared to control subjects.[12] In a longitudinal multicenter study it was shown that in patients surviving for 15 years or more, falls, autonomic disturbance, neuropsychiatric complications, and dementia were common features. All of these features are not responsive to levodopa, which is the most commonly prescribed medication for the treatment of PD's motor symptoms.[13] Additionally, motor fluctuations and dyskinesias may emerge as complications of the dopaminergic treatment used to alleviate some of the motor disturbances of the disease. The clinical spectrum of PD is no longer considered to be restricted to movement disoderders, but is nowadays characterized by a broad spectrum of motor and nonmotor features.

Pathogenesis

A definite diagnosis of PD requires post-mortem findings of neuronal loss and depigmentation of substantia nigra as well as Lewy bodies in the brain stem.[3] Lewy bodies and Lewy neurites are abnormal filamentous protein inclusions in neurons and neurites respectively, but inclusions may also occur in glia and presynaptic terminals. A major component of the Lewy bodies and Lewy neurites is aggregated or misfolded alphasynuclein.[14]

For a long time, PD has been considered a clinicopathologic entity caused by selective dopaminergic cell loss in the substantia nigra. However, this view has changed dramatically, since pathologic and genetic data have emphasized the important role for alphasynuclein in PD. The widespread presence

of alphasynuclein pathology in the peripheral and central nervous system has positioned PD as a multi-system disorder, involving not only the dopaminergic system, but also the noradrenergic, serotonergic, cholinergic, and other central neurotransmitter systems.[15,16]

Braak and colleagues have proposed a six-stage system, indicating a topographically caudo-rostral predictable sequence of intracerebral formation of abnormal proteinaceous Lewy bodies and Lewy neurites.[17] The pre-clinical stages 1 and 2 are characterized by pathology confined to the olfactory bulb and the anterior olfactory nucleus, as well as the lower brainstem. Subsequently, degeneration of the substantia nigra, ventral tegmental area, nucleus basalis of Meynert, and other nuclear grays of the basal midbrain and forebrain occurs in stages 3-4. Stages 5-6 are characterized by severe involvement of the brain, including the limbic structures and the neocortex.[17] However, in retrospective clinico-pathologic studies, up to 43% of the cases did not follow the proposed caudo-rostral progression patterns of Lewy body pathology as suggested by Braak and colleagues.[14] Furthermore, relationships between the Braak stages and clinical severity of PD could not be confirmed.[14] Recently, a new unified staging system was proposed based on research on post mortem data, allowing classification not specifically for PD, but for all Lewy body disorders.[18] Other Lewy body disorders that were studied include dementia with Lewy bodies, incidental Lewy body disease, and Alzheimer's disease with sparse predominantly limbic Lewy bodies. In this new staging system, presence or absence of alphasynucleinopathy is scored in four stages. In the first stage, alphasynucleinopathy is confined to the olfactory bulb. In the second stage, alphasynucleinopathy is either dominant in the brainstem (IIa) or the in the limbic structures (amygdala; IIb). In stage III both the brainstem and limbic structures are affected, while in stage IV the neocortical area is involved as well.[18] With the new staging system, an agreement of over 80% was found between clinical classification of patients and pathological findings. PD patients in successive stages showed a stepwise worsening in terms of substantia nigra pigmented neuron loss, cognitive functioning and motor impairment.[18,19] Nevertheless, the role of Lewy bodies is still debated. Lewy bodies have been proposed to be pathogenic, but others have argued that they are protective or merely incidental.[14,15,20] Results of a study on a Drosophila model suggested that Lewy bodies might be a protective response controlling neurotoxicity.[21] Furthermore, Lewy bodies have not been found in all patients with the PD phenotype; some patients had tau aggregates (common in Alzheimer's disease) or no aggregates at all. [14,15,20] Hence the predictive validity of protein aggregates is doubtful and the two facts together suggest that Lewy bodies may not have a direct pathogenic role in the neurodegenerative process.[14,15,20] It has been suggested that the formation of Lewy bodies is one of several response patterns to the pathologic process, and that the actual cell loss or the associated synaptic dysfunction might be a more suitable marker.[22] Nevertheless, Lewy bodies might still be helpful markers of the neurodegenerative process by reflecting changes in the cellular environment, thereby indicating affected neurons and because of this possibly elucidating the pathogenic mechanism.[14,20]

Current hypotheses of the pathogenic mechanism in PD include mitochondrial dysfunction, oxidative stress, and protein aggregation. These pathways may also interact in the pathogenesis of PD. [23-25] Mitochondrial dysfunction was linked to PD after the finding of mitochondrial complex I deficiency in the substantia nigra.[24,25] Inhibition of mitochondrial complex I can impair oxidative phosphorilation and can thereby increase free radical generation. Conversely, mitochondrial function may also be negatively influenced by oxidative stress.[24,25] In eukaryocitic cells, the quality of proteins is monitored, and misfolded proteins are refolded. If damaged proteins cannot be repaired, they are normally cleared by the so-called ubiquitin-proteasome system. Mitochondrial defects and free radicals can negatively affect the function of this ubiquitin-proteasome system. Defects in the ubiquitin-proteasome system or

excessive production of misfolded proteins result in accumulation of misfolded proteins with detrimental effects on the cell function and usually subsequent cell death.[23-25]

Aetiology

Genetic factors

For a long time, PD was thought to be a sporadic disease. However, with the identification of mutations in several genes that can cause both familial and sporadic PD, the role of genetic factors in the aetiology in PD is gradually becoming more important. Although a positive family history of PD was previously considered an exclusion criterion for the diagnosis of PD, this is no longer the case.[22,26] Still, 90% of the cases is considered sporadic PD.[1] In the PROfiling PARKinson's disease (PROPARK) cohort (described in more detail below) known genetic variations were found in only 4% of the patients.[27]

To date, dominant inherited mutations have been identified in two genes, namely the *alphasynuclein (SNCA)* gene and the *leucine rich repeat kinase 2 (LRRK2)* gene.

Mutations in the *SNCA* gene *(PARK1, PARK4)* may lead to amino acid changes, which in turn lead to accumulation and aggregation of alphasynuclein. The clinical phenotype is characterized by a progressive disease that is responsive to levodopa and which is associated with cognitive decline and autonomic dysfunction. The age-at-onset ranges from 38 to 65 years. Patients with SNCA triplications have a more rapid progression and a younger age-at-onset.[26,28]

Mutations in the *LRRK2 (PARK8)* gene are the most common cause of autosomal-dominantly inherited PD. Phenotypic characteristics are highly variable and the age-at-onset ranges from 50 to 70 years.[26] The associated pathology is variable as well: in cases with mutations the typical Lewy body disease has been found, but also tau-aggregates, and nigral degeneration without protein aggregations. It is still not clear how *LRRK2* mutations lead to neurodegeneration.[26,28]

Several recessive genes have been identified, that are related to early onset parkinsonism and include *Parkin (PARK2), PTEN –induced kinase 1 (PINK1; PARK6)* and *DJ1 (PARK7).*

Parkin is related to the ubiquitin-proteasome system. It attaches ubiquitin to damaged proteins as a signal for degradation, which is impeded by mutations in *Parkin.* Consequently, the function of the ubiquitin-proteasome system is disrupted.[24] Patients with *Parkin* mutations often present with dystonia, motor fluctuations, and dyskinesias. Patients are responsive to low doses of levodopa and have a slow disease progression. The age-at-onset is around 30 years.[26,28]

PINK1 mutations are related to mitochondrial dysfunction and oxidative stress. *PINK1* and *Parkin* may act in a common pathway.[24,28] The phenotype of patients with *PINK1* mutations is also characterized by a response to low doses of levodopa, a slow disease progression, rapid development of dyskinesias, dystonia and an age-at-onset between 20 and 40 years. Depression and anxiety are common features in *PINK1*-associated PD. [26,29]

Mutations of *DJ1* cause an increased susceptibility to oxidative stress and are related to mitochondrial dysfunction. Wild type *DJ1* inhibits aggregation of alphasynuclein, whereas this effect is lost with the *DJ1* mutation.[24,28] The phenotypic expression of this mutation is slow disease progression, psychiatric disturbance, dystonia, and an age-at-onset between 20 and 40 years.[26,29]

Furthermore, there are several known genes and polymorphisms that are not exclusively present in PD patients, yet may increase the susceptibility for PD or specific PD features. One of these genes

is the *glucocerebrosidase (GBA) gene,* known to cause Gaucher disease; PD patients were found to have a five-fold increased risk for a mutation in the *GBA* gene as compared to controls. How mutations in this gene contribute to the pathogenesis of PD, and whether mutations are associated with specific phenotypic characteristics, needs to be further examined.[30,31]

Nongenetic factors

The identification of drug-induced parkinsonism following ingestion of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) raised awareness of the potential role of environmental factors in the aetiology of PD.[32,33] Since then, several environmental factors have been suggested to increase or decrease the risk of developing PD. Aging, male gender, personality traits, drinking well water, head trauma, physical and emotional stress, are reported factors that may increase the risk of PD. Smoking, caffeine intake, use of some NSAID's, an elevated level of uric acid are reported factors that may decrease the risk of PD.[22,32] However, studies on the relation between these factors and PD showed inconsistent results. Further, the results of prospectively designed studies may be influenced by a phenomenon that is called 'reversed causality': in the pre-symptomatic period patients may have changed their behaviour (for instance food intake) as a consequence of the disease. Since the exact duration of the preclinical period is unknown, risk factors may erroneously be thought to have an aetiological role. Hitherto, older age and smoking habits respectively, are the only factors that have consistently been found to increase or decrease the risk of PD.[1]

In conclusion, PD can be explained by well-defined genetic or environmental causes in only a minority of patients, whereas in the majority of patients multiple interactions between (susceptibility) genes and nongenetic factors are assumed to contribute to the development of PD. Thus, the aetiology of PD is most likely the result of complex interactions between genes, environment, and an aging nervous system.[1,22,24]

Subtypes of Parkinson's disease

In 1888, the clinical heterogeneity of PD was already subject of study. Although patients with 'paralysis agitans' were considered to be characterized by tremor, in one of his lessons Charcot presented a patient with PD who did not have tremor. This was one of the reasons why he suggested to refer to the disease as *'Parkinson's disease'* instead of *'paralysis agitans' ('shaking palsy')*; this term did not accurately characterize the disease.[34]

Clinical heterogeneity of PD is not limited to rigidity and tremor. Compared to tremor dominant patients, patients with predominant bradykinesia and rigidity had more severe cognitive impairment and depressive symptoms.[35-37] A subtype with dominant Postural-Instability-and-Gait-Difficulty (PIGD) was found to be associated with cognitive impairment and depression.[38-40] Furthermore, PD patients may vary in age-at-onset and rate of progression.[41] Patients with younger age-at-onset showed a slower rate of disease progression,[40-42] but more rapidly developed motor complications.[42]

As PD is characterized by variability both in clinical presentation and in pathological pathways, phenotypic differences may represent different underlying pathogenic mechanisms.[33,43] Compared to the tremor-dominant subtype, the akinetic-rigid subtype was found to have a greater extent of neurodegeneration in several neuroanatomical structures, including the substantia nigra, striatum, globus pallidus and locus coeruleus,[44-46] and was associated with a greater burden of cortical Lewy body pathology.[47] As described above, some genetic mutations may contribute to a different phenotypic expression.

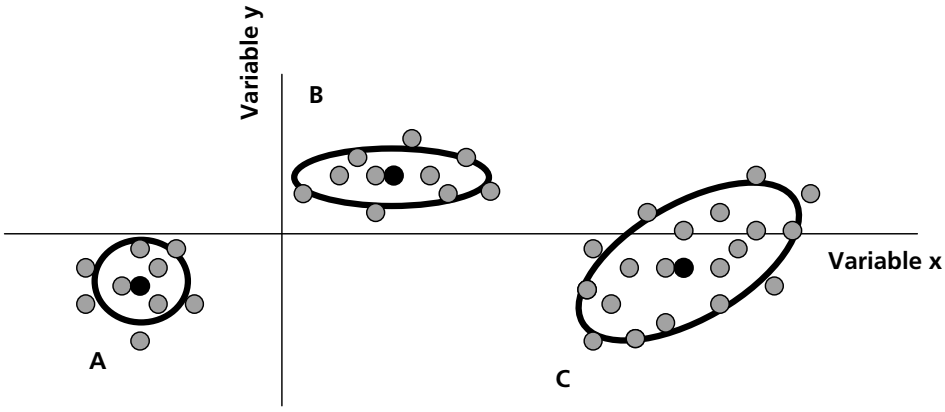
Heterogeneity influences the power of studies on underlying mechanisms and genetics, since

groups with a homogeneous clinical presentation are likely to have stronger pathological coherence as well. As a result, there is an increasing awareness of the importance of the identification of clinical subtypes. Moreover, the identification of subtypes may have consequences for management strategies, since subtypes may differ in disease progression, response to treatment, and vulnerability to complications of therapy.

Methods identifying subtypes

Clinical subtypes have often been defined on the basis of the investigator's hypotheses. Patients were classified according to pre-specified criteria, usually based on the clinical characteristics of a single domain, after which differences in other clinical variables were evaluated.[41] The potential bias inherent to this approach is that less obvious or unexpected patterns may be missed. Alternatively, the presence of subtypes can be objectively examined by data-driven methods like cluster analysis (CA) without any a priori assumptions with respect to clinical characteristics of subtypes. In CA, individuals are classified into groups, rendering small differences within each group of patients, but large differences between different groups (figure 1).[48] In this so-called unsupervised classification, the profiles of subtypes arise from the data without any a priori clinical assumptions.

Figure 1. An example of a scatterplot showing three clusters (A, B, C) with their specific characteristics on 'variable x' and 'variable y'.



PROfiling PARKinson's disease

The PROPARK study is a longitudinal cohort study, in which 400 patients are profiled on genotype, phenotype, disabilities, and global outcomes of health.[49] This project started in 2003; during six years patients were annually subjected to an extensive standardized assessment, which included evaluation of a broad spectrum of PD domains, physical and psychosocial disability, quality of life, demographics, family history of PD, and medication use. The measurement instruments were derived from a previous project, the SCales for Outcomes in PArkinson's disease (SCOPA) project, which was carried out between 1999 and 2003. The aim of the SCOPA project was to develop rating scales for clinically relevant domains of PD. Measurement instruments had to meet prespecified criteria of good reliability, validity, and responsiveness, and had to be short and practical.

Aims of the thesis

The general objective of this thesis was to identify clinical subtypes in PD by a data-driven approach. To this end, we first systematically reviewed the methodology and results of CA studies in PD to gain a better understanding of the robustness of identified subtypes and of the methodological issues that may influence the results (***chapter 2***). An important step in establishing subtypes of phenotype profiles in PD is to critically select which variables are included in the CA. A comprehensive view of domain interrelations as well as their associations with other clinical and nonclinical parameters was the first step in a data-driven determination of subtypes. Using the data of the first annual PROPARK assessment, we constructed a model of factors that influence health related quality of life (HRQoL) in order to evaluate how impairments and disabilities contribute to HRQoL (***chapter 3***). In ***chapter 4,*** we first applied a confirmatory factor analysis to evaluate the coherency of motor impairments as assessed by the SPES/SCOPA rating scale. Subsequently, we studied patterns of coherency in the broad spectrum of motor and nonmotor domains ***(chapter 5)***. In ***chapter 6,*** a model based CA was performed in order to identify subtypes in PD that were solely based on motor and nonmotor features of the disease, using data of two independent European cohorts. We used a data-driven approach and did not define hypotheses in advance, which means that the profile of the subtypes arose from the data without any a priori clinical assumptions. Finally, the main conclusions are summarized and discussed in ***chapter 7***.

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The identification of Parkinson's disease subtypes using cluster analysis; a systematic review.

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Abstract

The clinical variability between patients with Parkinson's disease (PD) may point at the existence of subtypes of the disease. Identification of subtypes is important, since a focus on homogeneous groups may enhance the chance of success of research on mechanisms of disease and may also lead to tailored treatment strategies. Cluster analysis (CA) is an objective method to classify patients into subtypes. We systematically reviewed the methodology and results of CA studies in PD to gain a better understanding of the robustness of identified subtypes. We found seven studies that fulfilled the inclusion criteria. Studies were limited by incomplete reporting and methodological limitations. Differences between studies rendered comparisons of the results difficult. However, it appeared that studies which applied a comparable design identified similar subtypes. The cluster profiles 'old age-at-onset and rapid disease progression' and 'young age-at-onset and slow disease progression' emerged from the majority of studies. Other cluster profiles were less consistent across studies. Future studies with a rigorous study design that is standardized with respect to the included variables, data processing, and CA technique may advance the knowledge on subtypes in PD.

Introduction

Parkinson's disease (PD) is clinically characterized by a broad spectrum of motor and nonmotor manifestations.[1] There is, however, considerable variability between patients with PD concerning the clinical phenotype, which may indicate that there are subtypes of the disease.[2] Identification of PD subtypes may be important for research on underlying disease mechanisms, since homogeneous groups of patients are more likely to share pathological and genetic features. Second, the identification of subtypes may ultimately lead to tailored management strategies.

In 2002, Foltynie et al. explored the concept of heterogeneity in PD from several perspectives, including the clinical phenotype. It appeared that on a clinical level, subtypes generally were classified according to prespecified or hypothesized criteria that were based on predominant clinical features (tremor, bradykinesia/rigidity, postural instability, cognitive impairment), age-at-onset, and rate of progression.[2] The potential bias inherent to this approach is that less obvious or unexpected patterns may be missed.

When no a priori structure of the data is known, a data-driven method like cluster analysis (CA) may be a very suitable method to study subtypes. CA can be used to explore whether individuals can be classified into groups in such a way that differences within a group of patients are small, while the differences between groups are large.[3] In this so-called unsupervised classification, the characteristics of the subtypes arise from the data. Next to this apparent advantage, it is important to be aware that the results of CA are dependent on choices that are made in the process of analysis, such as the variables selected for analysis, the clustering technique and the number of clusters.[2,3] In the review on heterogeneity by Foltynie et al.[2] only one study was reported that explored the existence of clinical subtypes in PD by CA, but several other studies have been published since. In the present systematic review we evaluated which clinical subtypes of PD have been identified by CA, discuss their robustness and reflect on the methodological issues that may influence the results.

Methods

Search strategy

The following databases were searched on April 27th, 2009: PubMed (1949 to April 2009), EMBASE (OVID-version, 1980 to April 2009), and Web of Science (1945 to April 2009). The search consisted of the combination of the following terms: (1) Parkinson disease, and (2) heterogeneity, cluster analysis, K-means, self organizing maps, mixture models, data driven, or cluster combined with fuzzy, kernel based, or hierarchical. The search strategy was optimized for all consulted databases, taking into account the differences of database-specific technical variations. Additionally, the reference lists of all included articles were searched. The results were limited to articles in English, German, and Dutch.

Methods of review

The selection procedure was performed by two independent reviewers (SR, JM). This assessment was not blind with respect to authors or institutions. The obtained articles were first screened by title, after which the abstracts of potentially relevant articles were reviewed. If the abstract was considered relevant, the full text of the article was studied. Studies were included if (1) the study population consisted of PD patients, (2) the existence of subtypes was evaluated by CA and (3) the CA was based on clinical characteristics. Studies that focused on a specific domain of the disease were excluded to avoid incomparable findings.

Data extraction

Study methods and results were abstracted by one of the authors (SR). Whenever information was incomplete or unclear, the authors of that study were contacted with the request to provide additional information. Since the outcomes of CA are dependent on the applied method, the variables included in the analysis, the characteristics of the involved sample and the way data are processed,[2,3] all information pertaining to these issues was collected and recorded on a standard score sheet. Specifics of these issues are detailed below.

Sample characteristics Characteristics of the included sample may affect the cluster structure. Therefore, it is important to know whether a sample represents a population of interest, e.g. de novo patients.[4] Additionally, the sample size is of relevance for the generalizability of the findings, since small studies will yield less precise estimates.–

Variables selected for CA. It is important to select variables that are considered relevant in phenotyping and discriminating subtypes of the disease.[4]

Data preprocessing. Variables are generally measured with different units of measurement. To adjust for differences due to scaling of the measurement instrument, the variables are usually standardized, for instance by transformation into Z-score or range.

Clustering algorithm. CA can be performed by different techniques, of which hierarchical clustering and K-means clustering are the most common. K-means CA is a partitioning method, meaning that patients are assigned to a prespecified (K) number of clusters without a hierarchical structure. K initial clusters are formed, after which patients are assigned to the cluster they most resemble. Subsequently, cluster means are calculated after which the distance to each cluster mean is calculated for each patient. Patients are reassigned to another cluster if they are closer to that cluster mean than to the mean of the cluster they were allocated to in the previous step. In the next step cluster means are recalculated followed by calculation of the patients' distances to the cluster means. This iterative process stops when no patients need to be reassigned, and the optimal solution

for the clusters is achieved.[3]

Local optimum. Cluster methods that involve iterative processes stop when an optimum is achieved. This optimum, however, may not be the optimal solution among all possible solutions but represent a so-called local optimum. The process of partitioning is sensitive to the starting points. To reduce the risk of ending in a local optimum, the clustering can be repeated a number of times with randomly chosen different starting points, after which the optimal solution is selected.[5]

Determination of number of clusters. The validity of the cluster result is dependent on the estimation of the number of clusters.[6] In K-means CA the number of clusters has to be indicated by the investigator. This optimal number can be estimated by statistical methods, of which the Calinski and Harabasz index (pseudo F-statistic)[7] was considered most appropriate.[8] It is important to report on which statistical grounds or other rationale the choice of the number of clusters was determined.

