­­Parkinson’s disease subtypes

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# Abstract (< 400 words)

*Keywords: a, b, c, d, e*

# Introduction

Parkinson’s disease has been classically considered a motor disorder, with resting tremor, rigidity and bradykinesia as its core features. However, the concept of Parkinson’s disease has changed considerably in the last few years, now prompting a revision of its diagnostic criteria to include non-motor symptoms (NMS) in the core parameters (Marras and Chaudhuri 2016; Postuma *et al.* 2015). While motor symptoms remain a part of the core diagnostic criteria, NMS are now known to predate motor symptoms for up to 20 years (Hawkes 2016) and underpin the prodromal stage of Parkinson’s (Berg *et al.* 2015). The range of NMS in Parkinson’s disease have been categorized into dopaminergic, non-dopaminergic, fluctuating, as well as drug-induced and genetic categories (Todorova *et al.* 2014). NMS mostly arise from the multipeptid dysfunction that is now recognized in Parkinson’s disease, in addition to the fact that the pathophysiology involves the central nervous system as well as many extra cerebral organs including the gut and the heart (Jellinger 2012). Cluster analysis based studies have already identified several non-motor clusters in PD patients (Erro *et al.* 2013; Onset PD 2015), while clinical observational studies also suggest the existence of robust and specific non-motor subtypes (Sauerbier *et al.* 2015; Marras and Chaudhuri 2016). These observations show the remarkable variability in the expression of PD. The progression of NMS in Parkinson’s have been poorly studied and appear to be variable from one patient to another, while the presence or accumulation of symptoms may differ broadly between individuals (Thenganatt and Jankovic, 2014).

This variability in the course and expression of the disease has promoted the search of specific subtypes whose identification could provide knowledge on their pathophysiology, tailored treatment, progression rate, and prognosis. Several subtypes of PD have been identified, including the motor subtypes classified by Jankovic *et al.* (1990), Scheiss *et al.* (????), and Eggert *et al.* (????). Nonetheless, studies have shown these phenotypes to be unstable over time. **Why? Citation?**

However, non-motor symptoms are an important part of the disorder and several studies have explored PD subtypes considering motor subtypes and their association with several non-motor facets of the disease such as psychopathology and cognition (Graham and Sagar, 1999; Reijnders *et al*., 2009; Selikhova *et al*., 2009; Burn *et al*., 2012; Damholdt *et al*., 2012), REM sleep behavior disorder (Romenets *et al*., 2012); and visual daily activities (Seichepine *et al*. 2011).

Subtypes exclusively based on NMS have also been proposed (Sauerbier *et al*., 2016), but few studies have been carried out exploring the combination of the motor disturbances and a wide diversity of NMS for obtaining a more complete picture of the reality in regard to the potential existence of subtypes characterized by a specific mixture of motor and non-motor manifestations (van Rooden *et al*., 2011; Erro *et al*., 2013; Fereshtehnejad *et al*., 2015; Ba *et al*., 2016), with prognostic connotations (de Lau *et al*., 2014).

The present study was aimed at using cluster analysis techniques to search for PD subtypes with a wide database of PD patients using a combination of motor cardinal features (bradykinesia, rigidity, tremor, axial signs) and NMS features assessed using specific rater-based scales.

# Materials and Methods

## Experimental Design

Combination of data from two independent international studies: the validation study of the Non-Motor Symptoms Scale (NMSS) () (Martinez-Martin *et al*., 2009a) and baseline data from the Nonmotor International Longitudinal Study (NILS) () (on going) sharing most of the protocol and assessments (Ray Chaudhuri *et al*., 2013). **More detail**

## Patients

Consecutive patients, both genders, any disease stage, diagnosed with PD by a neurologist with competence in movement disorders and according to internationally recognized criteria (Gibb and Lees, 1988; Lees *et al*., 2009). For the NMSS study, patients had to be older than 30 years, but for inclusion of NILS patients there was no age limit. Exclusion criteria were: inability to read, understand, or answer written questionnaires; comorbidity, sequelae, or any disorder interfering assessment of PD manifestations; and inability for giving informed consent. Patient recruitment was carried out across 15 countries in America, Asia, and Europe from 2007 to 2011.