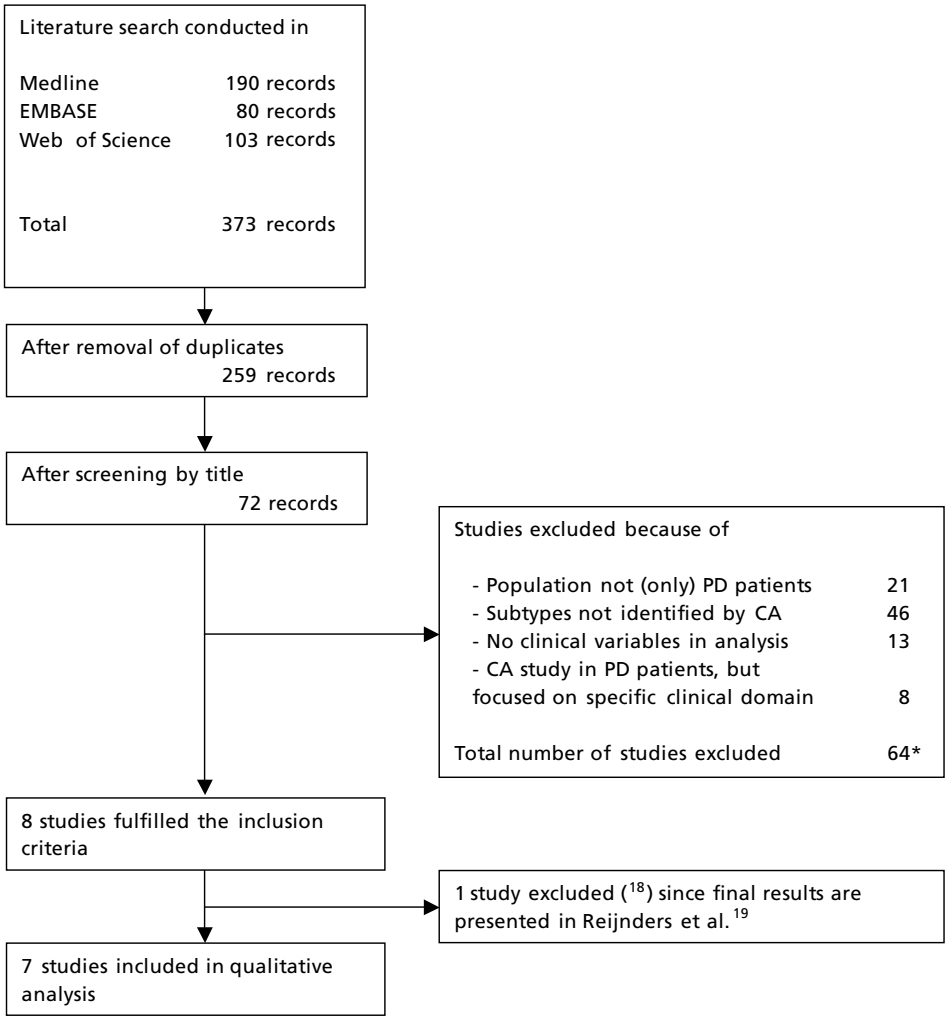
Cluster validation. Validation of the results is an important step since CA methods can always generate a division in clusters, which do not necessarily represent true subtypes.[6] The results are preferably replicated in an independent sample. Other methods are cross-validation, the demonstration of stability, and face validity.[2,4,9]

Interpretation of cluster results. The final goal of CA is to evaluate whether the cluster sizes and profiles are meaningful and clinically interpretable. A discriminant function analysis can be performed to evaluate which combination of variables best differentiates the subtypes. In contrast, F-values only provide insight in the magnitude of univariate differences between clusters. In post-hoc analyses, clusters can be further characterized on variables which were not included in the CA. This may provide insight in factors that play a role in the development of a specific phenotype profile.

Results

The search strategy yielded 259 studies of which eight were judged eligible by at least one reviewer. The overall inter-reviewer agreement for the inclusion of the studies by reviewing titles and abstracts was 99.6% (Cohen's Kappa 0.93). Differences were reconciled by consensus, after which eight studies were considered eligible for this review. Eight other studies performed CA in PD but focused on a specific domain of the disease and were therefore excluded.[10-17] One eligible study was published as a congress abstract[18] and as an article in a peer-reviewed journal.[19] We included only the latter publication, resulting in seven included studies (Table 1). The selection process is presented in Figure 1.

Figure 1. Flow chart of study search and selection



PD: Parkinson's Disease

CA: cluster analysis

**) Sum of studies excluded per criterion does not equal the total number of excluded studies, since some studies were excluded because of more than one exclusion criterion.*

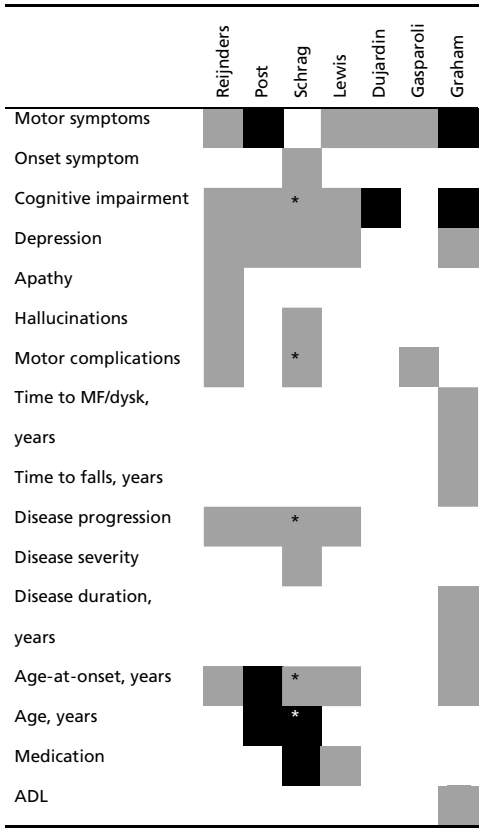
Table 1. Methodology of cluster analyses on the spectrum of PD

Methodological steps	Reijnders 2008 [19]	Post 2008 [26]	Schrag 2006 [28]	Lewis 2006 [27]	Dujardin 2004 [20]	Gasparoli 2002 [25]	Graham 1999 [21]
No. of patients	346	131	124	120	44	103	176
Inclusion criteria, in addition to PD	None	De novo	None	H&Y I - III	Time since diagnosis 3 yrs	Time since diagnosis 5 yrs	None
Sample characteristics (means, (SD))							
- age, yrs	70.4*	66.7 (10.4)	71.9 (11.0) §	64.4 (9.3)	66 (median)	NS	63.2 (10.2)
- disease duration, yrs	8.2	1.7 (0.9)	6.1 (4.4) §	7.8 (5.4)	4 (median)	NS	7.5 (6.4)
- H&Y	2.7	1.8 §	2.8 §	2.1 §	NS	NS	NS
Data preprocessing	Z-scores	Z-scores §	No§	Z-scores §	NS	‡	NS
Clustering algorithm	K-means	K-means	K-means	K-means	K-means	‡	K-means
Basis of the determination of the number of clusters	Non-statistical †	No criteria	No criteria	Non-statistical **	Statistical ††	Non-statistical #	No criteria
Cluster validation on independent sample	Yes	No	No	No	No	No	No
Evaluation of discriminative variables	No	Yes, F -values	Yes, F -values	No	Yes, discriminant analysis	No	Yes, F -value
Post hoc analysis of variables not included in CA	Yes	Yes	Yes	Yes	Yes	Yes	Yes

PD: Parkinson's disease, H&Y; Hoehn and Yahr stage, yrs: years, SD: standard deviation, NS: Not Specified, CA: cluster analysis

*§) Personal communication. *) Total sample is built op from two samples: N=224, age 73.2 (8.4), disease duration 9.5 (5.7), H&Y 2.8 (1.0); N=122, age 65.3 (10.0), disease duration 6.7 (5.0), H&Y 2.4 (0.8) (mean (SD)). ‡) Unknown. †) Based on changes in cluster distances in successive steps; face validity. **) Based on a clear distinction in clusters with a sufficiently large size. ††) Pseudo F-statistic, Cubic Clustering Criterion, squared correlation ratio. #) Aim to find two clusters.*

Table 2. Variables included in the cluster analyses



MF: motor fluctuations, dysk: dyskinesias, ADL: activities of daily living

Grey and black marked variables were included in the cluster analysis; the variables marked in black were discriminative variables that emerged from discriminant analysis or had large F-values. Details of measures and measurement instruments are provided in the Supplementary Appendix.

**) A cluster analysis was performed with all marked variables and with only the variables marked with *. Both analyses resulted in similar solutions (personal communication).*

Methodological appraisal

Study characteristics are presented in Table 1 and 2.

Sample characteristics All but one study analyzed >100 patients, with samples ranging from 44[20] to 176[21] patients. All studies applied validated criteria to diagnose PD.[22-24] Four studies applied additional inclusion criteria, which were based on disease duration in three[20,25,26] and on disease severity in one study.[27] One study did not provide patient characteristics for the total group.[25] Only in the study of Post et al. age-at-onset was specified, which was 65.1(10.4) (mean (SD)).[26] In the other studies, except that of Gasparoli et al.[25], information on mean age-at-onset can be obtained by subtracting disease duration from age, but the SD is unknown. Mean age-at-onset was 55.7[21], 56.6[27], 62[20], 62.2[19], and 65.8[28] years.

Variables selected for CA. Studies showed large variability, not only in included variables, but also in

measures or measurement instruments for a similar clinical domain (Table 2 and Supporting Appendix). Six of the seven studies included motor symptoms assessed by the Unified Parkinson's Disease Rating Scale (UPDRS), although different sum and subscores were used.[19-21,25-27] Motor symptoms were combined with measures of cognition in five studies,[19-21,26,27] of which four also included depression[19,21,26,27] and age-at-onset.[19,21,26,27] Three of these latter four studies also included a measure of disease progression.[19,26,27] Other variables were less frequently included (Table 2).

Data pre-processing. In five studies scores were standardized before analysis,[19-21,26,27] which concerned transformation into Z-scores in three.[19,26,27] One study presented results based on an analysis with unstandardized scores. However, repeating the analysis with scores transformed into Z-scores revealed similar findings (personal communication).[28]

Clustering algorithm. Information on the applied CA method was not reported in one study;[25] all other studies used K-means CA.

Local optimum. None of the studies reported how they tried to avoid local optima.

Determination of number of clusters. One study determined the optimal number of clusters on statistical grounds by three different indices (Pseudo F-statistic, Cubic Clustering Criterion, squared correlation ratio).[20] One study indicated that the aim was to find two clusters.[25] Two studies evaluated two to five-cluster solutions after which the optimal number was determined based on changes in cluster distances in successive steps and face validity in one study[19] and based on a clear distinction in clusters with a sufficiently large size in the other study.[27] Two studies evaluated both two and three-cluster solutions and one a five-cluster solution without determining the optimal number of clusters.[21,26,28]

Cluster validation. Only the study of Reijnders et al.[19] verified the cluster solution in a second sample; based on the cluster means and covariance matrices of the first sample they evaluated the probability of a cluster membership of patients in a second sample. That study, as well as two other studies,[26,27] also evaluated post-hoc how variables that were not included in the CA differed between the clusters. Lewis et al.[27] also evaluated to which extent patients consistently grouped together in the 3, 4, and 5 cluster solutions. Four studies did not report any information about validation of the cluster solution.[20,21,25,28]

Interpretation of the results

The studies identified five[21], four[19,27], three[20,26], and two[25,28] clusters. The sizes of all clusters were >5% of the total sample in all studies, except one in the study by Dujardin et al..[20] In the latter study, however, this small cluster was discarded after the analysis because authors concluded that the patients in this cluster had developed Alzheimer's disease (Table 3).

It is important to emphasize that all studies included a different set of variables in the CA (see Table 2). Since both the number and nature of included variables have a prominent role in the outcomes of the CA, all following results should be considered in the context the total set of variables that was included in the CA in each study. Consequently, the findings of different studies have limited comparability.

Discriminative variables

Only one study performed a discriminant analysis to evaluate which variables best discriminated the subtypes.[20] Three other studies presented F-values, indicating which variables showed large differences between clusters.[21,26,28] It appeared that in two studies cognitive dysfunction, specifically executive dysfunction, best differentiated between clusters.[20,21] In two other studies age-at-onset had large F-values,[26,28] in combination with age and axial motor symptoms in one,[26] and levodopa dose in the other study.[28] As stated above, these discriminating variables should be considered in the context of the total set of variables, which varied betweens studies (see Table 2).

Table 3. Identified cluster profiles and cluster sizes (% of total sample)

Cluster characteristic	Reijnders	Post	Schrag	Lewis	Dujardin	Gasparoli	Graham
Old age-at-onset / rapid disease progression	6	40	64	17		39	21
Young age-at-onset / slow disease progression	29	34	36	41		61	
Intermediate onset, anxiety, depression		27					
Tremor dominant	47			17			
Non-tremor dominant	17			26			
More severe motor & cognitive impairment					36		32
Mild motor & mild cognitive impairment					59		
Motor only							47
	100	100	100	100	95 *	100	100

*) *Sum of percentages does not equal 100, because one of the clusters was discarded.*

Cluster profiles

The majority of studies reported two clusters with a largely similar profile regarding age-at-onset and rate of disease progression (Tables 3 and 4).

The sizes of the clusters with the profile 'Rapid disease progression and old age-at-onset' differed considerably and ranged from 6% to 64% of the total sample. The mean age-at-onset ranged from 61.0[21] to 72.9[26] years. Four studies found an association with axial impairment, either directly from the cluster profile[19,26] or through post-hoc analyses.[21,25] Three studies found an association between this profile and predominance of bradykinesia/rigidity (cluster profile [19]; post hoc analysis[21,25]). Conflicting results for this cluster profile were found with respect to the association with motor complications (sporadic[28] and frequent[25]) and cognitive impairment (unaffected[27], mildly impaired[19], and impaired[21]).

Clusters with the profile 'Slow disease progression and young age-at-onset' also differed in size ranging from 29%[19] to 61%[25] of the total sample. Mean age-at-onset ranged from 50[27] to 59.1[28] years. This cluster profile was further characterized in three studies by mild motor symptoms[25-27] and absence of cognitive impairment.[19,26,27] Conflicting results were reported on the association between this profile and the severity of motor complications (sporadic[25] and severe[19,27]) and depressive symptoms (mild[27] and severe[28]).

Lewis et al.[27] and Reijnders et al.[19] also distinguished a 'bradykinesia/rigidity and PIGD-dominant' and a 'tremor-dominant' profile. Notably, since these were the only studies that included the subdomains tremor, bradykinesia, and rigidity in the CA, this profile could not have been identified in other studies.[19,27] The first cluster profile showed similarities with the 'rapid disease progression and old age-at-onset' cluster profile whereas the latter was comparable to the 'slow disease progression and young age-at-onset' cluster profile. However, each profile had specific characteristics.

Table 4. Cluster characteristics and associations

Cluster profiles	Other characteristics of the cluster profile	Cluster-associated variables not included in the CA
Rapid disease progression and old age-at-onset [19,21,25-28]	- motor impairment (total score) [21] - bradykinesia/ rigidity [19] - bradykinesia/ rigidity/tremor [26] - axial impairment [19,26]	- predominance bradykinesia/rigidity [21,25] - axial impairment [21,25] - bilateral PD signs at onset [25]
	- cognitive impairment [21] - mild cognitive impairment [19] - no cognitive impairment [27] - frequent motor complications [25] - sporadic motor complications [28]	
		- frequent symptomatic orthostasis [21] - low L-dopa dose [27,28] - short disease duration [19] - higher H&Y stage [26] - higher level of disability [26] - low level QoL (physical) [26]
Slow disease progression and young age-at-onset [19,25-28]	- mild motor symptoms [25-27]	- predominance tremor [25] - absence of gait disturbance [25] - unilateral PD signs at onset [25]
	- no cognitive impairment [26-28]	
	- severe depression [28] - mild depression [27]	
	- severe motor complications [19] - sporadic motor complications [25]	- severe motor complications [27]
	- high L-dopa dose [28]	- large proportion using DA [27] - relatively long disease duration [19] - younger age [19,28]
Tremor dominant [19,27]	- modest motor symptoms [27] - no cognitive impairment [19,27] - no depression [19,27]	- frequent tremor at onset [27]
		- anti-cholinergic medication [27] - relatively short disease duration [19] - lower H&Y stage [19]
Dominance of bradykinesia/ rigidity, PIGD [19,27]	- cognitive impairment [19,27] - executive dysfunction [27] - depressive symptoms [19,27] - apathy [19] - hallucinations [19]	- cognitive impairment [27]
		- relatively long disease duration [19] - higher H&Y stage [19] - worse ADL [19] - worse QoL (mobility, cognition) [27]

CA: Cluster analysis, PD: Parkinson's disease, L-dopa: levodopa, H&Y: Hoehn and Yahr, QoL: quality of life, DA: dopamine agonists, PIGD: postural instability and gait disorder, ADL: activities of daily living

Discussion

We found seven studies that performed CA techniques on a combination of PD features with the aim to identify clinical subtypes in PD. The cluster profiles 'old age-at-onset and rapid disease progression' and 'young age-at-onset and slow disease progression' emerged from the majority of studies.[19,21,25-28] Two studies further distinguished a 'tremor-dominant' and a 'bradykinesia/rigidity and PIGD dominant' cluster profile.[19,27] Other profiles were less consistently identified. These results suggest that age-at-onset and rate of disease progression are important determinants for subtypes in PD and are related to each other. Further, several studies found that the 'old age-at-onset and rapid disease progression' cluster profile was also characterized by axial motor symptoms, bradykinesia, and rigidity, whereas 'young age-at-onset and slow disease progression' was associated with mild motor and cognitive impairment. However, the results of the studies for either of these two profiles also clearly differed with respect to further characterization of the profiles and cluster sizes.

Differences in design may at least partly account for the differences in cluster results between studies, since choices in the process of CA will affect the results. However, large variability between studies in characteristics of study populations, in variables included in the CA and in measurement instruments, and in the number of clusters in the solution rendered the comparison of the results between studies difficult. All these factors may have to some extent influence on the cluster result. As a consequence, it was impossible to indicate specific explanation for differences in, for instance, cluster profiles or prevalence. This was further complicated by incomplete reporting of methodological steps in most studies. Interestingly, studies that included a largely similar set of variables in the CA found four more or less similar profiles,[19,27] which indicates that these subtypes are rather robust considering the fact that they were consistently identified despite considerable differences in samples characteristics between studies. It may be expected that application of CA in a more standardized design will increase the yield of studies on subtypes.

The study populations showed differences in age, disease duration and severity. Information on age-at-onset and the distribution of this characteristic, which was found to be an important determinant for the cluster profiles, was lacking in the majority of studies, rendering results difficult to interpret and to compare between studies.

Additionally, we identified several issues regarding the selection of variables that were included in the CA to identify PD subtypes. First, large differences between studies were noted in the extent to which clinical domains of PD were included in the analysis. It is possible that domains essential in discriminating subtypes may have been missed. This also holds for subdomains with independent behavior with respect to associations with other variables. Second, all but two studies[20,25] included not only clinical impairments, but also variables like age-at-onset or medication. The use of mixtures of clinical and nonclinical variables in establishing distinct phenotypes is questionable and may yield phenotype profiles that are conceptually less meaningful. Third, since PD is a progressive disorder, the phenotypic expression of patients may change with increasing disease duration. Only the studies of Gasparoli et al.[25] and Dujardin et al.[20] included patients with similar disease duration; all other studies included patients with variable disease durations and thus ran the risk of identifying subtypes that reflect different stages of the disease rather than reflecting different phenotypic subtypes. It should be noted that all studies included in this review had a cross-sectional design which ruled out the possibility of detecting subtypes with different longitudinal patterns of change, that is, different disease courses. Longitudinal studies could provide important information, in addition to the phenotypic profiles that are identified by cross-sectional studies.

K-means, the CA technique applied by at least six of the seven included studies, does not indicate how many clusters are optimal, which is unfortunate since the number of clusters in the solution has consequences for

the cluster profiles and sizes. Only one study dealt with this problem by calculating indices to determine the optimal number of clusters.[20] A second limitation of this clustering technique is that K-means is sensitive to outliers. In that respect, it is irrational that one study discarded one of the clusters after the analysis, since the excluded patients possibly had deviant scores and thus could have distorted the results.[20] Third, K-means is an iterative clustering method and thus studies ran the risk of ending in a local optimum. However, none of the studies reported that they attempted to avoid local optima.

Another important observation is that only one study validated the outcomes in a second sample, an essential step to obtain insight in the robustness and generalizability of the findings.[19]

In spite of these methodological limitations and variations rendering comparisons difficult, the advantages of studying subtypes in an objective manner were also noted. When compared to studies on clinical subtypes based on prespecified criteria as described in the review of Foltynie et al.[2] two important differences between the studies of interest in both reviews were noticed. First, the subtypes as described in the study by Foltynie et al.[2] were classified by only one dimension, i.e., one variable, whereas in the studies included in this review subtypes were classified and characterized on the basis of different dimensions. Additionally, four studies included in the present review allowed insight in the extent to which each variable contributed to the classification of the subtypes.[20,21,26,28] Second, in the studies reported in the review by Foltynie et al.[2] young age-at-onset, for example, was defined as < 40 years, while the mean age-at-onset of the young onset subtypes that were found in the studies included in the present review ranged from 50 to 60 years and already showed clear differences with profiles with an old age-at-onset. Thus researcher-based cut-off criteria may differ from mean values of clusters that are determined by CA and this may have consequences for the subtypes.

In conclusion, although CA has a great potential in identifying subtypes, the current review shows that the findings of different CA studies in PD are difficult to compare because of methodological differences between studies. These differences combined with methodological limitations in many of the studies lead to not fully conclusive results. In spite of the methodological differences, a profile characterized by higher age-at-onset and faster rate of disease progression and a profile characterized by lower age-at-onset and slower rate of disease progression, emerged from most studies. Since the identification of subtypes potentially has consequences for studies on the etiology of PD as well as for patient care, there is a need for CA studies with a rigorous design using a standardized approach. Future studies are recommended to 1) select a sample of PD patients with a preferably similar disease duration; 2) critically select a set of conceptually similar clinical variables that adequately represent the clinical spectrum of PD and are relevant in discriminating phenotypic profiles; 3) take the limitations of K-means into account or apply another CA technique that does not have these limitations; 4) critically evaluate the cluster results: Are they clinically meaningful and interpretable? Which variables discriminate best between clusters? How do the clusters differ with respect to variables that were not included in the CA?; 5) validate the results in independent samples. Studies that apply a similar design in different cohorts and take into account the abovementioned recommendations will likely increase our knowledge on subtypes in PD.

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Supporting Appendix: Measures and measurement instruments of variables selected for cluster analysis

Motor symptoms

Reijnders[1]: Separate scores for tremor, hypokinesia-rigidity, and PIGD: Unified Parkinson's Disease Rating Scale (UPDRS) III items 16, 20, 21; 20,31; 13-15, 29, 30.[2]

Post[3]: Levodopa responsive symptoms (facial expression, tremor, rigidity, bradykinesia): sum of UPDRS III item 19-26, 31; levodopa non-responsive symptoms (speech, axial impairment): sum of UPDRS III item 18, 27-30.[2]

Lewis[4]: Tremor ratio score: UPDRS III items 5,7,12-15,18,19,27-44 divided by 16, 20-26.[2]

Dujardin,[5] Gasparoli,[6] Graham[7]: UPDRS III total score.[2]

Graham[7]: Alternate finger tapping test (left right separate scores); UPDRS III subscores for left and right.[2]

Cognitive impairment

Reijnders,[1] Post,[3] Schrag,[8] Lewis[4]: Mini-Mental State Examination (MMSE).[9]

Lewis[4]: National adult reading test,[10] Pattern recognition memory,[11] Tower of London planning test.[12]

Dujardin[5]: Mattis Dementia Rating Scale,[13] Grober and Buschke test,[14] Stroop word-colour test, semantic task, alternating task.[15]

Graham[7]: Blessed Dementia Scale Information-Memory-Concentration test,[16] CANTAB subtests: Spatial Recognition Memory,[11] Spatial Working Memory,[17] Digit Ordering Paradigm,[18] Attentional Set Shifting,[19] Letter Fluency Assessment.[20]

Depressive symptoms

Reijnders[1]: Montgomery-Åsberg Depression Rating Scale.[21]

Post[3]: Hospital Anxiety and Depression Scale.[22]

Schrag,[8] Lewis[4]: Beck Depression Inventory.[23]

Apathy

Reijnders[1]: UPDRS I, item 4.[2]

Hallucinations

Reijnders[1]: UPDRS I, item 2.[2]

Schrag[8]: Presence of hallucinations.

Motor complications

Reijnders[1]: UPDRS IV.[2]

Schrag[8]: Presence of motor fluctuations/ dyskinesias.

Gasparoli[6]: Measure is not presented in the study.

Disease progression

Reijnders,[1] Lewis[4]: UPDRS I-III divided by disease duration.[2]

Post[3]: UPDRS III divided by disease duration.[2]

Schrag[8]: Hoehn and Yahr stage divided by disease duration.[24]

Disease severity

Schrag[8]: Hoehn and Yahr scale.[24]

Medication

Schrag[8]: Levodopa dose.

Lewis[4]: 3 categories: 1) no levodopa; 2) <1000 mg levodopa, with or without concomitant dopamine agonists or dopamine agonists monotherapy; 3) >1000 mg levodopa with or without concomitant dopamine agonists.

Activities of daily living

Graham[7]: UPDRS II.[2]

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3

A comprehensive model of Health-related Quality of Life in Parkinson's disease: challenges for patient management

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Abstract

Objective: Insight in how impairments and disabilities related to Parkinson's disease (PD) influence health related quality of life (HRQoL) is required to review adequacy of current management strategies.

Methods: The Scales for Outcomes in Parkinson's disease (SCOPA) evaluation was used to assess impairments and disabilities. HRQoL was assessed with the EuroQol-5D Visual Analogue Scale. 378 patients with PD who participated in the SCOPA/PROPARK cohort were assessed while on their usual treatment. Multiple linear regression analysis and structural equation modelling were used to construct a model of factors that influence HRQoL.

Results: A model with good fit was constructed that identified various impairments and disabilities as important contributors to HRQoL in PD. Of the disabilities, psychosocial well-being had a larger impact on HRQoL than physical functioning. Of the impairments, depression had the largest contribution to HRQoL, followed by axial motor symptoms, gastrointestinal symptoms, and urinary symptoms. In addition, pain, psychiatric and motor complications, and daytime sleepiness had small but significant influences on HRQoL.

Conclusions: Multiple factors, including disabilities, nonmotor symptoms and axial motor symptoms, affect HRQoL in patients with PD. In patients who are on symptomatic treatment aiming to alleviate mainly motor symptoms, there is a large impact on HRQoL of nonmotor and nondopaminergic symptoms. Research is warranted to develop and evaluate management strategies for the aspects that currently impact on HRQoL as psychosocial well-being, depressive symptoms, axial motor symptoms, gastrointestinal symptoms, and urinary symptoms. These findings call for a multidisciplinary approach in the care of these features.

Introduction

Parkinson's disease (PD) is generally known as a movement disorder in which dopamine replacement therapy may alleviate some of the motor symptoms early in the disease but eventually fails with the progression of the disease. However, there is now an increasing awareness that the clinical spectrum is much broader, encompassing also many nonmotor features including depression, autonomic dysfunction, cognitive dysfunction, night-time sleep problems and daytime sleepiness.[1] Additionally, dopaminergic treatment may induce both motor and psychiatric complications. Together, the debilitating effects of PD and its therapy have a considerable impact on health, physical and psychosocial well-being, and are associated with a decrease in health-related quality of life (HRQoL). HRQoL is defined as those aspects of self-perceived well-being that are related to or affected by the presence of disease or its treatment.[2] Numerous factors impact on HRQoL in PD, including disease severity, disease duration, postural instability and falls, motor complications, depression, anxiety, pain, sleep, cognitive impairment, hallucinations and problems with activities of daily life (ADL).[3-5] However, for some of these factors, like motor complications, studies have yielded inconsistent findings.[6,7] Furthermore, many studies have explored relations between one or two domains and HRQoL without taking into account the broadness of the clinical spectrum of PD or the complex interplay of domains that make up the pathway that links impairments to disability to HRQoL. The Scales for Outcomes in Parkinson's disease (SCOPA) model is a comprehensive evaluation of PD that is based on the disablement process: a pathway linking impairments, disability and global outcomes of health.[8] Using the SCOPA evaluation, we aimed to identify which impairments and disabilities contribute to HRQoL and to construct a model based on these disease-specific determinants in PD.

Methods

Study design

The study is part of the "PROfiling PARKinson's disease" (PROPARK) study, a longitudinal cohort study of patients with PD, who are profiled on phenotype, genotype, disability, and global outcomes of health. Valid and reliable measurement instruments for the different domains of PD were derived from the SCOPA project. (www.scopa-propark.eu) Data obtained from the first annual evaluation of 420 patients who were included in the period from May 2003 to March 2006 was used for analysis.

Participants

All patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD.[9] Age-at-onset and disease duration are important determinants of disease course in PD and are related to various manifestations of the disease.[10,11] To obtain an adequate distribution of these characteristics across the cohort, we constructed four strata, based on age-at-onset (onset of the first symptoms as perceived by the patient (≤/ > 50 years)) and disease duration (≤ / > 10 years). Recruitment stopped if approximately 100 patients per stratum were included. The principal centre (Leiden University Medical Centre (LUMC) recruited 186 patients (44%), other university hospitals recruited 54 patients (13%) and regional hospitals recruited 180 patients (43 %). No other selection criteria were applied. The study was approved by the medical ethical committee of the LUMC and all participants gave informed consent.

Outcome measures

Information was obtained on clinical and sociodemographic variables and included age-at-onset, disease duration, disease severity measured with the Hoehn and Yahr scale (H&Y),[12] medication, falls in the last year, age, marital stage, educational level, and employment status. Levodopa equivalent (LDE) units were calculated according to the formula described by Esselink.[13]

The following domains were assessed:

Impairments: Motor symptoms and motor complications (SPES/SCOPA, sections motor symptoms (MS) and motor complications (MC)),[14] cognitive dysfunction (SCOPA-COG)[15] and Mini Mental State Examination (MMSE),[16] psychiatric complications (SCOPA-PC),[17] depressive symptoms (Beck Depression Inventory (BDI)),[18] night-time sleep problems (NS) and daytime sleepiness (DS) (SCOPA-SLEEP sections NS and DS) ,[19] autonomic dysfunction (SCOPA-AUT),[20] and pain (Visual Analogue Scale (VAS) for pain). Patients were asked to rate their average pain in the last month on a line ranging from 0 (no pain) to 100 (worst imaginable pain).

Disability: Activities of Daily Living (SPES/SCOPA-ADL)[14] and psychosocial wellbeing (SCOPA-PS).[21]

Quality of Life: HRQoL was measured using the VAS from the EuroQoL (EQ-5D), a generic HRQoL instrument.[22] Patients were asked to rate their current health status on a line ranging from 0 (death) to 100 (best imaginable health state).

Except for the SCOPA-COG and the EQ-VAS, higher scores reflect more problems.

Data were collected by means of self-report questionnaires (SCOPA-SLEEP NS and DS, SCOPA-AUT, BDI, SCOPA-PS, EQ-VAS, VAS-PAIN), which patients completed at home two weeks before their assessment. Furthermore, a trained researcher assessed the SPES/SCOPA sections MS, MC, and ADL, SCOPA-COG, and the modified PPRS. A partner, relative, or caregiver was requested to be present during the examination. The majority of the patients were assessed at the LUMC. To avoid bias towards recruiting less severely affected patients, patients who were unable to come to the hospital were assessed at home.

Statistical analysis

If patients had 25% or more missing data on one of the impairment or disability domains, they were excluded from the analysis. If patients had less then 25% missing data on a scale, the missing data were imputed by the mean values of the non-missing items. Means and standard deviations for all impairment and disability domains and HRQoL were calculated. Pearson correlations were calculated between all impairment and disability domains and HRQoL.

Path analysis was used to test the linkages among model variables.[23]

Estimating path coefficients: Using SPSS 14.0, path coefficients were estimated using multiple linear regressions for the following dependent variable in the model: the (1) SPES/SCOPA-ADL and (2) SCOPA-PS as dependent variable and all impairment domains as independent, and (3) the EQ-VAS as dependent variable and all impairment and disability domains as independent variables. Non-significant path coefficients were excluded from the model.

Multiple linear regressions were also performed using subdomain scores instead of the total score for domains that significantly contributed to the model, in order to get more insight in their contribution. The SPES/SCOPA-MS was divided into the subdomains "bradykinesia-rigidity" (items 3a,b + 4a,b), "tremor" (items 1a,b + 2a,b), and "axial symptoms" (items 5,6,7,8,9,10). The SPES/SCOPA-MC was divided into dyskinesias" (items 18 + 19) and "motor fluctuations" (items 20 + 21). The SCOPA-AUT consists of the subdomains "Gastro-intestinal" (GI), "Urinary" (UR), "Thermoregulatory" (TR), "Cardiovascular" (CV), Pupillomotor" (PM), and "Sexual Dysfunction" (SX).

Model fitting: The overall fit of the final model was assessed using the structural equation modelling program EQS 6.1 for Windows.[24] Multiple indices can be calculated that show how well the data fit the model. The chi-square test for goodness-of-fit should be nonsignificant (indicating that the model does not differ from the data) but is sensitive to sample size. Five other goodness-of-fit indices were evaluated. The Bentler-Bonnet normed fit index (NFI), the nonnormed fit index (NNFI), and the comparative fit index (CFI) range between 0 and 1, whereby 0.90 is the minimally acceptable value, with 0.95 being the minimum if the chi-square test is significant. The root means square error of approximation (RMSEA) estimates the lack of fit in a model compared to a perfect model; above 0.1 indicates a poor fit, under 0.08 indicates a reasonable fit, and under 0.05 indicates a good fit.[25] The standardized root mean square residual (SRMR) indicates good fit if the value is less than 0.08.[26]

Results

Patients

Forty-two patients (10%) had more then 25% missing data in one of the scales and were excluded from the analysis. Complete data was obtained from 378 PD patients (66% men). The mean (SD) age was 60.0 (11.2) years and the mean (SD) disease duration was 10.2 (6.4) years (Table 1). Patients who were excluded from the analysis because of missing data were significantly older, had longer disease duration, a higher H&Y stage, and were more often female. Furthermore, these patients had a significant lower HRQoL (worse) and scored higher (worse) on all other domains.

The mean scores of the impairment and disability domains and HRQoL are presented in Table 2.

Correlations and multiple linear regression

The SPES/SCOPA-ADL had high correlations with the SPES/SCOPA-MS (r=0.67) and the SCOPA-AUT (r=0.54) (Table 3). The SCOPA-PS had the highest correlations with the BDI (r=0.69) and the SCOPA-

AUT (r=0.57), whereas the EQ-VAS for HRQoL had the highest correlations with the SCOPA-PS (r=-0.59) and the BDI (r=-0.56).

Table 1. Patient characteristics

N	378
men/women (%man)	250/128 (66.1%)
Age, yrs (SD)	60.0 (11.2)
Years of education (SD)	12.1 (4.1)
Patient with partner (%)	310 (82.0 %)
Employment status: employed	103 (27.2%)
not employed	275 (72.8%)
Disease duration, yrs (SD)	10.2 (6.4)
Age onset, yrs (SD)	49.8 (11.8)
H&Y stages 1 / 2/ 3/ 4/ 5 / missing	15 / 190 /105 / 59 / 4 / 3
MMSE (SD) (N< 24, %)	27.0 (2.5) (35, 9.3 %)
Falls in last year (SD)	1.3 (61.5)
Patients on levodopa, N (%)	246 (65%)
Patients on dopamine agonist, N (%)	266 (70%)
Levodopa equivalent units (mg)	591.9 (460.9)
Family history of PD (%)	98 (25.9%)

H&Y, Hoehn and Yahr ; MMSE, Mini Mental State Examination

Table 2. Outcome measures

Domain	Outcome measure (scale range)	Mean (SD)
Motor symptoms	SPES/SCOPA-MS (0-42)	13.1 (4.6)
Motor complications	SPES/SCOPA-MC (0-12)	1.6 (2.4)
Cognitive dysfunction	SCOPA-COG (0-43)	26.2 (5.9)
Depressive symptoms	BDI (0-63)	9.8 (6.3)
Autonomic dysfunction	SCOPA-AUT (0-69)	17.5 (8.4)
Psychiatric Complications	Modified PPRS (0-18)	2.0 (1.9)
Night-time sleep problems	SCOPA-SLEEP NS (0-15)	4.4 (3.7)
Daytime sleepiness	SCOPA-SLEEP DS (0-18)	4.7 (3.7)
Pain	VAS-PAIN (0-100)	28.8 (25.2)
ADL	SPES/SCOPA-ADL (0-21)	8.6 (3.3)
Psychosocial function	SCOPA-PS (0-33)	8.4 (4.9)
Health related Quality of Life	EQ-VAS (0-100)	67.8 (14.2)

SPES/SCOPA-MC: SPES/SCOPA motor complications; BDI: Beck Depression Inventory; Modified PPRS: Modified Parkinson Psychosis Rating Scale; SCOPA-SLEEP NS: SCOPA-SLEEP Night-time sleep; SCOPA-SLEEP DS: SCOPA-SLEEP Daytime sleepiness; SPES/SCOPA-ADL: SPES/SCOPA Activities of Daily Living; SCOPA-PS: SCOPA-Psychosocial functioning; EQ-VAS: EuroQol-Visual Analogue Scale

Table 3. Pearson correlation matrix of impairment and disability domains and health related quality of life

	EQ-VAS	SPES/SCOPA-ADL	SCOPA-PS
SPES/SCOPA-MS	-0.33[1]	0.67[1]	0.42[1]
SPES/SCOPA-MC	-0.28[1]	0.37[1]	0.26[1]
SCOPA-COG	0.24[1]	-0.27[1]	-0.20[1]
BDI	-0.56[1]	0.31[1]	0.69[1]
SCOPA-AUT	-0.40[1]	0.54[1]	0.57[1]
SCOPA-PC	-0.31[1]	0.38[1]	0.42[1]
SCOPA-SLEEP NS	-0.33[1]	0.16[2]	0.38[1]
SCOPA-SLEEP DS	-0.19[1]	0.32[1]	0.28[1]
VAS-PAIN	-0.28[1]	0.18[1]	0.18[1]
SPES/SCOPA-ADL	-0.42[1]	-	0.51[1]
SCOPA-PS	-0.59[1]	0.51[1]	-

SPES/SCOPA-MC: SPES/SCOPA motor complications; BDI: Beck Depression Inventory; Modified PPRS: Modified Parkinson Psychosis Rating Scale; SCOPA-SLEEP NS: SCOPA-SLEEP Night-time sleep; SCOPA-SLEEP DS: SCOPA-SLEEP Daytime sleepiness; SPES/SCOPA-ADL: SPES/SCOPA Activities of Daily Living; SCOPA-PS: SCOPA-Psychosocial functioning; EQ-VAS: EuroQol-Visual Analogue Scale

[1]correlation is significant at the 0.001 level

[2]correlation is significant at the 0.01 level

[3]correlation is significant at the 0.05 level

The impairment domains motor symptoms, motor complications, autonomic dysfunctions, and daytime sleepiness explained 57% of the variance in the ADL domain. The impairment domains depressive symptoms, psychiatric complications, motor symptoms, and autonomic dysfunction explained 58% of the variance in the PS domain. The disability domains ADL and PS and the impairment domains pain and depressive symptoms together explained 43% of the variance in the HRQoL. Two impairment domains that did not significantly contribute to this model were cognitive dysfunction and night-time sleep problems.

The group of patients that was excluded because of missing values had significant lower SCOPA-COG scores (26.2 (5.9) versus 20.8 (7.2) p=0.000) and higher SCOPA-SLEEP NS scores (4.4 (3.7) versus 6.0 (4.0) p=0.010). However, the correlation between SCOPA-COG and EQ-VAS were the same in both groups, r=0.24, whereas the correlation between the SCOPA-SLEEP NS and EQ-VAS was lower for the group that was excluded (r=-0.33 versus r =-0.08).

Model evaluation

The overall fit of the final model that encompassed only the significant paths was assessed using EQS. The chi-square test was significant, which was expected given the large sample size. The other fit indices, however, fulfilled the cut-off criteria of a good model fit (Table 4). Except for depressive symptoms and pain, which have a direct influence on HRQoL, most impairment domains have an indirect relation through the disability level (Figure 1).

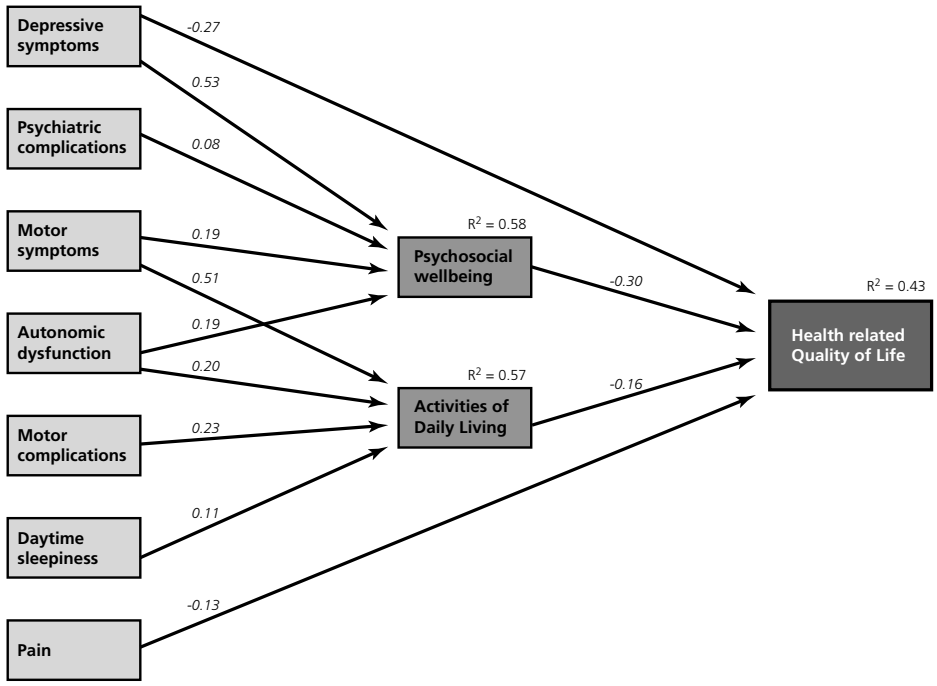
Table 4. Summary of final model fit statistics

2 (df)	27.808 (12) P= 0.006
NFI	0.979
NNFI	0.955
CFI	0.988
SRMR	0.021
RMSEA (90% CI)	0.059 (0.030-0.088)

2, model chi-square value; df, model degrees of freedom; NFI, Bentler-Bonett normed fit index; NNFI, Bentler-Bonett non-normed fit index; CFI, Bentler's comparative fit index; SRMR, standardized root mean square residual; RMSEA, root mean square error of approximation; CI, confidence interval around RMSEA.

Depressive symptoms had the largest contribution to HRQoL, which was established through a direct relation with HRQoL and an indirect relation via the PS domain. Motor symptoms and autonomic dysfunction had indirect relations with HRQoL through both the PS and ADL domains. The indirect relation from psychiatric complications occurred through the PS domain, whereas the indirect relation of daytime sleepiness and motor complications occurred through the ADL domain.

Figure 1. Model of health-related quality of life in PD



All path coefficients are statistically significant at P =0.05. Covariances between impairment domains are not shown for reason of readability.

Model evaluation with subdomains

"Axial symptoms" was the only motor subdomain that contributed significantly to the PS domain and explained 31% of the variance. All three motor subdomains contributed significantly to the ADL domain explaining 60% of the variance, in which axial symptoms had the largest contribution and tremor the smallest contribution. Both motor fluctuations and dyskinesias contributed significantly to the ADL domain, explaining 14% of the variance. Only the subdomains GI, UR and PM of autonomic dysfunction contributed significantly to the ADL domain, and explained 32% of the variance. The subdomains GI, TR, UR, and CV contributed significantly to the PS domain, explaining 33% of the variance in the PS domain. The GI and UR subdomains were the most important contributors to both the PS and ADL domain.

Model evaluation in subgroups

To evaluate the influence of disease duration in the model, the path analysis was performed in two subgroups based on disease duration (disease duration shorter (N=205) or longer (N=173) than 10 years) (Table 5).

Table 5. Significant domains in path analysis in PD subgroups.

	Disease duration	
	< 10 year	**> 10 year**
N	205	173
PS	Depressive symptoms	Depressive symptoms
	Autonomic dysfunction	Autonomic dysfunction
	Motor symptoms	Motor symptoms
	R^2 = 0.64	**R^2 = 0.51**
ADL	Motor symptoms	Motor symptoms
	Autonomic dysfunction	Autonomic dysfunction
	Motor complications	Motor complications
	R^2 = 0.44	**R^2 = 0.58**
HRQoL	Psychosocial functioning	Psychosocial functioning
	Depressive symptoms	Depressive symptoms
	Pain	
	ADL	
	R^2 = 0.44	**R^2 = 0.40**

PS: Psychosocial functioning

ADL: Activities of Daily Living

HRQoL: Health related quality of life

The models that emerged for each group were very similar, except for the pain and ADL, which lost their significant direct relation to HRQoL in patients with a disease duration longer than 10 years. Compared to the model that was based on all patients, the models for both disease duration groups lost the contribution of psychiatric complications to PS and DS to ADL.

Discussion

HRQoL represents the overall experienced impact of the disease and its consequences on a person's wellbeing. Some diseases are expressed in one impairment domain, and their impact on disability and HRQoL is generally straightforward. PD, however, is characterized by a broad spectrum of primary disease-related motor and nonmotor manifestations. On top of these primary PD-related impairments, medical interventions may induce motor or psychiatric complications or DS. The impact of PD on patients' HRQoL is thus determined by the complex interaction of the motor and nonmotor symptoms of the disease, the consequences of therapy and the functional consequences of the disease. This study shows that HRQoL in PD can be described by a good fitting model that disentangles the contributions of components in the pathway that links impairments and disabilities to HRQoL. Interestingly, on the disability level, the influence of the PS domain on HRQoL was larger than that of the ADL domain, underscoring the importance of psychosocial functioning in HRQoL of patients with PD.

Most impairments exerted an indirect influence on HRQoL through one or both of the disability domains. Pain was the only impairment domain with only a direct influence on HRQoL and its impact on HRQoL has been reported earlier.[5] In line with other studies,[27-29] our study highlights that depressive symptoms had the largest contribution to HRQoL, which was portrayed in our model by a direct influence on HrQoL as well as an indirect influence through the PS domain. As depressive symptoms have now been highlighted repeatedly as the main contributor to HRQoL in PD, it remains surprising that in both patient management and trials, depression is insufficiently prioritized. Both daytime sleepiness and motor complications were only related to ADL whereas autonomic dysfunction contributed to both physical (ADL) and psychosocial (PS) functioning. Within the autonomic domain, gastrointestinal and urinary symptoms had the largest influence on HRQoL. Within the motor complications, both motor fluctuations and dyskinesias were significant contributors to HRQoL.

Motor symptoms had only indirect relations with HRQoL through both disability domains, and its total contribution to HRQoL was less than that of depression. Of motor symptoms, axial symptoms had the largest influence on both psychosocial and physical functioning. Motor symptoms and ADL, which till recently dominated the content of assessment scales in PD, were not the main contributors to HRQoL in patients with PD. However, it is important to keep in mind that dopaminergic replacement therapy aiming to alleviate part of the motor symptoms is the mainstay treatment of PD. It can be assumed that the contributions to the total model on HRQoL in PD would have been different, if this treatment had not been available. The impact of dopaminergic therapy on the model is further underscored by our finding that "axial symptoms", which are mainly of nondopaminergic origin, had the largest influence on both the PS and ADL domain.

Neither cognition nor night-time sleep, contributed to HRQoL. Consistent with former studies,[30,31] the univariate correlations between HRQoL and night-time sleep problems (r=-0.33), and between HRQoL and cognitive dysfunction (r=0.24) were significant, but their influence disappeared in the final model. It is likely that the strong association between night-time sleep problems and depressive symptoms (r= 0.49) resulted in the exclusion of night-time sleep problems from the model.[32] The finding that cognition does not play a role in HRQoL is surprising, but robust, as two other studies have revealed similar results in multiple linear regression analysis.[33,34] Contrary to night-time sleep problems, cognitive

dysfunction was in this study not strongly correlated to other domains of PD (all $r < 0.40$) and therefore the question remains how this finding can be explained. One explanation could be that cognitive decline played little role in this cohort, or that patients with cognitive impairment had missing values and where therefore not included in these analysis. Although the patients that were excluded had indeed more cognitive problems, they had also a worse HRQoL and the correlation between cognition and HRQoL was the same in both groups. Another explanation could be that the cognitive assessment describes the current cognitive status and this does not automatically reflect cognitive decline since the premorbid variance of normal cognition is large. For most other domains, like motor symptoms or psychiatric complications, a score of zero is expected before the onset of PD and a higher score therefore implies more severe problems. A longitudinal study that assesses the influence of change in cognition in relation to change in HRQoL is necessary to get more insight in this issue.
The HRQoL model that was constructed appears robust, as it largely remained the same when evaluated in subgroups with a short and long disease duration. Depressive symptoms, psychosocial well-being, and autonomic dysfunction apparently remain important contributors to HRQoL along the course of the disease. The most prominent difference between the models of the two subgroups is the lack of a significant contribution of ADL to HRQoL in patients with long disease duration.

A limitation of the study was the selective exclusion of patients with too many missing values. In addition, the stratification of the cohort based on age-at-onset and disease duration and the high recruitment of patients from academic hospitals (57%) may make the group less representative of the PD community. However, the remaining group of patients was still large and reflected the full spectrum of PD, with mean disease duration of 10 years and disease stages ranging from H&Y stage 1 to 5. The model incorporates only disease-specific aspects that explain 43 % of the variance in HRQoL. This implies that other aspects not incorporated in the model play a role as well. Educational level, mastery, or psychological adjustment have indeed been described to impact on HRQoL in PD.[33,35,36] Incorporating more variables in the model would on the one hand increase the amount of explained variance but conversely decrease the comprehensibility of the model. The main objective of this study was to evaluate the contribution of disease-specific factors to HRQoL, so as to highlight issues that require further attention in the management of patients with PD. Indeed, multiple factors affect HRQoL in patients with PD on symptomatic treatment. Research is warranted to develop and evaluate management strategies for the aspects that currently impact on HRQoL as psychosocial well-being, depressive symptoms, axial motor symptoms, gastrointestinal symptoms, and urinary symptoms. These findings call for a multidisciplinary approach in the care of these features.

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4

Motor patterns in Parkinson's disease: a data-driven approach

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Abstract

Objective: To identify patterns of motor disturbances in Parkinson's disease (PD) and evaluate their relation with other PD domains.

Methods: A cohort of 399 PD patients was randomly divided into two samples. Factors within the motor section of the SPES/SCOPA were identified by exploratory factor analysis on data from the first sample and next tested by confirmatory factor analysis in the second sample. Relations with other PD domains were evaluated by regression analyses.

Results: A four factor model was found to be valid. This included a tremor, a bradykinetic-rigid, and two axial factors. One axial factor ('rise', 'gait', 'postural instability') was associated with age and cognition, while the other axial factor ('freezing', 'speech', 'swallowing') was related to dopaminergic medication and complications of therapy. Both other factors showed no relevant associations with demographic and clinical characteristics.

Conclusions: The identification of motor factors and their relation with other domains of the disease may help to elucidate the mechanisms responsible for these associations and provide an objective base for further research on subtypes in PD.

Introduction

In Parkinson's disease (PD) is considerable heterogeneity in the expression of clinical manifestations and progression of the disease, suggesting the existence of subtypes. Several motor subtypes of the disease have been suggested, mostly based on clinical observations: a tremor dominant subtype, associated with mild disease progression[1-3]; an akinetic-rigid subtype, associated with more severe cognitive impairment and depressive symptoms than patients with tremor[4,5]; a subtype in which postural instability and gait dysfunction (PIGD) are most prominent, associated with cognitive impairment and a more progressive disease course.[1,3,6,7]

When studying subtypes through a more data-driven approach, studies have analyzed the motor domain in various ways such as a total score,[8] as a ratio of tremor and non-tremor items,[9] and as subscores of tremor, hypokinesia/rigidity, PIGD.[10] An objective determination of groups of variables that group together as manifestations of an underlying construct may provide a stronger basis for classification into subtypes and enhance our understanding of the underlying pathophysiology. Exploratory factor analysis (EFA) is a method that can be used in this respect; it identifies groups of closely related variables ('factors') among a larger set of variables.[11] Several studies applied EFA on the items of the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS)[12-15] and the Short Parkinson's Evaluation Scale (SPES).[12] These studies yielded inconsistent results, likely because of differences in scale content and size and composition of samples. Confirmatory factor analysis (CFA) is a method to test hypotheses on constructs that underlie a set of variables and is more powerful than EFA. Only one study performed CFA on the motor items of the UPDRS, which resulted in five main factors (rigidity; tremor; bradykinesia; axial impairment; speech/hypomimia), as well as two separate factors reflecting laterality.[16]

As the first step in a data-driven determination of subtypes, this study aimed to identify patterns of motor impairments in PD by both exploratory and confirmatory factor analysis. Secondly, the relation between motor factors and nonmotor impairments of PD were evaluated.

Methods

The study is part of the "PROfiling PARKinson's disease" (PROPARK) study, a longitudinal cohort study of patients with PD, who are profiled on phenotype, genotype, disability, and global outcomes of health using valid and reliable assessment instruments for PD (www.scopa-propark.eu). Findings obtained from the first annual evaluation of 417 patients, assessed between May 2003 and March 2006, were used for analysis. The study was approved by the medical ethical committee of the Leiden University Medical Centre and all patients gave informed consent.

All patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD, with the exception that positive family history was not regarded as an exclusion criterion.[17] Patients who underwent stereotactic surgery were excluded from analysis. The recruitment procedure has been described elsewhere.[18]

To assess the motor impairments of patients, the motor section of the SPES/SCOPA rating scale was used.[19] This scale has a good balance between items reflecting motor features of early and late stage disease, and has good metric properties.[19] The SPES/SCOPA-motor consists of 10 items with response options ranging from 0 to 3, where higher scores reflect poorer motor function. For the current study, data obtained for cognition (SCOPA-COG),[20] autonomic symptoms (SCOPA-AUT),[21] depressive symptoms (Beck Depression Inventory (BDI)),[22] psychotic symptoms (SCOPA-Psychiatric Complications (SCOPA-PC), items 1-5),[23] nighttime sleep problems and excessive daytime sleepiness (SCOPA-SLEEP),[24] and motor complications (SPES/SCOPA-Motor Complications)[19] were used for post-hoc analyses. In all scales higher scores also reflect more severe symptoms, except for the SCOPA-COG. For reasons of comparability, these scores were inversed. Instruments were either self-completed (SCOPA-AUT, BDI, SCOPA-SLEEP) or administered by trained research associates (SCOPA-COG, SCOPA-PC, SPES/SCOPA motor and motor complications). All patients who used antiparkinsonian medication were assessed while they benefited from their medication. When exhaustion or off-periods were detected, patients were allowed to take a break or medication. For each patient, a levodopa dose equivalent (LDE) was calculated.[25]

Statistical analyses

In the SPES/SCOPA, the items rest tremor, postural tremor, bradykinesia and rigidity are separately evaluated for the left and right arm. For the present analyses, scores of both sides both sides were added up, resulting in one score for each symptom.

Exploratory and confirmatory analyses

The total group was randomly divided into two samples, which was expected to yield two approximately equally large groups. Next, an EFA with oblique rotation was performed on the first sample, using all 10 items of the SPES/SCOPA-motor. The oblique rotation method was used, because factors emerging from the motor domain were expected to be correlated.[26] The number of factors was determined by inspection of the scree plot and Kaiser's criterion (i.e. eigenvalue>1). Data of the second sample were used for cross-validation. In structural equation modeling (SEM), relations between measured and proposed latent variables (factors) can be evaluated. CFA is a special case of SEM and tests how well data fit an a priori hypothesized model of variables that group together in factors.[27] Based on the result of the EFA, a model was constructed. The chi-square test for goodness-of-fit was calculated. This test should be nonsignificant (P>0.05, indicating that the model does not significantly differ from the data), although it should be noted that the test is sensitive to sample size and to small to moderate discrepancies

of the data to normality.[26,28] Therefore measures estimating the lack of fit (the root means square error of approximation (RMSEA) and the standardized root mean square residual (SRMR)) were also calculated, supplemented with a measure to test the model's goodness of fit (comparative fit index (CFI)).[29] RMSEA values >0.1 indicate a poor fit, <0.08 reasonable fit, and <0.05 good fit. The SRMR reflects a good fit if the value is <0.08. A CFI close to 0.95 is indicative of a good fit.[28,29]

Pearson correlations (r; two-tailed) were calculated to assess the correlation between each of the resulting motor factors and the other impairment domains of PD, and demographic and disease related variables. Correlation coefficients were defined as very weak (r=0.00-0.19), weak (r=0.20-0.39), moderate (r=0.40-0.59), strong (r=0.60-0.79), or very strong (r=0.80-1.00).[30] Multiple forward linear regression analysis with separate blocks was used to explore the contribution of the impairment domains to the motor factors, while taking differences in demographic and disease related variables into account (block 1: age, disease duration, LDE; block 2: impairment domains).

Statistics were performed in SPSS 16.0, except for CFA which was carried out with EQS 6.1 for Windows.[31]

Results

After excluding patients who underwent stereotactical surgery (N=18), data of 399 patients were available for analysis, of whom 344 had no missing values on any item of the SPES/SCOPA-motor. The mean (SD) age was 60.8 (11.6) years, the mean (SD) disease duration was 10.1 (6.2) years and the mean (SD) LDE was 570 (452) mg. EFA was performed on 171 patients, while CFA was performed on 173 patients. The samples did not differ with respect to age, disease duration, or LDE (age: mean difference -1.2, 95% CI -3.7 to 1.2; disease duration: mean difference -1.6, 95% CI -4.1 to 0.95; LDE: mean difference 51, 95% CI -45 to 147).

Table 1. Results of the exploratory factor analysis of the SPES/SCOPA motor section (oblique rotation)

Motor items SPES/SCOPA	Factor 1	Factor 2	Factor 3	Factor 4
Rise from chair	0.844			
Postural instability	0.851			
Gait	0.588			
Speech		0.744		
Swallowing		0.714		
Freezing during on		0.666		
Postural Tremor			0.899	
Rest Tremor			0.892	
Rigidity				0.863
Bradykinesia				0.706
% of variance explained by factor	29.1	16.7	11.7	10.5

Factor loadings <0.4 have been omitted from the table.

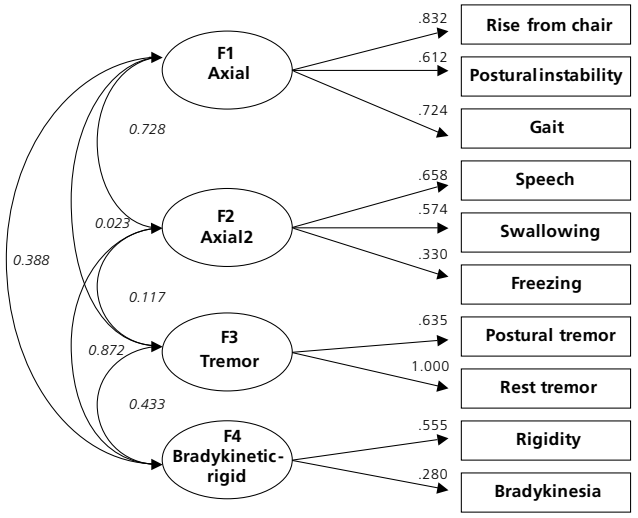
Exploratory factor analysis

The screeplot indicated a four-factor solution. Four factors had an eigenvalue >1, explaining 68.0% of the variance (factor 1: 29.1%, factor 2: 16.7%, factor 3: 11.7%, factor 4: 10.5%; see Table 1). Factor 1 consisted of items that relate to axial motor function, namely 'rise from chair', 'gait', and 'postural instability'. A second 'axial' factor (factor 2) consisted of the items 'freezing during on', 'speech' and 'swallowing'. 'Rest tremor' and 'postural tremor' grouped in factor 3, whereas 'rigidity' and 'bradykinesia' formed factor 4.

Confirmatory factor analysis

Based on the four factors a model was constructed (Figure 1). The chi-square test was significant (χ^2 = 52.33, degrees of freedom = 29, P = 0.01). Other fit indices reflected a good fit: The CFI was 0.94, the RMSEA 0.07 (90% confidence interval 0.04 – 0.10) and the SRMR 0.06.

Figure 1. Model of factor structure of the SPES/SCOPA motor section



Standardized solution of the model as tested in the confirmatory analysis. The circles represent the latent variables or factors; the arrows on the right point at the items (in the rectangles) of which the factors are composed; the numbers above the arrows represent the path coefficients (equivalent of factor loading in exploratory factor analysis); the arrows on the left indicate that intercorrelations between the factors were allowed, and the numbers indicate the magnitude of the intercorrelations.

Association between motor factors and demographic, clinical and disease related characteristics

Both axial factors showed significant weak to moderate correlations with most of the impairment domains. Both factors moderately correlated with autonomic symptoms. The first axial factor further showed moderate correlations with age, whereas the second axial factor moderately correlated with psychotic symptoms. The bradykinesia-rigidity factor only had weak or non-significant correlations, whereas the tremor factor hardly showed any significant correlation. In the multiple regression analysis, a total of 34% of the variance of the first axial factor was accounted for, with 21% being

explained by higher age and longer disease duration (block 1), and more autonomic symptoms, more depressive symptoms, and more cognitive impairment together accounting for the other 13% (block 2). A total of 34% of the variance of the second axial factor was explained, with longer disease duration contributing 15% in the first block, and higher LDE, more severe autonomic symptoms, more psychotic symptoms, more severe dyskinesias, more depressive symptoms, and less severe nighttime sleep problems explaining the other 19% (Table 2). Only 3% of the variance of the tremor factor could be explained by longer disease duration and less severe sleep problems. More cognitive impairment, more autonomic symptoms, and less severe dyskinesias together accounted for the 9% explained variance of the bradykinesia-rigidity factor.

Table 2. Regression analyses of the motor factors

Motor factor	Independent variables *	Beta ‡	R^2
Axial 1 [a,b]	Age	0.21	0.14
	Disease duration	0.17	0.07
	Autonomic symptoms	0.24	0.09
	Depressive symptoms	0.17	0.03
	Cognitive impairment	0.12	0.01
	Total	-	0.34
Axial 2 [a,c]	Disease duration	0.15	0.15
	LDE	0.14	0.04
	Autonomic symptoms	0.18	0.09
	Psychotic symptoms	0.14	0.02
	Dyskinesias	0.15	0.02
	Depressive symptoms	0.17	0.01
	Sleep problems	-0.11	0.01
	Total	-	0.34
Tremor [a]	Duration	0.13	0.01
	Sleep problems	-0.12	0.02
	Total	-	0.03
Bradykinetic-rigid [a]	Cognitive impairment	0.23	0.06
	Autonomic symptoms	0.16	0.02
	Dyskinesias	-0.14	0.01
	Total	-	0.09

** Variables are ordered in the table as they appeared in the model.*

‡ Standardized beta.

[a] Multiple forward linear regression analysis with variables entered in two blocks: block 1: age, disease duration, levodopa dose equivalent; block 2: cognition, autonomic symptoms, depressive symptoms, psychotic symptoms, sleep problems, daytime sleepiness, motor fluctuations, dyskinesias.

[b] axial 1: factor consisting of the items 'rise', 'gait', 'postural instability'

[c] axial 2: factor consisting of the items 'freezing', 'speech', 'swallowing'

LDE; levodopa dose equivalent.

Discussion

Exploring and characterizing interrelations of assumed different clinical features of disease may contribute to the understanding of shared underlying mechanisms. Four motor factors were identified by EFA and confirmed by CFA in an independent sample. All factors showed different correlation patterns with other characteristics important in PD, thus underscoring their differential nature. Interestingly, two factors related to axial motor symptoms and collectively explained 46% of the variance of the motor items. The factor that explained most of the variance was related to the so-called PIGD component of PD and included 'rise from chair', 'gait', and 'postural instability'. Previous studies that applied different rating scales have identified a similar PIGD factor, in spite of the application of different rating scales. The consistency of these findings thus underscores the importance of this motor component of PD.[14-16]

In contrast to the other studies, we also found a second axial factor, consisting of 'freezing', 'speech', and 'swallowing'. This contrast may simply be explained by the fact that in the UPDRS these items are part of the ADL section, which was not included in the factor analyses of previous studies. The relation between speech and swallowing most likely reflect a shared impairment of oral-pharyngeal motor control. The association with freezing is less obvious. However, in one study speech in addition to gait, consistently was associated with freezing and with the risk of developing freezing.[32] Additionally, freezing frequency correlated with speech and writing in patients who were "on", while improvement of freezing frequency by levodopa strongly correlated with improvement of tremor and speech.[33] In both studies swallowing was not analyzed.

Both axial factors correlated with each other and showed similar correlations with disease duration, autonomic symptoms, and depression. Although our findings suggest some commonality between both axial factors, regression analyses also showed clear differences. The axial factor with PIGD items was related to higher age and more cognitive impairment, which is in line with previous studies.[6,7,34] The second axial factor showed relations with dopaminergic medication and complications of therapy (psychotic symptoms and dyskinesias). Because dopaminergic treatment may provoke freezing,[35,36] the association between this axial factor and complications of therapy is not unexpected. Consistent with findings of other studies, a tremor factor was identified.[13,15,16] This factor clearly behaved as the most independent component of the motor spectrum, as illustrated by the lower correlations with other factors and the lack of relations with most nonmotor impairments.

Finally we identified a bradykinesia-rigidity factor, which was described in one earlier study.[15] This factor was marginally explained by other disease related variables. However, relations with other domains may be masked by a generally stronger effect of dopaminergic medication on bradykinesia and rigidity in comparison with other motor features.[37]

Of previous studies that performed factor analysis on motor symptoms in PD, some analyzed tremor, bradykinesia and rigidity separately for each extremity,[14,16] while others did not.[13,15] Stebbins et al. used exploratory factor analysis and found side sensitivity for bradykinesia, but not for tremor and rigidity. Stochl et al. performed a confirmatory factor analysis and found two factors reflecting laterality (right and left) in addition to five factors that reflected symptoms. Since PD may present with an asymmetrical appearance of tremor, bradykinesia, or rigidity, which persists over the disease course,[38] the finding of a laterality factor is not unexpected. To date it is unclear if laterality is informative with respect to distinct motor subtypes or their underlying biological constructs. Anomalies of asymmetry of motor impairments were found in 11% of the patients with PD, including a rest tremor most pronounced in one upper limb and the contralateral lower limb, rest and postural tremor most

pronounced in opposite extremities, and unilateral dominance of rigidity, bradykinesia and rest tremor, followed by development of predominance of all three features on the contralateral side.[39] Asymmetric manifestations of the disease have been suggested to be stochastically determined and not by genetic, environmental, structural or neurochemical causes.[38] Aim of our study was therefore to detect patterns of interrelations between the various motor symptoms in PD irrespective of side differences.

Items that involve motor features that are responsive to levodopa will likely have been scored as less severe compared to the situation in which they did not benefit from their medication (i.e., were 'off') and this may have altered the strength of the correlations between items. However, the overall effect on the factor structure is probably limited, because Stebbins et al., who performed factor analyses both in the 'on' and 'off' phase, showed that both situations resulted in an identical factor structure.[14,40]

In conclusion, we identified four distinct components of the motor spectrum of PD through a data-driven approach. Based on their different relations with demographic characteristics and clinical domains of the disease, these components may reflect the different nature of causes, including disease process, aging and dopaminergic treatment. Additionally, these motor components may facilitate future research aiming to identify clinical subtypes of PD.

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Patterns of motor and nonmotor features in Parkinson's disease

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Abstract

Objective: To evaluate the presence and nature of patterns of coherency among the motor and nonmotor domains in Parkinson's disease (PD) and to examine which clinical parameters are related to the potential patterns.

Methods: A cohort of 397 PD patients was randomly divided into two samples. Exploratory factor analysis (EFA) was performed on the motor and nonmotor symptoms in PD in the first sample. Findings of the EFA were used to construct a model which was tested in the second sample by confirmatory factor analysis. Multiple regression analyses on the resulting factors were performed to evaluate the influence of clinical parameters upon these factors.

Results: Four factors were identified. The first and strongest factor (cognitive impairment, autonomic dysfunction, psychotic symptoms, depression, daytime sleepiness, and axial symptoms) reflected advancing disease. Another factor largely reflected motor complications of therapy and was related to dopaminergic medication. The other two factors reflected sleep/depression and tremor/bradykinesia/rigidity, and were only marginally related to disease severity or medication.

Conclusions: The motor and nonmotor features in PD can be characterized by four distinct patterns of coherency, which provide insight in the contributions of the primary disease process and anti-parkinsonian medication to the broad clinical spectrum of PD. One factor, consisting of predominantly nonmotor symptoms together with axial features, clearly reflected disease severity and may provide a new basis for monitoring disease progression in PD.

Introduction

Parkinson's disease (PD) encompasses not only a variety of well-known motor features, but also a broad spectrum of nonmotor symptoms, including cognitive impairment, psychotic symptoms, depression, sleep disorders, and autonomic dysfunction.[1] However, when considering the full spectrum of the disease, there is still limited information on the coherency of the various motor and nonmotor symptoms. This may be partly due to the fact that past research mainly focused on the motor signs of PD as well as to the limited availability of PD specific and clinimetric sound measurement instruments to assess the nonmotor impairments.[2] From more recent studies that characterized specific domain interrelations, it is apparent that differential relations exist between the various motor and nonmotor domains.[1,3-5] However, in these studies not all impairment domains were studied simultaneously, which is required to unravel domain coherency. Knowledge on the coherency of motor and nonmotor domains is important because it may suggest underlying constructs that provide new insight in the contributions of the primary disease process and anti-parkinsonian medication to the broad clinical symptom profile of PD.

In the PROPARK study valid and reliable instruments for each of the relevant impairment domains have been applied simultaneously in a large cohort of patients with PD (www.scopa-propark.eu). As this approach allows a more comprehensive view of domain interrelations, the aim of this study is to evaluate the presence and nature of patterns of coherency among the motor and nonmotor domains in PD and to examine which clinical parameters are related to the potential patterns.

Method

Study design

The study is part of the "PROfiling PARKinson's disease" (PROPARK) study, a longitudinal cohort study of patients with PD, who are profiled on phenotype, genotype, disability and global outcomes of health using valid and reliable assessment instruments for PD. Findings obtained from the first annual evaluation of 415 patients who were assessed between May 2003 and March 2006 were used for the present analysis.

Study participants

All patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD.[6] Patients were recruited from outpatient neurology clinics of university and regional hospitals in the western part of The Netherlands. The majority of the patients were assessed at the Leiden University Medical Centre (LUMC); patients who were unable to come to the hospital were assessed at home. Age-at-onset and disease duration are important determinants of disease course in PD and are related to various manifestations of the disease.[7,8] To obtain an adequate distribution of these characteristics across the cohort, we aimed to construct four strata of 100 patients each, based on age-at-onset (onset of the first symptoms as perceived by the patient; $\leq$ / > 50 years) and disease duration ($\leq$ / > 10 years). The study was approved by the medical ethical committee of the LUMC and all participants gave informed consent.

Outcome measures

Information on clinical and sociodemographic variables was obtained and included age, age-at-onset, disease duration, disease severity (measured with the Hoehn and Yahr (H&Y) scale),[9] and medication. Levodopa equivalent units were calculated for levodopa and dopamine agonists.[10]

The following domains were assessed: motor signs and motor complications (SPES/SCOPA, sections motor evaluation (ME) and motor complications (MC)),[11] cognitive impairment (SCOPA-COG),[12] psychotic symptoms (SCOPA-PC, items 1-5),[13] autonomic dysfunction (SCOPA-AUT, items 4-6, 8-16),[14] depressive symptoms (Beck Depression Inventory (BDI))[15], nighttime sleep problems (NS) and daytime sleepiness (DS) (SCOPA-SLEEP sections NS and DS).[16] Cognitive impairment, autonomic dysfunctioning, and motor signs were evaluated as either total or subscores. Subdomains of the SCOPA-COG include memory, attention, executive functioning, and visuospatial functioning. From the SCOPA-AUT, subscores were calculated for constipation (items 4-6), urinary dysfunction (items 8-13), and cardiovascular dysfunction (items 14-16). We excluded domains from the SCOPA-AUT that were less relevant (pupillomotor), were composed of opposite items (thermoregulatory) or yielded too many missing values (sexual dysfunction, because patients indicated these items were "not applicable"). Motor signs were evaluated by subdomains, resulting from a previously performed factor analysis on the SPES/SCOPA-motor,[17] and included tremor (rest and postural tremor), bradykinesia and rigidity, axial symptoms (rise, gait, postural instability), and a second axial factor (freezing, swallowing, speech).

Instruments were either self-completed (SCOPA-AUT, BDI, SCOPA-SLEEP) or administered by trained research associates (SCOPA-COG, SCOPA-PC, SPES/SCOPA). Domains and subdomain scores of the SCOPA-COG were inversed to arrange that all scores were in the same direction, with higher scores reflecting more severe impairment. For reasons of comparability, all patients who used anti-parkinsonian medication were assessed while they benefited from their medication. When exhaustion or off-periods were detected, patients were allowed to take a break or medication.

Statistical analysis

The total group was randomly divided into two subgroups. In the first sample, the impairments were subjected to an exploratory factor analysis (EFA) with oblique rotation. Since factors emerging from the spectrum of PD domains are expected to be correlated, an oblique rotation, which allows for correlation of factors, was applied. [18] The results of the EFA in the first sample were next used to construct a model that was tested for model fit in the second sample, using confirmatory factor analysis (CFA). To evaluate how well the data fitted the model measures estimating the lack of fit (the root means square error of approximation (RMSEA) and the standardized root mean square residual (SRMR)) were calculated, supplemented with a measure to estimate the model's goodness of fit (comparative fit index (CFI)).[19] RMSEA values >0.1 indicate poor fit, whereas values <0.08 and <0.05 indicate reasonable and good fit, respectively. The SRMR reflects a good fit if the value is <0.08. A CFI close to 0.95 is indicative of a good fit.[19,20] Factor loadings >0.32 were considered poor, >0.45 fair, >0.55 good, >0.63 very good, and >0.71 excellent, which correspond with squared variances of 0.1, 0.2, 0.3, 0.4, and 0.5, respectively.[21]

Multiple forward linear regression analysis with two blocks was used to explore the relation between the different factors and the disease process and medical therapy, while removing all variation due to demographic characteristics by entering age and sex separately in block 1 (block 1: age, sex; block 2: disease duration, Hoehn and Yahr stage (H&Y), levodopa dose (LDE L-dopa), agonist dose (LDE DA)). Age-at-onset was not entered in the regression model, because it is determined by including age and disease duration and thus could have resulted in collinearity.

Statistics were performed with SPSS 14.0, except for CFA which was carried out with EQS 6.1 for Windows.[22]

Table 1. Patient characteristics

Characteristics	Total group	Sample EFA	Sample CFA	*P*
N	397	196	201	-
men/women, N (% men)	253/144 (64%)	134/62 (68%)	119/82 (59%)	0.06 [a]
Age, yrs, mean (SD)	61.2 (11.5)	60.9 (10.9)	61.6 (12.0)	0.58 [b]
Age onset, yrs, mean (SD)	51.0 (11.8)	50.8 (11.5)	51.2 (12.2)	0.71 [b]
Disease duration, yrs, median (IQR) [d]	9.2 (5.2-14.0)	9.6 (5.2-14.1)	8.9 (5.0-13.9)	0.86 [c]
H&Y stage, median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	0.66 [c]
Patients on L-dopa, N (%)	264 (67%)	131 (67%)	133 (67%)	0.89 [a]
Patients on DA, N (%)	276 (70%)	144 (74%)	132 (66%)	0.09 [a]
LDE L-dopa, mg, median (IQR) [d]	300 (0-540)	300 (0-600)	300 (0-500)	0.70 [c]
LDE DA, mg, median (IQR) [d]	188 (0-375)	200 (0-400)	180 (0-329)	0.27 [c]

[a]) Chi-square

[b]) Independent samples t-test

[c]) Mann-Whitney U-test

[d]) Data were not normally distributed, therefore median (IQR) is presented.

EFA; exploratory factor analysis, CFA; confirmatory factor analysis, IQR; interquartile range, H&Y; Hoehn and Yahr, L-dopa; levodopa, DA; dopamine agonists

Results

Eighteen patients who underwent stereotactical surgery were excluded from the analysis. Characteristics of the 397 patients who remained for analysis, and of the subsamples used for exploratory and confirmatory analysis, are presented in table 1. The two subsamples did not significantly differ on any of the characteristics (all ***P***-values >0.05).

Exploratory analysis

An initial EFA of all domains, including the subdomains of cognitive impairment (memory, attention, executive and visuospatial functioning) autonomic dysfunctioning (constipation, urinary dysfunction, cardiovascular dysfunction) and motor signs (tremor, bradykinesia/rigidity, two axial factors), showed that the subdomains of cognition and autonomic impairment grouped together, but the motor subdomains did not. Therefore a second EFA was performed in which the total scores of cognitive impairment and autonomic dysfunction, and the subdomain scores of motor signs were included.
Four factors with an eigenvalue >1 were identified, which together explained 62% of the variance (Table 2). These factors were similar to the factors resulting from the first EFA. The first factor, explaining 31% of the variance, comprised psychotic symptoms, daytime sleepiness, autonomic dysfunction, and cognitive impairment, depression and both axial symptoms. Nighttime sleep problems, motor fluctuations and depression clustered in the second factor, and explained 12% of the variance. The third factor, comprising dyskinesias, motor fluctuations, and axial symptoms 2 (freezing, swallowing, speech), explained 11% of the variance. Factor four explained 9% of the variance and included the remaining motor subdomains, that is, tremor and bradykinesia/rigidity. Three domains showed dual loadings, namely depression (factor 1 and 2), axial symptoms 2 (factor 1 and 3) and motor fluctuations (factor 2 and 3).

Table 2. Exploratory factor analysis of impairment domains

	Factor 1	Factor 2	Factor 3	Factor 4
Psychotic symptoms	0.75			
Autonomic dysfunction	0.72			
Daytime sleepiness	0.62			
Cognitive impairment	0.62			
Axial symptoms1 *	0.61		0.45	
Axial symptoms2 **	0.60		0.56	
Depression	0.60	0.61		
Nighttime sleep problems		0.84		
Motor fluctuations		0.60	0.65	
Dyskinesias			0.83	
Tremor				0.83
Bradykinesia/ rigidity				0.62
% of variance	31	12	11	9

Structure matrix of exploratory factor analysis with oblique rotation. Factor loadings <0.45 have been omitted. Four factors with eigenvalue >1, explaining 61.9% of the variance.

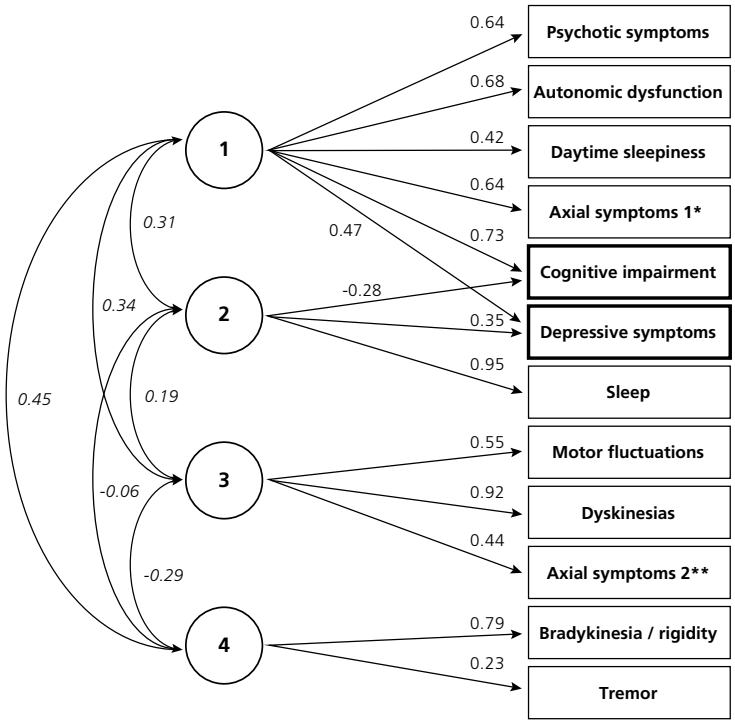
** Axial symptoms 1: Rise, gait, postural instability;*

*** Axial symptoms 2: Freezing, speech, swallowing.*

Confirmatory analysis

A model for CFA was constructed, based on the results from the second EFA (factor loadings >0.55). The fit of this model was insufficient. A model with good fit was obtained when cognitive impairment was allowed to load on factor 2 and axial symptoms 2 was allowed to load on factor 4 (Figure 1). The CFI of this model was 0.95, while the SRMR was 0.05 and the RMSEA 0.06 (95% CI 0.03-0.08). The factor loadings of axial symptoms 2 on factor 1 and 4, and the factor loading of motor fluctuations on factor 2 had a positive, albeit non-significant, contribution to the fit of the model. The factor loadings of the variables loading on factor 1 were in a similar range of very good (psychotic symptoms, autonomic dysfunction, and axial symptoms 1) to excellent (cognitive impairment). The loading of depression on factor 1 was fair while the loading of daytime sleepiness on this factor was poor. Factor 2 was mainly determined by sleep, which had an excellent factor loading, while depression and cognition poorly loaded on this factor. Notably, cognitive impairment had a negative loading on factor 2. Of the three variables loading on factor 3, the loading for dyskinesias was excellent, while these were good for motor fluctuations, and nearly fair for axial symptoms 2. Rigidity and bradykinesia most strongly determined factor 4 with an excellent factor loading, whereas the factor loading of tremor was poor.

Figure 1. Model of factor structure of all impairment domains of Parkinson's disease



Standardized factor loadings are indicated next to the arrows. Non-significant factor loadings with a positive contribution to the fit of the model are not displayed in the figure (axial symptoms 2 on factor 1 and 4; motor fluctuations on factor 2).

** Axial symptoms 1: Rise, gait, postural instability;*

*** Axial symptoms 2: Freezing, speech, swallowing.*

Table 3. Regression analyses of the factors

	Independent variables *	Beta ‡	*P*-value beta	R^2
Factor 1 [a,b]	**Age**	0.21	0.00	0.18
	H&Y stage	0.43	0.00	0.23
	LDE L-dopa	0.14	0.00	0.03
	Disease duration	0.14	0.00	0.01
	Total	-		0.45
Factor 2 [a,c]	**Age**	-0.20	0.00	0.03
	Sex	-0.14	0.01	0.02
	LDE DA	0.15	0.01	0.03
	LDE L-dopa	0.15	0.01	0.02
	Total	-		0.10
Factor 3 [a,d]	**Age**	-0.08	0.06	0.02
	LDE L-dopa	0.44	0.00	0.31
	Disease duration	0.26	0.00	0.09
	LDE DA	0.14	0.00	0.01
	H&Y stage	0.13	0.00	0.01
	Total	-		0.44
Factor 4 [a,e]	**Age**	0.01	0.82	0.02
	Sex	0.19	0.00	0.01
	H&Y stage	0.30	0.00	0.08
	LDE DA	-0.13	0.01	0.02
	Total	-		0.13

** Variables are ordered in the table as they appeared in the model.*

[‡] Standardized beta.

[a] Multiple forward linear regression analysis with variables entered in two blocks: block 1: sex, age; block 2: levodopa dose equivalent levodopa, levodopa dose equivalent dopamine agonists, Hoehn and Yahr stage, disease duration.

[b] Factor 1, including psychotic symptoms, autonomic dysfunction, daytime sleepiness, axial symptoms (rise, gait, postural instability), cognitive impairment, depressive symptoms.

[c] Factor 2, including nighttime sleep problems, depressive symptoms, cognitive impairment.

[d] Factor 3, including motor fluctuations, dyskinesias, axial symptoms (freezing, speech, swallowing).

[e] Factor 4, including bradykinesia and rigidity, tremor.

LDE; levodopa dose equivalent, L-dopa; levodopa, DA; dopamine agonists, H&Y; Hoehn and Yahr.

Relations with disease and medication related variables

In the multiple regression analyses controlling for age and sex, 45% of the variance of factor 1 was explained, with H&Y stage contributing 23%. A total of 44% of the variance of factor 3 was accounted for, with LDE L-dopa explaining 31% and disease duration 9%. Only 10% of the variance of factor 2 and 13% of factor 4 was explained (Table 3).

Discussion

Identification of factors among motor and nonmotor impairment domains may aid in unraveling the nature of underlying constructs. Using EFA, we identified four factors in the spectrum of motor and nonmotor symptoms in our sample of patients with PD. With only minor modifications, this factor structure was confirmed by CFA in an independent sample, thereby strengthening the results. The first and strongest factor comprised most of the nonmotor domains. The main contributors to this factor were cognitive impairment, autonomic dysfunction, psychotic symptoms and the axial symptoms that reflect Postural Instability Gait Difficulty (PIGD; rise, gait and postural instability). Daytime sleepiness and depressive symptoms had a smaller contribution to this factor. The second factor was mainly characterized by sleep disturbances and showed a moderate contribution of depressive symptoms and cognitive impairment. The third factor comprised both types of motor complications with a smaller additional contribution of the axial symptoms freezing, speech, and swallowing. The classical motor features of PD (tremor, bradykinesia and rigidity) grouped together in the fourth factor.

In trying to understand the nature of the encountered patterns, multiple regressions analysis was used to evaluate relations between the factors and variables that reflect disease severity and duration as well as dopaminergic treatment. This approach revealed H&Y stage as the variable most strongly related to factor 1 with negligible contributions of LDE L-dopa and disease duration (1-3%). LDE L-dopa was the variable most strongly related to factor 3 with disease duration showing a small (9%) contribution. Notably, for both factors, more than half of the variance is unexplained. The variables in the regression model together explained only a negligible proportion (10-13 %) of the variance of factors 2 and 4.

The coherence of the domains in factor 1 corroborates the results from previous studies.[23] The relation with H&Y stage and to a lesser extent disease duration most likely indicate that symptoms in this factor cumulate with increasing disease severity or Lewy body pathology.[24] The load of Lewy body pathology is related to the alpha-synuclein gene dosage, which in turn is also influenced by aging.[25] In earlier studies, visual hallucinations, frequent falls, and cognitive impairment have all been found to occur at a similar time to death, which was not proportional to disease duration.[23,26] If, in the development of these symptoms, time to death is a more important determinant than disease duration, age is expected to be more closely related to these symptoms than disease duration. We indeed found that age explained 18% of the variance in factor 1, while the relation with disease duration was negligible.

Factor 3 was predominantly related to LDE L-dopa, whereas a smaller part was explained by disease duration. Total daily dose, duration of exposure, and age at initiation of L-dopa, together with disease severity, are well known risk factors of motor complications.[27,28] The relation between medication and freezing, speech and swallowing is somewhat unexpected, but in agreement with findings of others.[29,30] In a previous factor analysis on motor signs of PD, axial symptoms presented as two separate factors, namely one reflecting rise, gait and postural instability, and the other reflecting freezing, speech and swallowing.[17] Our current findings showed a differential behaviour of both axial factors with respect to their contribution to the four factors and thus may indicate that they represent distinct motor components of PD.

The relation between sleep and depression, as found in factor 2, has been found in several studies.[31-33] A negative relation between sleep and cognition has also been reported previously.[4] Of the 10% variance of this factor that could be explained, half was accounted for by LDE L-dopa and LDE

DA. The relation between insomnia and dopaminergic medication has been found by others[32,33] and may possibly be due to the negative influence of dopaminergic medication on sleep depth or REM sleep.[34] In line with findings from other studies, no relation emerged between this factor and disease severity.[31-33] Possibly this is explained by the finding that in PD, insomnia is an inconsistent and reversible complaint.[31] The dual loading of depression on factors 1 and 2 is most likely explained by the multifactorial etiology of depression.[35,36]

Factor 4, comprising the motor signs tremor, bradykinesia and rigidity, showed a marginal correlation with DA dose, which is in line with previous findings.[37] A similar marginal correlation was found for disease severity, although others have reported a stronger association.[38] Because bradykinesia and rigidity are responsive to dopaminergic treatment, these marginal correlations may reflect a masking effect of dopaminergic medication.[39] Additionally, our findings again underscore that tremor has a distinct behavior within the motor spectrum of PD.[38,40]

In the present study, the full spectrum of motor and nonmotor symptoms of PD was evaluated in a large cohort, using measurement instruments specifically developed for PD. We found distinct patterns of domain coherency among motor and nonmotor symptoms, with the first and strongest factor (cognitive impairment, autonomic dysfunction, psychotic symptoms, PIGD, daytime sleepiness and depressive symptoms) reflecting advancing disease.

Hitherto, the severity and longitudinal course of PD is evaluated by the Hoehn and Yahr staging system, which, from a conceptual point of view, is a peculiar mixture of impairments and disabilities.[9] Stages are determined by the presence of tremor, bradykinesia or rigidity on one or both sides of the body in the early phase of the disease, and by postural instability and the degree of disability in the more advanced stages. In view of the growing awareness that the clinical spectrum of PD is much broader than motor signs only, this staging system does not do justice to the clearly more complicated nature of the disease. In the present study disease severity was found to be best characterized by the nonmotor domains and PIGD motor features that constitute factor 1. Together these domains may provide a better basis of a future disease severity staging system. Additionally, motor complications as reflected in the third factor, are an important consequence of the treatment in PD. Since motor complications are only marginally related to disease severity, this domain likely is better evaluated on a separate axis.

Factors 2 (sleep and depression) and 4 (bradykinesia, rigidity and tremor), though distinct, are not related to either disease severity or complications of therapy. Therefore, these domains have limited applicability in a disease severity staging system. However, information of these domains may have important consequences for disease management and for future studies on patient subtypes. Further research in independent samples is needed to confirm our results.

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6

Clinical subtypes of Parkinson's disease

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Abstract

Objective: The clinical heterogeneity of Parkinson's disease (PD) may point at the existence of subtypes. Since subtypes likely reflect distinct underlying etiologies, their identification may facilitate future genetic and pharmacotherapeutic studies. Aim of this study is to identify subtypes by a data-driven approach applied to a broad spectrum of motor and nonmotor features of PD.

Methods: Data of motor and nonmotor PD symptoms were collected in 802 patients in two different European prevalent cohorts. A model-based cluster analysis was conducted on baseline data of 344 patients of a Dutch cohort (PROPARK). Reproducibility of these results was tested in data of the 2nd annual assessment of the same cohort, and validated in an independent Spanish cohort (ELEP) of 357 patients. The subtypes were subsequently characterized on clinical and demographic variables.

Results: Four similar PD subtypes were identified in two different populations and are largely characterized by differences in the severity of nondopaminergic features and motor complications: subtype 1 was mildly affected in all domains, subtype 2 was predominantly characterized by severe motor complications, subtype 3 was affected mainly on nondopaminergic domains without prominent motor complications, while subtype 4 was severely affected on all domains. The subtypes had largely similar mean disease durations (non-significant differences between three clusters), but showed considerable differences with respect to their association with demographic and clinical variables.

Conclusions: In prevalent disease**,** PD subtypes are largely characterized by the severity of nondopaminergic features and motor complications, and likely reflect complex interactions between disease mechanisms, treatment, aging, and gender.

Introduction

Parkinson's disease (PD) is generally known as a movement disorder, but there is an increasing awareness that the clinical spectrum of PD encompasses also many nonmotor domains like cognition and autonomic function.[1] PD patients exhibit conspicuous differences in the disease profile and progression rate.[2] This clinical heterogeneity may indicate the existence of subtypes. Identification of subtypes is important as homogeneous groups likely reflect stronger clinical, pathological, and genetic coherence, which, in turn, may facilitate our understanding of involved biological pathways. This may ultimately lead to tailored treatment strategies.

In studies on PD subtypes patients have often been classified according to predefined criteria (e.g. young versus old age at onset (AO), or dominance of tremor versus bradykinesia/rigidity), after which other clinical variables were compared between the resulting groups.[2] Alternatively, subtypes may be identified through a data-driven approach like cluster analysis (CA), in which the profile of the subtypes arise from the data without a priori clinical assumptions.

In a systematic review, seven studies were identified that used CA to identify subtypes in the broad clinical spectrum of PD.[3] The majority of those studies identified a subtype with 'old age-at-onset and rapid disease progression' and a subtype characterized by 'young age-at-onset and slow disease progression'. However the results of these studies were difficult to compare because of methodological differences. Studies focused on different PD domains, which were occasionally combined with other variables such as AO and dopaminergic therapy, resulting in conceptually unclear cluster solutions. Further, the applied CA techniques showed some limitations.[3] The aim of the present study is to identify PD subtypes based on motor and nonmotor features of PD, by using a data-driven approach applied to data of two large independent European cohorts.

Method

Patients

Data were obtained from two European longitudinal cohorts, the PROfiling PARKinson's disease cohort (PROPARK; n=415; www.scopa-propark.eu) and the Estudio Longitudinal de pacientes con Enfermedad de Parkinson cohort (ELEP; n=387).[4] Data of the first and second annual assessment of the PROPARK cohort were collected between May 2003 and April 2007. Data of first annual assessment of the ELEP cohort were collected between March and December 2006.

Patients in both cohorts fulfilled the United Kingdom PD Society Brain Bank criteria for idiopathic PD.[5] The recruitment procedure of the PROPARK cohort has been described in detail elsewhere.[6] In short, patients were recruited from outpatient departments of three university and six regional hospitals, and assessed at the Leiden University Medical Centre. Four equally large strata based on AO (</>50 years) and disease duration (</>10 years) were constructed across the cohort to ensure an adequate distribution of factors that are considered to be important determinants of the disease course. Patients in the ELEP cohort were assessed at 20 centers in Spain. Here, six equally large strata were constructed based on sex, AO (30-60/>60 years), and disease duration (</>5 years). In both cohorts AO was defined as onset of first symptom(s) as perceived by the patient. Patients who underwent stereotactic surgery were excluded since this intervention may influence the expression of the phenotype. No other selection criteria were applied. All patients gave written informed consent. Studies were approved by the medical ethics committees of the Leiden University Medical Centre (PROPARK), and the Research Committee of the Carlos III Institute of Public Health and the Clinical Research Ethics Committee of the Hospital de la Princesa, Madrid (ELEP).

Measurement instruments

Except for depression, patients in both cohorts were assessed with the same instruments, which have been described in more detail elsewhere.[7] The following features were assessed: Motor symptoms and Motor Complications (MCs) (SPES/SCOPA sections Motor and Motor Complications), cognitive functioning (SCOPA-COG), autonomic symptoms (SCOPA-AUT), psychotic symptoms (SCOPA-PC), items 1-5), nighttime sleep problems and excessive daytime sleepiness (SCOPA-SLEEP), and depressive symptoms (PROPARK: Beck Depression Inventory (BDI); ELEP: Hospital Anxiety and Depression Scale (HADS)[8]). Based on results of our previous study[9] motor features were evaluated by a tremor factor including rest and postural tremor, a factor consisting of bradykinesia and rigidity, and two axial factors, i.e. one factor comprising rise, gait, and postural instability, reflecting what is commonly known as Postural-Instability-Gait-Difficulty (PIGD), and one factor comprising freezing during on, speech, and swallowing (FOSS). Autonomic dysfunction was evaluated with the gastrointestinal, urological, and cardiovascular items (4-6, 8-16) of the SCOPA-AUT, since these items were considered most relevant for phenotyping. Higher scores reflect poorer function for all scales except the SCOPA-COG; scores of this latter scale were inversed to facilitate interpretability. Patients using antiparkinsonian medication were assessed in "on" state. For each patient, a total levodopa (L-dopa) dose equivalent (LDE) was calculated.[10]

Statistical analysis

If 25% or more of the items of a scale was missing, this patient was excluded from statistical analyses. If, for a particular patient, less than 25% of the items of a scale were missing, missing data

were imputed by the mean value of the nonmissing items of that scale of that patient.
Because severity of PD features increases with longer disease duration and, thus, may act as a potential confounder in the process of identifying distinct phenotypes, each variable was adjusted for disease duration: for each clinical feature the residual value was obtained from a linear regression with the clinical feature as the dependent and disease duration as an independent variable. Finally, all variables were transformed into z-scores to obtain scale invariant outcomes.

Cluster analysis

To identify subtypes we performed a model-based CA on data of PROPARK year 1. Clusters were tested for reproducibility in data of PROPARK year 2. The selected model was validated in data of the ELEP cohort by comparing the characteristics of the same model as selected in PROPARK year 1.
Model-based CA assumes that the dataset is built up from a number of normal distributions. In model-based CA the relative model fit of different models varying in complexity (i.e., with respect to volume, shape, and orientation, which may either be equal or variable) is estimated. In the simplest model the clusters are spherical and have an equal volume and shape, while more complex models allow more variability between clusters. For reasons of generalizability, and in view of the size of the cohort, we focused on the five least complex clustering models with 3, 4, and 5 clusters; fifteen models in total. A Bayesian Information Criterion (BIC) is provided, which is a likelihood-based measure that indicates which clustering model and number of clusters have a maximized fit with a minimal number of parameters. The models are estimated with the Expectation Maximization algorithm. First, initial parameters of the model are estimated, after which patients' probabilities for a cluster membership are estimated. Based on these probabilities model parameters are re-estimated. This iterative process is continued until the model no longer improves.[11-13]
Since any iterative method may end in a local optimum, rather than the optimum of all possible solutions, the Expectation Maximization algorithm was repeated 50 times with randomly chosen starting points, after which the optimal model was selected for each clustering model. Although model-based CA shares similarities with k-means CA, several aspects are specific for model-based CA. First, patients are not allocated to one cluster, but assigned to a cluster according to a probability. Second, there are no strict boundaries between clusters, they may overlap. Third, in contrast to k-means where clusters are always spherical, this method allows more flexibility for clusters to vary in size, shape, and orientation. Various clustering models of increasing complexity are simultaneously estimated for any number of clusters. Fourth, a fit statistic is provided to select the optimal model and optimal number of clusters.
Selection of the optimal model and number of clusters for data of PROPARK year 1 was guided by BIC; models with a 5% lower BIC than the optimal model were also considered.
To warrant stability of the cluster solution the selection of the model was further guided by the following considerations:
1. Models with stronger associations between clustering models of different complexity and between the 3, 4, and 5-cluster solutions of models with the same complexity, were preferred over models with less strong associations. This was tested with Cramer's V.
2. The cluster profiles and patient's cluster allocation in data of the first annual assessment were evaluated for reproducibility in data of the second annual assessment for each of the fifteen models. Models with higher reproducibility were preferred.
To obtain clinically meaningful cluster results model selection was further guided by the following considerations:

3. Simpler clustering models were preferred over more complex clustering models to avoid the risk of overfitting and increase the generalizability to data of other cohorts.
4. Models with very small clusters (<5% of the total group) were discarded, since they carry the risk of reflecting outliers.

Caracterization of clusters

Cluster profiles were graphically displayed in heatmaps. Clusters were characterized for clinical-, demographic-, and disease related variables using data of PROPARK year 1. Differences between clusters were evaluated using ANOVA and Chi-square tests, using Bonferroni correction for multiple testing. A P-value <0.05 was considered significant.

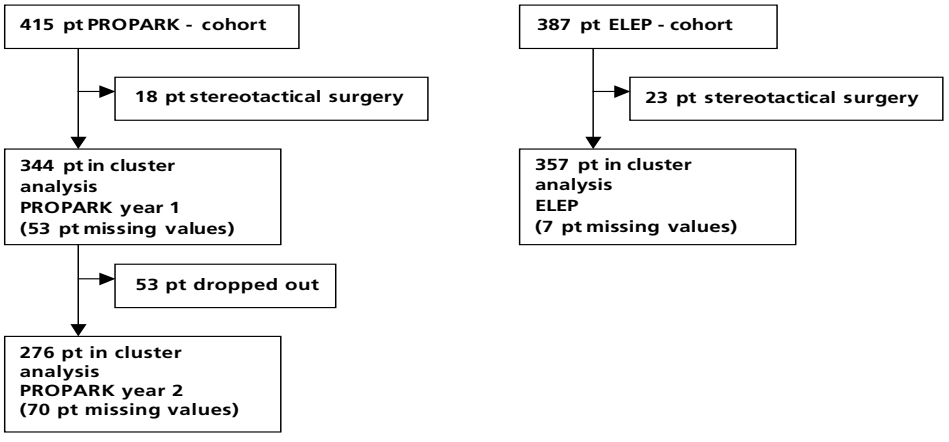
To evaluate which features best discriminated the clusters of the PROPARK and ELEP cohort, a discriminant analysis was performed with the clusters as dependent and the PD features as independent variables. A second discriminant analysis was performed on the PROPARK cohort with demographic- (age and sex) and disease-related (AO, disease duration, and LDE) as independent variables.

CAs and cluster visualization were performed with SubtypeDiscovery 1.11 (https://gforge.nbic.nl/projects/subtypediscover/) in R 2.7.0 (www.r-project.org). Other statistical analyses were performed using SPSS 16.0 (SPSS Inc, Chicago, IL, USA).

Results

Data of 344 patients (1st assessment) and 276 patients (2nd assessment) of the PROPARK cohort and 357 patients of the ELEP cohort were available for analysis (Figure 1, Table 1). A total of 48 (1%) values were imputed to replace missing values of 45 (13%) of the patients in the dataset of the first PROPARK assessment; 46 (1%) of the values were imputed to replace missing values of 38 (14%) patients in the dataset of the second PROPARK assessment. No data were missing for the ELEP cohort.

Figure 1. Flow chart of patients.



pt: patients

Table 1. Patient characteristics

	PROPARK cohort, year 1	PROPARK cohort, year 2	ELEP cohort
N	344	276	357
Sex, men/women (% men)	226/118 (66%)	184/92 (67%)	193/ 164 (54%)
Disease duration, yrs, mean (SD)	9.9 (6.2)	11.0 (6.2)	7.7 (5.8)
Age, yrs, mean (SD)	60.8 (11.3)	61.5 (11.0)	66.2 (11.2)
Age at onset, yrs, mean (SD)	50.8 (11.9)	50.5 (11.8)	58.5 (11.7)
H&Y, median (IQR)	2 (2-3)	3 (2-4)	2 (1-2)
Patients on L-dopa, N (%)	223 (65%)	199 (72%)	267 (75%)
Patients on DA, N (%)	234 (68%)	192 (70%)	242 (68%)

H&Y; Hoehn and Yahr stage, IQR; interquartile range, L-dopa; levodopa, DA; Dopamine agonists

Cluster characteristics

The VVI-5 model was optimal according to the BIC table (Table 2). However, the EII-4 model (<5% lower than the optimal BIC score) was selected based on the additional criteria:

1. The 4-cluster solutions showed more stability than the 5-cluster solutions, since they exhibited larger agreement between different models: Cramer's V: 4-cluster solutions range 0.462-0.909; 5-cluster solutions range 0.488-0.655; agreement between EII-3 and EII-4 0.832; agreement between EII-4 and EII-5 0.925.
2. The EII-4 model showed good reproducibility in data of year 2: Agreement in cluster allocation year 1 and 2: 65% for the total group, and 87% for patients with a ≥95% cluster probability.
3. The EII model is the simplest model.
4. The sizes of the 4 clusters of the EII-4 model were all >5% of the total sample size.

Table 2. BIC table of the model based cluster analysis on data of PROPARK year 1.

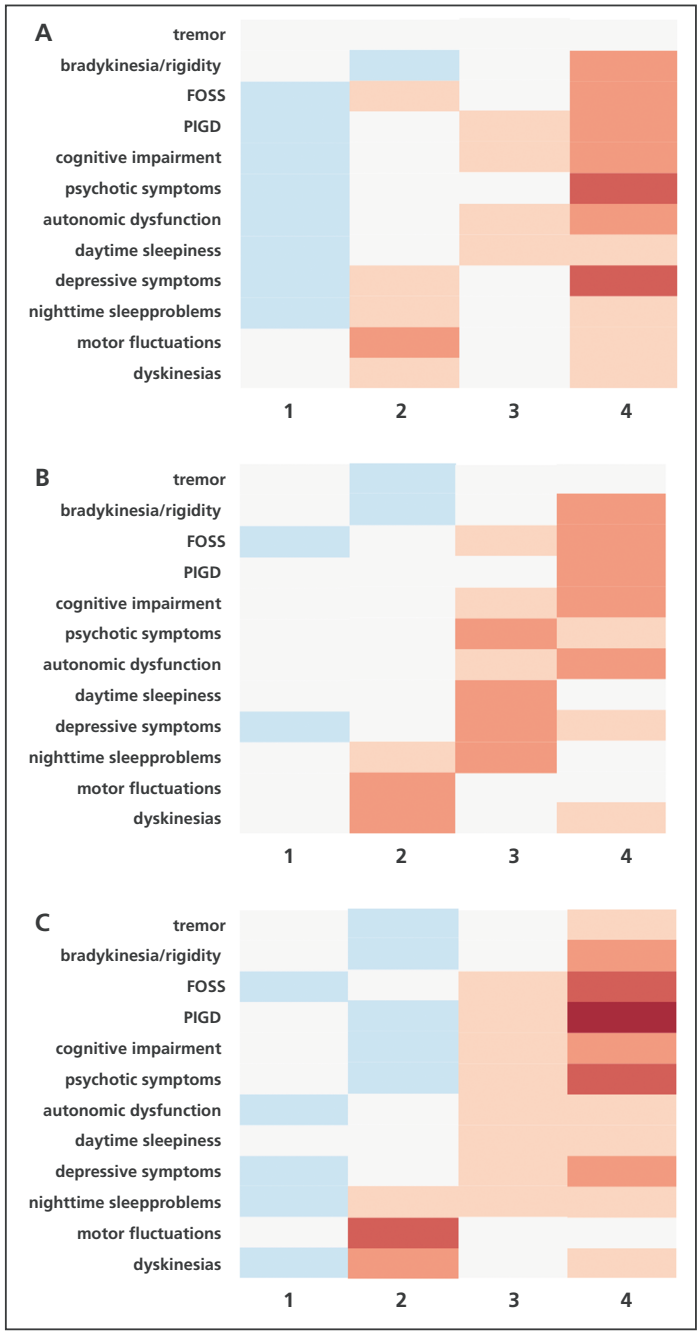
Number of clusters	EII	VII	EEI	VEI	VVI
3	4.37	3.05	4.40	2.98	1.19
4	4.21	2.74	4.18	2.76	0.18
5	4.12	2.90	4.05	2.55	0.00

BIC results for different models with increasing complexity. The complexity of the models increases downwards (larger number of clusters) and from left to right (models increasing in complexity, i.e. a larger number of parameters is estimated). The BIC values of the other models are expressed in percentages lower than the optimal one. The model with the BIC value of 0 is the optimal one, which is the VVI model for 5 clusters in this data set.

Cluster 1 (49%) was characterized by an overall mild severity in all clinical domains. These patients were relatively young, had a younger AO and had lower intake of and shorter exposure to L-dopa.

Cluster 2 (13%) was characterized by severe and frequent MCs, and moderately severe sleep problems and depressive symptoms. These patients had longer disease duration and higher intake of and longer exposure to dopaminergic medication than patients in other subtypes. Patients in this subtype were comparatively young and had the youngest AO, and the proportion of women was relatively large.

Figure 2 a – c. Heatmaps of the EII – 4 models.



A: PROPARK cohort year 1, B: PROPARK cohort year 2, C: ELEP cohort
Foss: an axial motor factor consisting of 'freezing during on', 'swallowing', 'speech'. Pigd: an axial motor factor consisting of 'rise', 'gait' and 'postural instability'.
Each column represents a cluster. The colors indicate whether the cluster mean severity of a symptom is lower (blue color) or higher (red color) than the mean of the total group.

Cluster 3 (30%) showed intermediate severity in nondopaminergic domains, while MCs were mild and less frequent. Patients were relatively old and had a higher AO.

Cluster 4 (8%) included patients who were severely affected in most domains, although tremor was relatively mild. MCs were prominent but less severe than in Cluster 2. This cluster was characterized by relatively high age and AO, long duration of L-dopa use, and a comparatively large proportion of women.

Disease duration did not significantly differ between Clusters 1, 3, and 4.

See figure 2A, tables 3 and 4.

Table 3: Cluster characteristics of the four clusters of PROPARK cohort year 1.

Symptoms (range scores)	Cluster 1	Cluster 2	Cluster 3	Cluster 4
N (%)	169 (49%)	45 (13%)	104 (30%)	26 (8%)
Bradykinesia/rigidity (0-12)	4.7 (1.7) [2,3,4]	3.8 (1.7) [1,3,4]	5.5 (1.8) [1,2,4]	7.4 (2.0) [1,2,3]
Tremor (0-12)	3.6 (1.9)	3.1 (1.8) [3]	4.1 (2.2) [2]	3.1 (1.5)
PIGD (0-9)	1.2 (1.1) [2,3,4]	2.2 (1.5) [1,3,4]	3.1 (1.7) [1,2,4]	4.8 (1.8) [1,2,3]
Cognitive impairment (0-43)	14.7 (5.5) [3,4]	15.8 (4.8) [3,4]	19.7 (5.4) [1,2,4]	25.7 (5.1) [1,2,3]
Psychotic symptoms (0-15)	1.0 (1.1) [2,3,4]	2.4 (1.7) [1,4]	2.3 (1.7) [1,4]	4.8 (2.0) [1,2,3]
Autonomic dysfunction (0-36)	7.1 (4.1) [2,3,4]	11.3 (4.4) [1,3,4]	13.5 (5.1) [1,2]	15.7 (6.1) [1,2]
Daytime sleepiness (0-18)	2.9 (2.6) [2,3,4]	4.4 (3.9) [1,3]	7.7 (3.5) [1,2]	6.4 (3.0) [1]
Depression (0-63)	6.7 (4.0) [2,3,4]	13.9 (5.5) [1,3,4]	10.6 (4.9) [1,2,4]	21.5 (8.3) [1,2,3]
Nighttime sleep problems (0-15)	3.1 (3.1) [2,3,4]	7.7 (3.0) [1,3]	4.5 (3.8) [1,2,4]	7.0 (3.6) [1,3]
Motor fluctuations (0-6)	0.3 (0.8) [2,4]	2.8 (1.2) [1,3,4]	0.4 (0.9) [2,4]	1.2 (1.5) [1,2,3]
Dyskinesias (0-6)	0.5 (1.3) [2,4]	2.3 (1.9) [1,3]	0.4 (1.2) [2,4]	1.8 (1.8) [1,3]
FOSS (0-9)	1.5 (1.2) [2,3,4]	3.0 (1.9) [1,4]	2.6 (1.6) [1,4]	4.2 (1.5) [1,2,3]

Means (SD) presented for all variables. For all PD signs and symptoms: higher scores reflect more problems.

In the columns presenting data of Clusters 1-4 only significant differences are indicated:

[1]) Significant difference (P< 0.05) with Cluster 1 (ANOVA)

[2]) Significant difference (P< 0.05) with Cluster 2 (ANOVA)

[3]) Significant difference (P< 0.05) with Cluster 3 (ANOVA)

[4]) Significant difference (P< 0.05) with Cluster 4 (ANOVA)

PIGD; rise, gait, postural instability, FOSS; freezing, speech, swallowing.

Table 4. Cluster characteristics on variables that were not included in the cluster analysis (PROPARK cohort year 1).

	Cluster 1	Cluster 2	Cluster 3	Cluster 4
Disease duration, yrs [a]	9.1 (6.3) [2]	12.3 (5.3) [1]	10.3 (6.4)	9.9 (4.6)
Age, yrs [a]	57.8 (10.6) [3,4]	57.8 (9.6) [3]	65.9 (10.3) [1,2]	64.7 (14.2) [1]
Age onset, yrs [a]	48.7 (11.5) [3]	45.4 (9.3) [3,4]	55.6 (10.8) [1,2]	54.9 (14.3) [2]
Sex, m/w (% men) [b]	119/50 (70) [2]	22/23 (49) [1]	73/31 (70)	12/14 (46)
1st and 2nd degree relatives with PD, N (%) [b]	42 (25)	13 (29)	22 (21)	5 (19)
Side of onset, N (%) [c]				
left	54 (38)	14 (38)	31 (44)	3 (33)
right	80 (56)	19 (51)	34 (49)	4 (44)
both	9 (6)	4 (11)	5 (7)	2 (22)
H&Y, median (IQR) [b]	2 (2-2) [2,3,4]	3 (2-3) [1,4]	3 (2-3) [1,4]	4 (3-4)[1,2,3]
Presence of motor fluctuations, % yes [b]	14 [2,4]	96 [1,3,4]	19 [2]	42 [1,2]
Presence of dyskinesias, % yes [b]	14 [2,4]	69 [1,3]	14 [2,4]	53 [1,3]
LDE, mg [a]	436 (379) [2]	989 (556) [1,3,4]	570 (375) [2]	606 (394) [2]
LDE L-dopa, mg [a]	230 (283) [2,3,4]	585 (403) [1,3]	377 (334) [1,2]	432 (323) [1]
LDE DA, mg [a]	205 (226) [2]	405 (247) [1,3,4]	193 (191) [2]	173 (210) [2]
Exposure to L-dopa, yrs [a]	2.7 (4.2) [2,3,4]	7.3 (5.2) [1,3]	4.9 (5.3) [1,2]	7.5 (4.6) [1]
Exposure to DA, yrs [a]	2.7 (3.2) [2]	5.4 (3.2) [1,3]	3.5 (3.9) [2]	4.2 (3.9)
Patients on clozapine, N (%) [b]	4 (2)	3 (7)	3 (3)	3 (12)
Patients on amantadine, N (%) [b]	46 (27) [4]	17 (38)	42 (40)	15 (58) [1]

Means (SD) presented for all variables unless stated otherwise.

[a]) ANOVA, post – hoc t – test with Bonferroni correction for multiple testing

[b]) Chi square test, Bonferroni correction for multiple testing

[c]) Kruskal-Wallis

In the columns presenting data of Clusters 1-4 only significant differences are indicated:

[1]) Significant difference (P< 0.05) with Cluster 1

[2]) Significant difference (P< 0.05) with Cluster 2

[3]) Significant difference (P< 0.05) with Cluster 3

[4]) Significant difference (P< 0.05) with Cluster 4

H&Y; Hoehn and Yahr stage, IQR; interquartile range, LDE; levodopa dose equivalent, L-dopa; levodopa, DA; dopamine agonists.

The discriminant analysis showed that motor fluctuations, PIGD, and depression best discriminated the four subtypes of the PROPARK cohort. Based on those variables 251 (73%) patients were correctly classified. Of the demographic- and disease-related variables, AO and total LDE best discriminated the four subtypes; based on these variables 170 (50%) patients were correctly classified. When AO was substituted by age, 167 (49%) patients were correctly classified.

Cluster validation

The EII-4 model of the ELEP cohort was similar to the one obtained in the PROPARK cohort (Figure 2c). Clusters 1-4 comprised 58%, 11%, 27% and 5% of the patients, respectively. This distribution did not significantly differ from the distribution of the PROPARK subtypes (χ^2=6.21; df=3; *P*=0.102). Discriminant analysis showed that motor fluctuations, PIGD, and autonomic dysfunction correctly classified 286 (80%) patients in the ELEP cohort. Using the same discriminative variables as in the PROPARK cohort (depression instead of autonomic dysfunction), 274 (77%) patients were correctly classified.

Discussion

Conspicuous clinical heterogeneity exists among PD patients, which is most likely attributable to differences in the mechanisms that underlie PD and complications of dopaminergic treatment. In this study we aimed to identify clinical subtypes in PD and found four subtypes. The strengths of this study are the use of a data-driven approach in a large number of patients who were extensively characterized on a broad array of motor and nonmotor domains. Moreover, the results were validated in an independent Spanish cohort, in which patients were assessed by similar measurement instruments as in the PROPARK cohort. The latter finding emphasizes the transcultural validity of these subtypes and underscores their robustness in spite of differences in sample collection and sample characteristics.

By comparing the profiles of the subtypes (Figure 2) it appeared that two subtypes (Clusters 1 and 4) differed only by a severity gradient (benign versus malignant), regardless the clinical domain of interest. However, the profile of the other subtypes (Clusters 2 and 3) showed that, based on severity, certain clinical domains grouped together. This grouping of clinical domains is consistent with the results from an earlier study on the coherency of motor and nonmotor domains.[7] Two subtypes (Clusters 3 and 4) had prominent involvement of PIGD, cognitive impairment, autonomic dysfunction, psychosis, daytime sleepiness, and depression; predominantly nondopaminergic features (PND complex). In our previous study this PND complex was associated with both disease severity and age and most likely reflects advancing disease.[7] PIGD has been previously identified as an important motor phenotype associated with cognitive decline, a higher risk for depression, and a more progressive course.[14-18] When PD is viewed from a broader perspective, PIGD may actually be the motor component of the much larger PND complex.

A tremor dominant subtype associated with a more favorable disease course[14-16] was not identified in this study. Recently, a clinicopathologic study showed that tremor is not an independent indicator of a benign disease course.[19] In addition, a longitudinal study showed that with the development of PIGD, the number of tremor pre-dominant patients gradually decreased.[17] Hence, the prevalent character of both cohorts used in this study (mean disease durations 10 and 8 years), may explain why a tremor dominant subtype was not identified.

The two subtypes with prominent involvement of the PND complex (Clusters 3 and 4) had higher AO and age than the two other subtypes (Clusters 1 and 2). Because of the cross-sectional nature of this study and largely similar mean disease duration of the subtypes, it is impossible to unravel whether AO or age most strongly determined disease severity. In the previous CA studies, cluster profiles were characterized on higher AO and rapid disease progression.[3] However, in longitudinal studies on cognitive impairment in PD where both AO and age were taken into account, only the latter was found related to faster rate of cognitive decline.[20,21] Compelling data from other studies suggest that advancing age is also an important determinant of clinical progression in PD, as reflected by

PIGD, cognitive decline, and hallucinations.[19,22] Notably, clusters with a similar AO and age also showed remarkable differences in severity of the PND complex (Clusters 1 versus 2 and 3 versus 4); underscoring that in addition to aging, other disease-modifying factors must play a role in the progression of PD. Levy proposed an appealing model in which nondopaminergic manifestations result from biologic interaction between the disease process and aging.[20] The PND complex likely reflects advancing Lewy body pathology,[23] which has been related to the enhanced level of alpha-synuclein.[24] Interestingly, the latter is influenced by both the disease process and aging.[25] Aging may influence the progression of PD through shared involvement of processes fundamental to neuronal vitality, including the maintenance of protein homeostasis and mitochondrial function.[26]

Our results further identified two subtypes with pronounced MCs (Clusters 2 and 4). Young AO, female gender, higher (cumulative) L-dopa dose, longer duration and higher severity of the disease have been reported risk factors for MCs.[27-29] Except for disease severity, all reported determinants were identified in Cluster 2. Conversely, in Cluster 4, only female gender and disease severity were identified determinants. Because younger AO is considered a risk factor for development of MCs [27,30] it was surprising that also a substantial number of patients with an older AO clustered in a subtype with pronounced MCs. The finding that female gender was the only common risk factor in both subtypes with MCs highlights that subtype-specific interactions between medication and disease related variables may result in a certain susceptibility to MCs. Subtypes with prominent MCs also exhibited more severe mood and sleep disturbances. MCs may directly affect sleep and mood, but clustering of these symptoms may also be linked by factors related to female gender, since insomnia and depression are more frequent in women.[31]

In conclusion, PD subtypes are largely characterized by the severity on two axes: the PND complex and MCs. Axial function and MCs, derivatives of both axes, discriminated best between subtypes, providing further support for this classification. Our findings further show that subtype expression is based on complex interactions between disease mechanisms, treatment, aging, and gender. These findings may have consequences for epidemiologic studies and trials, which hitherto have considered PD a homogeneous disorder, since risk factors and treatment effects may be subtype-specific. The contribution of genetic factors in the subtypes was not evaluated, since a previous screening for mutations in the *Parkin, DJ-1, PINK1, LRRK2,* and *SNCA* gene in the PROPARK showed that pathogenic variations were demonstrated in only 4% of the patients.[32] Hence, it seems unlikely that differences between clusters can be explained by these known mutations.

With the model-based CA, we have tried to avoid the disadvantages of hierarchical and k-means CA. In contrast to these methods, model-based CA is not sensitive to outliers and the model and number of clusters is not arbitrarily chosen but guided by a fit statistic.[11,33,34] This method estimates different models, varying in assumptions on the distribution of the clusters, thereby resulting in more precise solutions.[11,34] And, more importantly, we were able to validate the results in an independent sample. The recruitment strategy of PROPARK, aimed at obtaining an equal distribution of AO and disease duration, may limit generalization of our findings. However, this study aimed to identify subtypes and not their prevalence. Furthermore, despite different sample characteristics of the ELEP cohort, we identified similar subtypes. Because disease duration may influence the phenotypic expression of the disease, we aimed to correct each variable for the influence of disease duration. Small differences in mean disease duration between the subtypes nevertheless remained (range, 9.1-12.3 years), which was significant only between Clusters 1 and 2. Thus, it seems unlikely that these differences play a decisive role in the differential expression of subtypes. Nevertheless, the cross-sectional design of the study precludes the possibility to determine whether patients within clusters had followed

similar disease courses. Moreover, given the prevalent nature of both cohorts, it is impossible to determine which factors at disease onset predict the subsequent development into particular subtypes. Collectively, this knowledge could be important for the development of tailored treatment strategies, and, also, highlights the need for longitudinal studies on incident cases.

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7

Summary and conclusions

Summary

The clinical heterogeneity of Parkinson's disease (PD) patients may reflect the existence of subtypes of the disease. PD subtypes have often been defined by a classification according to researcher-specified criteria, such as age-at-onset or predominant clinical motor features. The general objective of this thesis was to identify and characterize clinical subtypes in PD by a data-driven approach, based on a comprehensive assessment of all relevant PD domains. In order to obtain insight in the associations and coherence of impairments that are involved in the disease, we evaluated the contributions of impairment and disability domains to health-related quality of life in patients with PD. Subsequently, the data of the PROPARK cohort was used to study coherency patterns within the motor domain and in the spectrum of motor and nonmotor domains. In our study on subtypes, first, we systematically evaluated the results of earlier studies that performed cluster analysis (CA) to identify subtypes in PD, after which we applied CA on data of the PROPARK cohort in order to identify subtypes of the disease. In this final chapter, the results are summarized and discussed and possible directions for future research are suggested.

We systematically reviewed the methodology and results of CA studies in PD to gain a better understanding of the robustness of identified subtypes in **chapter 2**. Seven studies fulfilled the inclusion criteria. The cluster profiles 'old age-at-onset (AO) and rapid disease progression' and 'young AO and slow disease progression' emerged from the majority of studies. Other cluster profiles were less consistent across studies. However, studies were limited by incomplete reporting and methodological shortcomings and differences between studies in methodology rendered comparisons of the results difficult. Studies which applied a comparable design identified similar subtypes, supporting the importance of a standardized approach in CA studies. Since CA studies with a rigorous, standardized design may increase our knowledge on subtypes, we made recommendations for future studies with respect to the sample, the included variables, data processing, and CA technique.

In **chapter 3**, the aim was to create insight in how impairments and disabilities related to PD influence health related quality of life (HRQoL) of these patients. This insight is an important prerequisite to evaluate the adequacy of current management strategies. Impairments and disabilities were assessed in 378 PD patients from the SCOPA/PROPARK cohort. HRQoL was assessed with the EuroQol-5D Visual Analogue Scale. Using multiple linear regression analysis and structural equation modelling a model of factors that influence HRQoL with a good fit could be constructed. Of the disabilities, psychosocial well-being had a larger impact on HRQoL than physical functioning. Of the impairments, depression had the largest contribution to HRQoL, followed by axial motor symptoms, gastrointestinal symptoms, and urinary symptoms. In addition, pain, psychiatric and motor complications, and daytime sleepiness had small but significant influences on HRQoL. It can thus be concluded that in PD patients HRQoL is affected by multiple factors, including disabilities, nonmotor domains and axial symptoms. It should be realized that in patients who are on dopaminergic treatment, intended to alleviate mainly motor symptoms, there is a large impact of nonmotor and nondopaminergic symptoms on HRQoL. Research is warranted for management strategies with a multidisciplinary approach for these aspects of the disease that impact on HRQoL.

The goal of **chapter 4** was to identify patterns of motor disturbances in PD and evaluate their relation with other PD domains. For this purpose, a cohort of 399 PD patients was randomly divided

into two samples. On data of the first sample, an exploratory factor analysis was performed to identify factors in the items of the motor evaluation section of the SPES/SCOPA. These factors were next evaluated by confirmatory factor analysis in the second sample. Subsequently, relations with other PD domains were evaluated by regression analyses. A four factor model was found to be valid. This included a tremor, a bradykinetic-rigid, and two axial factors. One axial factor (containing the items "rise", "gait", "postural instability") was associated with age and cognition, while the other axial factor (containing the items "freezing", "speech", "swallowing") was related to dopaminergic medication and complications of therapy. Both other factors showed no relevant associations with demographic and clinical characteristics. It was concluded that the motor disturbances in PD could be classified into four factors. It is expected that different mechanisms underlie the different factors. The identification of motor factors and their relation with other domains of the disease may help to elucidate the mechanisms responsible for these associations. Furthermore, these factors provide an objective base for further research on subtypes in PD.

In **chapter 5** the presence and nature of patterns of coherency among the motor and nonmotor domains in PD was evaluated, as well as their relation with disease severity, disease duration, and dopaminergic therapy. A cohort of 397 PD patients was randomly divided into two samples. In the first sample, exploratory factor analysis (EFA) was performed on the motor and nonmotor symptoms in PD. Findings of the EFA were used to construct a model which was tested in the second sample by confirmatory factor analysis. Multiple regression analyses were performed on the resulting factors to evaluate the influence of clinical parameters upon these factors. Four factors were identified. The first and strongest factor (consisting of cognitive impairment, autonomic dysfunction, psychotic symptoms, depression, daytime sleepiness, and axial symptoms) was related to disease severity. Another factor largely reflected motor complications of therapy and was related to dopaminergic medication. The other two factors, consisting of sleep/depression and tremor/bradykinesia/rigidity, were only marginally related to disease severity or medication. Our findings show that the motor and nonmotor features in PD can be characterized by four distinct patterns of coherency, which provide insight in the contributions of the primary disease process and anti-parkinsonian medication to the broad clinical spectrum of PD. One factor, consisting of predominantly nonmotor symptoms together with axial symptoms, clearly reflected advancing disease and may provide a new basis for monitoring disease progression in PD.

Since the clinical heterogeneity in PD may point at the existence of subtypes, the objective of **chapter 6** was to identify PD subtypes by a data-driven approach based on a broad spectrum of motor and nonmotor features. We collected data of motor and nonmotor PD features in 802 patients in two different European prevalent cohorts. A model based CA was conducted on baseline data of 344 patients of a Dutch cohort (PROPARK). Reproducibility of these results was tested in data of the 2nd annual assessment of the same cohort, and validated in an independent Spanish cohort (ELEP) of 357 patients. The subtypes were subsequently characterized on clinical and demographic variables. Discriminant analysis was performed to determine which variables best discriminated the subtypes. Four similar PD subtypes were identified in two different populations: Patients in subtype 1 were mildly affected on all domains, subtype 2 was predominantly characterized by severe motor complications but only mildly affected on nondopaminergic symptoms, subtype 3 was mainly characterized by affected nondopaminergic symptoms without prominent motor complications, while patients in subtype 4 were severely affected on all domains. Post-hoc analyses showed that

the subtypes had largely similar disease duration, but clearly differed in age, AO, dopaminergic treatment and gender. We concluded that PD subtypes in prevalent disease are largely characterized by the severity of nondopaminergic features and motor complications. Complex interactions between disease mechanisms, treatment, ageing, and gender likely underlie these subtypes.

Concluding remarks

There is an increasing awareness of the potential importance of the identification of subtypes in PD because of the consequences for both our insight in underlying disease mechanisms and the development of tailored treatment strategies. Several studies aimed to identify subtypes in PD by CA, which is an objective method to group patients with similar phenotypes. Hitherto, studies that performed CA on the broad spectrum of PD features showed methodological limitations and variations in design rendered comparisons difficult. Recommendations were made regarding the methodology for future studies applying CA, which were followed optimally in the CA that was performed in this thesis. Identification of subtypes based solely on measures reflecting motor and nonmotor features of PD and not on demographic, medication or progression-related variables provide the opportunity to obtain conceptually clear solutions. When a classification is based on different levels like symptoms at onset, and age of disease onset, and rate of disease progression simultaneously (e.g. tremor dominant, early onset, rapid disease progression), patients may not exclusively belong to one subtype: Selikhova et al. demonstrated that patients, who were allocated to the subtype 'rapid disease progression' in a four-group classification, were mainly included in the 'tremor-dominant' and to a lesser extent in the 'non-tremor dominant subtype' in the three-group classification.[1]

Robust data-driven analysis (factor- and cluster analysis) on the broad array of clinical features resulted in the detection of distinct coherency patterns of impairments, as well as unique subtypes. Interestingly, coherency patterns of impairment domains which were revealed by the factor analysis, were also identified in the profiles characterizing subtypes of the disease. Four subtypes could be identified that were largely characterized by the severity of two important factor components, namely the PND complex (predominantly nondopaminergic symptoms; PIGD, cognitive impairment, autonomic dysfunction, psychosis, daytime sleepiness, and depression) and motor complications: across the four subtypes, the severity of the PND complex increased. Additionally, two subtypes were characterized by severe motor complications Patients in the four subtypes had largely similar disease duration, but showed considerable differences with respect to their association with age, AO, dopaminergic treatment, and gender. Likely, complex interactions between these features as well as genetic predisposition, compensatory mechanisms, and disease mechanisms, determine a subtype-specific susceptibility to the PND complex and motor complications, and thereby the phenotypic expression.[2-4] Thus, although the term 'Parkinson's disease' seems to imply a homogeneous entity, many studies, including studies presented in this thesis, show that PD should not be regarded as a homogeneous disorder.[5] Further, characterizing subtypes on the basis of one feature, e.g. PIGD-dominant, likely reduces the yield in studying subtypes since our results show that two axes (PND complex and motor complications) provide a better characterisation of the different subtypes. Additionally, classifying patients on a single clinical parameter, e.g. AO, would probably be too simplistic, since interactions between clinical parameters may determine the clinical expression on both axes and thereby the subtype.

Since the PND complex was associated with age and motor disease severity (as measured by Hoehn

and Yahr [H&Y] stage), this coherence pattern was considered to be key in characterizing the disease process. With a comprehensive model to study the impact of each of the motor and nonmotor impairments and disabilities on HRQoL it was shown that depression, axial symptoms, and autonomic dysfunction were the most important determinants of HRQoL. Interestingly, all three features are part of the PND complex. Further, subtypes could be well discriminated by axial symptoms and depression, in combination with motor fluctuations. Collectively, these findings underscore the relevance of these domains in the clinical practice. Notably, the classical PD features tremor, bradykinesia, and rigidity did not emerge as important determinants from any of these analyses. However, the effect of these symptoms may be masked by the dopaminergic replacement therapy.

Implications and future directions

Subtypes

The study on subtypes in PD is still in its infancy.[6] Firstly, the results of this thesis require confirmation in other cohorts. Since the publication of our studies, two other studies applying CA in order to identify subtypes have been published.[7,8] However, both studies have included different kinds of variables (PD signs and symptoms, demographic variables, measures of disease progression) in their analyses. Consequently the results of those studies cannot be compared with those of our study. Secondly, patients in the subtypes in our study had similar mean disease duration and thus it is likely that differences between subtypes reflect differences in progression of the disease. However, given that the results on subtypes in this thesis are derived from a cross-sectional study, it remains unclear if subtypes are also characterized by specific longitudinal patterns of change. An incident cohort with long-term follow-up may provide insight in differences between subtypes in progression and in determinants at baseline that predict subsequent development into a particular subtype. Thirdly, the results of this thesis need to be validated by objective markers. Biomarkers are measurable components along the pathway between disease and its underlying biological pathophysiology. With the identification of biomarkers mechanisms underlying the subtypes may be elucidated. Moreover, biomarkers have the potential to identify persons at-risk before overt expression of the disorder.

The nature of PD is complex and multiple factors may contribute to the development of different subtypes. Further research on these factors needs to be aimed at many areas. Two main directions will be discussed below. Finally, implications of the results of this thesis for treatment will be discussed.

Ageing

Our results indicated clear differences between subtypes in age at onset and age. In view of the cross-sectional nature of our cohort it is not possible to determine whether age at onset or age is the key in the expression of the subtype. An important role for age specifically with respect to the nondopaminergic symptoms has also been suggested in other studies.[9-11] In parallel, more fundamental studies also highlighted the importance of age in the pathologic mechanisms in PD. Neurodegenerative diseases like synucleinopathies and tauopathies do not clinically present until a certain age has been achieved, suggesting a role for the ageing process in the development of these diseases or common mechanisms of ageing and neurodegeneration.[12] Additionally, PD and Alzheimer's disease show an overlap in pathological processes and genetic features.[13-16] However, in our study, subtypes characterized by similar age and AO also showed differences in disease severity. Similarly, other studies showed that differences between subgroups in disease severity or higher cortical Lewy

body scores could not be explained by age.[1,11] In various studies, hallucinations, cognitive disability, regular falls, and need for residential care occurred at a similar time to death, irrespective of age, AO or disease duration.[10,17,18] This indicates that the occurrence of these symptoms, rather than age, reflects the pathological endpoint. Kempster et al. suggested that age influences the disease in the early and middle part of the disease, but not in the end stage.[10,17,18] A study on predictors of Alzheimer's disease showed that ageing, defined as 'age associated decline in health status' as reflected by a frailty index, appeared as a risk factor, in addition to age.[19,20] Age is an indicator for, but not identical to ageing; *'while some 70-year old persons need residential care, other 70-years olds still go hiking in the mountains'*. The patients who were evaluated on their clinical presentation in the years prior to death,[10,17,18] were likely in a similar stage of cellular ageing and neurodegeneration, but with a variable age. Considering this possibility, ageing may thus influence the disease at all stages. Obviously, these are hypotheses that require confirmation.

Recent studies suggested that cellular ageing and misfolding of the alphasynuclein protein are influenced by common genetic pathways, indicating an important relationship between the genetics of ageing and PD. [21,22] Also genetic pathways are identified that are related to ageing and PD, but with an increased expression level in PD, and genetic pathways were identified that are specific for PD.[23] A better understanding of processes that occur during "normal ageing", with respect to imbalance in protein homeostasis in the cells, and in the brain during the disease course of PD may have consequences for both our understanding of mechanisms of disease and the development of new therapeutic targets.[24]

Neural plasticity

Given the observations that large numbers of neurons in the substantia nigra die before clinical features emerge in PD patients and that some subjects have substantial amounts of alphasynulein pathology in the central nervous system without clinical manifestations, it is suggested that pathologic processes can be modulated by compensatory mechanisms. Through compensatory mechanisms or neural plasticity, the brain may adapt to neuronal loss, thereby maintaining neuronal functions.[4,15] However, plasticity is also known to induce negative effects: aberrant neural plasticity may be responsible for the development of dyskinesias.[25,26] Thus, differences in the expression of plasticity may explain differences between subtypes in the severity on both axes, namely disease severity as reflected by the PND complex and the severity of motor complications. The expression of plasticity is determined by genetic mechanisms which are also under the control of age and it may further be modulated by denervation and dopaminergic medication.[25,26] Recently, a polymorphism of the brain derived neurotrophic factor *(BDNF)* gene, which plays a role in modulating synaptic plasticity, appeared to be related to time to onset of dyskinesias.[27] Also, variations in the Catechol-***O***-methyltransferase *(COMT)* gene have been found related to increased susceptibility to the development of dyskinesias.[28] Further research on these and other polymorphisms, may provide insight in the underlying mechanisms of the subtypes and polymorphisms may eventually serve as predictors for the development into a particular subtype.

Treatment

In the PROPARK cohort the nondopaminergic symptoms appeared to have a large impact on disease severity, subtype characterisation, and HRQoL in patients with PD. However, these findings should be interpreted against the background of a cohort that is characterized by longstanding disease and use of dopaminergic medication, which reduces the severity of some typical motor features of the

disease and may have biased our findings. From data of an longitudinal incident cohort it appeared that a 'dopa-resistant subscore' including speech, posture, gait, postural instability, and rising from sitting, predicted more rapid progression to H&Y 3, and this dopa-resistant subscore appeared as an index of progression that was more sensitive than both the UPDRS 2 (section activities of daily living) and 3 (section motor examination), thus supporting our results.[29] These findings point out the need for better management strategies for the nondopaminergic symptoms, which now seems to be the greatest challenge.[30,31]

Since current available therapies cannot control these nondopaminergic features, neuroprotective or disease modifying therapies are being developed which aim at prevention or delay of the disease progression. However, hitherto no agent has given proof of a neuroprotective effect yet.[32-34] One of the issues that may influence the results of a trial testing an intervention with assumed neuroprotective action is the selection of a suitable outcome measure. Outcome measures that have been selected in previous trials included the slope of the UPDRS score and time to levodopa therapy, shift to H&Y stage III, or the development of motor complications.[32,34] Results in this thesis show that the spectrum of PD signs and symptoms consists of four different patterns of coherency, each of them associated with different characteristics. Information on the severity of at least two out of these coherency patterns is required to discriminate subtypes. Hence, in trials important information may be missed when a single primary outcome measure is selected: a positive effect on one outcome measure may coincide with a negative or no effect on another outcome measure. Alternatively, application of the Global Statistical Test methodology allows for a selection of several relevant outcomes in the evaluation of a treatment effect.[35] A second point, relevant not only for these trials but for all research in PD, relates to the notion that by regarding PD as homogeneous disease, subtype-specific risk factors or treatment effects may be missed. Hence, identification of determinants, ideally objective biomarkers, which predict a disease course of a particular subtype, is of great importance for disease management: In trials patients can be stratified, so that subtype-specific effects can be evaluated. Moreover, the effectiveness of therapy might be greatly improved when patient-specific treatment strategies can be applied. [36]

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List of abbreviations

χ^2	Chi-square
ADL	Activities of daily life/ Activities of daily living
AO	Age-at-onset
ANOVA	Analysis of variance
BDI	Beck Depression Inventory
BDNF	Brain derived neurotrophic factors
BIC	Bayesian Information Criterion
CA	Cluster analysis
CFA	Confirmatory factor analysis/ Confirmatieve factor analyse
CFI	Comparative fit index
CI	Confidence interval
CV	Cardiovascular
DA	Dopamine agonists
Df	Degrees of freedom
DS	Daytime sleepiness
Dysk	Dyskinesias
EFA	Exploratory factor analysis/ Exploratieve factor analyse
ELEP	Estudio Longitudinal de pacientes con Enfermedad de Parkinson
EQ-5D	EuroQol five dimension
EQ-VAS	EuroQol Visual Analogue Scale
Et al.	Et alii (and others)
Fig	Figure
FOSS	A factor comprising Freezing during on, Swallowing, and Speech
GBA	Glucoserebrosidase
GI	Gastrointestinal
H&Y	Hoehn and Yahr
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health related quality of life
I.e.	Id est (that is)
IQR	Interquartile range
JM	Johan Marinus
LDE	Levodopa dose equivalent
L-dopa	Levodopa
LRRK2	Leucine rich repeat kinase 2
LUMC	Leiden University Medical Centre
M	Men
MC	Motor complications
ME	Motor Evaluation
MF	Motor fluctuations
Mg	Milligram
MMSE	Mini Mental State Examination
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	Motor symptoms
NSAID	Non-Steroidal Anti-Inflammatory Drug
NFI	Normed Fit Index

NNFI	Nonnormed Fit Index
NS	Nighttime sleep problems
NS	Not specified
PBF	Prinses Beatrix Fonds
PD	Parkinson's disease
PDQ-39	Parkinson's Disease Questionnaire – 39 item version
PIGD	Postural instability and gait difficulty
PINK1	PTEN-induced kinase 1
PM	Pupillomotor
PND	Predominantly Nondopaminergic features
PPRS	Parkinson psychosis rating scale
Prof.	Professor
PROPARK	PROfiling PARKinson's disease
Pt	Patients
QoL	Quality of life
REM	Rapid eye movement
RMSEA	Root means square error of approximation
SCOPA	Scales for Outcomes in PArkinson's disease
SCOPA-AUT	SCales for Outcomes in PArkinson's disease – AUTonomic function
SCOPA-COG	SCales for Outcomes in PArkinson's disease – COGnition
SCOPA-PC	SCales for Outcomes in PArkinson's disease – Psychiatric Complications
SCOPA-PS	SCales for Outcomes in PArkinson's disease –PsychoSocial
SD	Standard deviation
SEM	Structural Equation Modeling
SPES	Short Parkinson Evaluation Scale
SPES/SCOPA	Short Parkinson Evaluation Scale/ SCales for Outcomes in PArkinson's disease
SPES/SCOPA-ADL	Short Parkinson Evaluation Scale/ SCales for Outcomes in PArkinson's disease – activities of daily living
SPES/SCOPA-MC	Short Parkinson Evaluation Scale/ SCales for Outcomes in PArkinson's disease – motor complications
SPES/SCOPA-MS	Short Parkinson Evaluation Scale/ SCales for Outcomes in PArkinson's disease – motor symptoms
SPSS	Statistical Package for Social Sciences
SR	Stephanie van Rooden
SRMR	Standardized root mean square residual
SX	Sexual dysfunction
TR	Thermoregulatory
UK	United Kingdom
UPDRS	Unified Parkinson's Disease Rating Scale
UR	Urinary
VAS	Visual Analogue Scale
W	Women
Yrs	Years

Nederlandse samenvatting voor niet-ingewijden

Na de ziekte van Alzheimer is de ziekte van Parkinson de meest voorkomende neurodegeneratieve aandoening. De ziekte wordt gekenmerkt door traagheid van bewegen (bradykinesie), beven (tremor), stijfheid (rigiditeit) en instabiliteit. Dit zijn de zogenaamde motorische kenmerken. Daarnaast is er nog een aantal kenmerken dat geen betrekking heeft op het bewegen, de non-motorische kenmerken. Dit zijn onder andere reukstoornis, problemen met het denkvermogen, slaapproblemen, slaperigheid overdag, depressieve symptomen, hallucinaties en zogenaamde autonome problemen, waaronder problemen met de spijsvertering, de bloedsomloop, het plassen en seksualiteit. Daarnaast kunnen patiënten als gevolg van de medicatie last krijgen van overbeweeglijkheid (dyskinesieën) en het plotseling niet werken van de medicijnen (motorische fluctuaties). Patiënten kunnen worden behandeld met levodopa, maar dit heeft alleen effect op de motorische problemen. Hoe de ziekte van Parkinson ontstaat is nog niet duidelijk. Eerst werd gedacht dat het verlies van dopaminerge cellen in de substantia nigra ("zwarte kern" in het brein) de oorzaak was van de ziekte. Inmiddels is bekend dat de ziekte zich niet beperkt tot één locatie in het brein, maar zich door de hersenen verspreidt. Er zijn genen gevonden die een rol spelen bij het ontstaan van de ziekte van Parkinson. Het is bekend dat het mannelijk geslacht, het drinken van water uit specifieke bronnen, stress en hoofdletsel de kans op de ziekte van Parkinson kan verhogen. Roken van sigaretten zou de kans op de ziekte van Parkinson verkleinen. De oorzaak van de ziekte is waarschijnlijk een complexe interactie tussen verschillende elementen en mechanismen.

In de 'PROfiling PARKinson's disease' (PROPARK) studie hebben we een grote groep mensen (een cohort van meer dan 400 patiënten) met de ziekte van Parkinson gedurende 6 jaar gevolgd. Ieder jaar hebben we met vragenlijsten en meetinstrumenten onderzocht hoeveel problemen patiënten hadden bij elk van de symptomen. Zo konden we in kaart brengen in welke mate de patiënten klachten hadden op de verschillende aspecten van de ziekte en hoe het ziekteverloop was gedurende de zes jaar. De analyses in dit proefschrift zijn uitgevoerd op de data van het eerste jaar.

In **hoofdstuk 3** hebben we onderzocht op welke wijze de klachten van de patiënten invloed hadden op de kwaliteit van leven, zoals de patiënten die beoordeelden op basis van hun gezondheid (gezondheidsgerelateerde kwaliteit van leven). We hebben hiervoor een model gemaakt. Het bleek dat psychosociaal welzijn een sterkere invloed had op de kwaliteit van leven dan fysiek functioneren. Van de symptomen van de ziekte van Parkinson had depressie de grootste invloed op de kwaliteit van leven, gevolgd door loopproblemen, problemen van het maagdarmstelsel (o.a. obstipatie) en problemen met plassen en incontinentie. Juist de niet-motorische symptomen bleken een grote invloed te hebben op de gezondheidsgerelateerde kwaliteit van leven. Hierbij moet wel worden opgemerkt dat de patiënten behandeld werden met medicijnen die met name de klachten van de motorische symptomen verminderen. Hierdoor kan de invloed van deze motorische symptomen op de kwaliteit van leven minder groot lijken. De resultaten van deze studie tonen aan dat er het van belang is om behandelstrategieën van de niet-motorische symptomen te onderzoeken.

In dit proefschrift is ook onderzocht hoe alle symptomen onderling met elkaar samenhangen. Dit hebben we gedaan voor de motorisch symptomen afzonderlijk (**hoofdstuk 4**), alsmede voor de motorische symptomen en niet-motorische symptomen samen (**hoofdstuk 5**). In verschillende modellen hebben we onderzocht welke "groepen van symptomen" sterk met elkaar samenhingen (factoren) binnen het totale spectrum van symptomen. Dit is interessant, omdat deze "groepen symptomen" of factoren waarschijnlijk worden beïnvloed door dezelfde onderliggende mechanismen.

We vonden factoren die samenhingen met de leeftijd, met de ernst van de ziekte, of met het gebruik van medicatie. Zo kunnen we beter begrijpen hoe de symptomen ontstaan en waardoor de ernst van de symptomen beïnvloed wordt. Daarnaast verschaffen deze factoren een objectieve basis voor verder onderzoek naar subtypen bij de ziekte van Parkinson.

De ziekte van Parkinson uit zich niet bij alle patiënten hetzelfde: Sommige patiënten ervaren de eerste symptomen al op jonge leeftijd, terwijl anderen veel ouder zijn als de ziekte begint; er is verschil in de mate van bijwerkingen tussen patiënten; de klachten kunnen langzaam of snel verergeren; bepaalde symptomen kunnen bij sommige patiënten veel problemen geven, terwijl bij andere patiënten andere klachten voorop staan. Deze verscheidenheid in de uiting van de ziekte wordt ook wel klinische heterogeniteit genoemd. Klinische heterogeniteit kan wijzen op het bestaan van subgroepen van patiënten ofwel subtypen; binnen het geheel zijn groepen patiënten te herkennen die meer verschijnselen met elkaar gemeen hebben dan patiënten uit andere groepen.
In eerdere onderzoeken naar subtypen bij de ziekte van Parkinson werd de indeling in de subtypen vaak bepaald door de onderzoeker. Subtypen kunnen ook worden geïdentificeerd door middel van een benadering die juist door de data wordt gestuurd. In dat geval bepaalt de onderzoeker niet hoe de groep wordt onderverdeeld in subtypen, maar wordt gekeken naar patronen in de data. Dit is een meer objectieve methode. Een voorbeeld van zo een methode is clusteranalyse. In **hoofdstuk 2** hebben we systematisch gezocht naar eerdere studies die door middel van clusteranalyse subtypen hebben geïdentificeerd bij de ziekte van Parkinson. Zeven studies voldeden aan de criteria die aan de studies gesteld waren. De clusters met de karakteristieken 'oude leeftijd bij aanvang van de ziekte en snelle ziekteprogressie' en 'jonge leeftijd bij aanvang van de ziekte en langzame ziekteprogressie' werden in de meeste studies gevonden. Andere clusterprofielen waren minder consistent gevonden. De studies hadden echter beperkingen in de methodologie en vertoonden een onvolledige rapportage. Verschillen tussen studies maakte het vergelijken van de resultaten moeilijk. Studies met een vergelijkbare onderzoeksopzet identificeerden gelijke subtypes. Dit geeft het belang van een gestandaardiseerde aanpak van clusteranalyse-studies aan. Er werd geconcludeerd dat studies met een grondige onderzoeksopzet, die gestandaardiseerd zijn met betrekking tot variabelen in de analyses, het verwerken van de data en de methodetechniek de kennis van subtypen bij de ziekte van Parkinson kunnen vergroten.
In **hoofdstuk 6** hebben we een clusteranalyse uitgevoerd om subtypen te identificeren en deze vervolgens te karakteriseren. We hebben het brede spectrum van motorische- en niet-motorische stoornissen van de ziekte van Parkinson geanalyseerd. We hebben een 'model-based' clusteranalyse uitgevoerd op de eerste meting van de patiënten uit de PROPARK studie. We hebben vervolgens gekeken of we dezelfde resultaten kregen uit de gegevens van de tweede meting van ons onderzoek en ook in het – onafhankelijke – Spaanse cohort van de ELEP studie.
Vier subtypen konden worden geïdentificeerd in zowel ons eigen als het Spaanse cohort: Subtype 1 was in lichte mate aangedaan op alle symptomen; subtype 2 werd voornamelijk gekarakteriseerd door ernstige motorische complicaties (overbeweeglijkheid en schommelingen in het effect van de medicatie) maar had weinig klachten bij het lopen, het denkvermogen, autonome problemen (vb obstipatie), hallucinaties, slaperigheid overdag en depressie (zogenaamde niet-dopaminerge symptomen); subtype 3 had met name ernstige niet-dopaminerge symptomen, maar geen ernstige motorische complicaties; subtype 4 was ernstig aangedaan op alle symptomen. De subtypes hadden een nagenoeg even lange ziekteduur, maar verschilden duidelijk in leeftijd, leeftijd bij aanvang van de ziekte, behandeling met Parkinson-medicatie en geslacht. Complexe interacties tussen

ziektemechanismen, behandeling, veroudering, en geslacht liggen waarschijnlijk ten grondslag aan deze subtypen.

Men is zich steeds meer bewust van het belang om inzicht te krijgen in subtypen bij de ziekte van Parkinson, vanwege de mogelijke gevolgen enerzijds voor het inzicht in onderliggende ziektemechanismen en anderzijds de ontwikkeling van specifieke behandelstrategieën. Grondige analyses van het brede spectrum van symptomen van de ziekte van Parkinson resulteerden in het identificeren van verschillende groepen van symptomen (factoren) en groepen van patiënten (subtypen). Interessant was dat de ernst van factoren kenmerkend was voor elk van de subtypen. De factoren zijn dus ook van belang voor het onderzoek naar de subtypen. Hoewel de term 'Ziekte van Parkinson' lijkt te duiden op een homogene aandoening, blijkt uit vele studies, inclusief de studies in dit proefschrift, dat de ziekte van Parkinson verschillende klinische uitingsvormen heeft. De 'ziekte**n** van Parkinson' is daarom misschien een beter passende naam.

Het onderzoek naar subtypen bij de ziekte van Parkinson staat nog in de kinderschoenen. Allereerst moeten de resultaten van dit proefschrift worden bevestigd in andere cohorten. Ten tweede geldt dat in onze studie de patiënten in de subtypen een vergelijkbare gemiddelde ziekteduur hadden. Dit duidt op de mogelijkheid dat de subtypes ook verschillen in ziekteprogressie. Hier kunnen echter geen uitspraken over worden gedaan, omdat deze resultaten zijn gebaseerd op cross-sectioneel onderzoek (onderzoek waarbij de gegevens op één moment in de tijd worden verzameld). Ten derde zouden de resultaten van dit proefschrift gevalideerd moeten worden door objectieve markers, zoals biomarkers. Biomarkers zijn meetbare elementen in het proces tussen de onderliggende afwijkende mechanismen in het lichaam en de uiting van de ziekte. Met de identificatie van biomarkers kunnen onderliggende ziektemechanismen worden blootgelegd. Bovendien zou mogelijk met biomarkers bepaald kunnen worden welke patiënten een risico hebben bepaalde symptomen te ontwikkelen, al voor dat deze ziekteverschijnselen zich presenteren.

De ziekte van Parkinson is een complexe aandoening en vele elementen kunnen een rol spelen in de ontwikkeling van verschillende subtypen. Toekomstig onderzoek naar de ziekteprocessen van de ziekte van Parkinson zal zich ook moeten richten op verschillende gebieden. Een van deze richtingen is 'veroudering'. De subtypen die in dit proefschrift werden gevonden verschilden in leeftijd. Twee subtypen met dezelfde leeftijd lieten onderling ook verschillen zien in ernst van de ziekte. Dus wellicht speelt niet zozeer leeftijd op zich, maar veroudering een rol in het ontwikkelen van symptomen. Andere studies laten ook zien dat veroudering een rol speelt bij de ziektemechanismen van de ziekte van Parkinson. Ook is er een samenhang gevonden tussen de genetica van het ouder worden en de ziekte van Parkinson. De betekenis van al deze resultaten moet verder onderzocht worden.
De resultaten van dit proefschrift hebben ook een betekenis voor toekomstig onderzoek naar de behandeling van de ziekte van Parkinson. In het PROPARK cohort bleken de niet-dopaminerge symptomen een grote impact te hebben op ziekte-ernst, karakterisering van subtypen en de kwaliteit van leven bij patiënten met de ziekte van Parkinson. Deze bevindingen wijzen op de behoefte aan betere behandelstrategieën van niet-dopaminerge symptomen en dit lijkt nu de grootste uitdaging lijkt te zijn. Een andere consequentie van de resultaten van dit proefschrift voor onderzoek naar de behandeling is dat, wanneer de ziekte van Parkinson wordt beschouwd als een homogene aandoening, subtype-specifieke risicofactoren of effecten van behandeling

zouden kunnen worden gemist. In toekomstig onderzoek zouden patiënten in groepen kunnen worden ingedeeld op basis van de subtypen, waardoor subtype-specifieke effecten kunnen worden geëvalueerd.

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Curriculum Vitae

Stephanie Maria van Rooden werd op 10 mei 1980 geboren in Leiderdorp. Na het behalen van haar VWO diploma in 1998 startte zij met de studie Farmaceutische wetenschappen aan de Universiteit Utrecht. Na een jaar verruilde ze dit voor de studie Fysiotherapie aan de Hogeschool Leiden, waarvoor ze in 2003 haar diploma behaalde. Voor haar afstudeerstage onderzocht zij de interbeoordelaarsbetrouwbaarheid van de Parkinson Activity Scale, op de afdeling Fysiotherapie van het Leids Universitair Medisch Centrum (LUMC). Na haar afstuderen werkte ze als fysiotherapeut bij een eerstelijns praktijk en op de afdeling Neurologie van LUMC bij het "SCales for Outcomes in PArkinson's disease (SCOPA)/PROfiling PARKinson's disease (PROPARK)"-onderzoek. Vanaf 2004 combineerde zij haar werk als onderzoeksassistent met de studie Bewegingswetenschappen aan de Vrije Universiteit te Amsterdam. In 2006 studeerde zij af in de richting Gezondheid/Revalidatie. Tijdens haar afstudeerstage onderzocht zij de associatie tussen handvoorkeur en de aanvangszijde van de ziekte van Parkinson. Na afronding van de studie begon zij aan haar promotieonderzoek, onder leiding van prof. dr. J.J. van Hilten, dr. J. Marinus en dr. M. Visser-Jeukens. Het promotieonderzoek is onderdeel van de PROPARK studie. Tijdens het afronden van haar proefschrift werkte zij op de afdeling ouderengeneeskunde (LUMC) op het Herstelzorgproject, onderdeel van het Nationaal Programma Ouderenzorg. Vanaf augustus 2012 werkt zij op de afdeling Medische Statistiek en Bioinformatica (LUMC), sectie Advanced Datamanagement, als data-analist.
Ze is getrouwd met Maikel Kuit.

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