## Assessments

Socio-demographic and historical data were recorded and the following assessments were applied:

1. The Scales for Outcomes in Parkinson’s Disease-Motor (SCOPA-Motor). A PD-specific rating scale with three dimensions: A. Examination (10 items); B. Activities of daily living (ADL, 7 items); and C. Complications (4 items). Each item scores from 0 (normal) to 3 (severe), the total score running from 0 to 75 (Marinus *et al*., 2004; Martinez-Martin *et al*., 2005).
2. The Non-Motor Symptoms Scale (NMSS), a 30-item scale with nine domains: cardiovascular (2 items), sleep/fatigue (4 items), mood/apathy (6 items), perceptual problems/hallucinations (3 items), attention/memory (3 items), gastrointestinal tract (3 items), urinary function (3 items), sexual function (2 items), and miscellaneous (4 items). Each item scores from 0 to 12 (severity, 0 to 3, multiplied by frequency, 1 to 4) and the theoretical NMSS total score vary from 0 to 360 (Chaudhuri *et al*., 2007; Martinez-Martin *et al*., 2009a), a Fig. representing the non-motor “symptomatic burden” (NMSB).
3. The original Hoehn and Yahr (HY) (Hoehn and Yahr, 1967).
4. The Clinical Impression of Severity Index for PD (CISI-PD), a global evaluation of motor signs; disability; motor complications; and cognitive status. Items are rated from 0, normal, to 6, very severe, the total score running from 0 to 24 (Martinez-Martin *et al*., 2006; Martinez-Martin *et al*., 2009b).

## Ethical aspects

The NMSS validation study received ethical approval from Carlos III Institute of Health, Madrid, Spain and local research ethics committees (Martinez-Martin *et al*., 2009a). The NILS is included in UK Department of Health portfolio of approved studies (UK CRN portfolio Nr. 10084) and has been approved in all relevant institutions and respective local EC/IRB of the participant researchers. Patients signed their informed consent before inclusion.

## Data analysis

Descriptive statistics (central tendency and dispersion, percentages) were applied to inform on the main characteristics of the sample. SCOPA-Motor Examination items were grouped for obtaining an estimation of the PD cardinal features scores: tremor (sum of items 1 and 2); bradykinesia (item 3); rigidity (item 4); and axial (sum of items 5 to 10). **Also include motor complications**

Out of the 951 patients in the study, we used listwise deletion to exclude 47 patients due to missing measurements in the variables of interest, resulting in 904 remaining patients. All variables were standardized before clustering, and unstandardized afterwards for interpretation. Analyses were conducted in R version 3.2.4 (www.r-project.org) and Stata version 14(http://www.stata.com/)**.**

## Cluster analysis

*k*-means was used for cluster analysis. We performed two analyses on the patients in the dataset: the first clustering on the nine aggregate non-motor symptom domains and the five cardinal motor signs (bradykinesia, rigidity, tremor, axial, and motor complications), henceforth the “domains clustering”, and the second on the 30 individual non-motor symptoms only, henceforth the “symptoms clustering”. Average-linkage hierarchical agglomerative clustering (UPGMA) on the 30 non-motor symptoms and 5 motor signs was also performed to observe how the symptoms group together.

## Determining *k*

Various formal measures were used to determine the optimal number of clusters for the dataset. For the domains clustering, the optimal according to the Gap Statistic and the 1-standard-error method suggested by Tibshirani *et al*.(2001) was (Supplementary Fig. 1a). Other cluster determination methods (within sum of squares error scree plot, minimum average silhouette width) suggested where simply divided the data uninformatively into groups with varying levels of overall PD severity. Thus was selected to offer a good blend of model fit, informativeness, and parsimony. The same method was applied for the symptoms clustering, and the optimal numbe r of clusters indicated was (Supplementary Fig. 1b). was tried to compare results to the domains clustering, but results were not interpretable.

## Interpretation

For the domains clustering, we displayed the distribution of each domain for the four clusters using boxplots, which allowed us to visualize the center and spread of each cluster. Since the number of variables was substantially larger for the symptoms clustering, we visualized results for the second analysis with a heatmap. Finally, for the hierarchical clustering on the symptoms themselves, we displayed results in a dendrogram and clustered the symptoms into six interpretable clusters.

For each variable in both clusterings, we used one-way ANOVA and tests to respectively check the equality of variable means and proportions across the clusters found, using Bonferroni correction for multiple testing with corrected *p*-value considered significant. Differences among pairwise clusters were tested post-hoc using Tukey’s range test for continuous means, or pairwise tests for proportions, with Bonferroni correction both for the within-variable pairwise tests and the multiple variable comparisons.

To compare the clusterings, we depicted cluster alignment with a contingency table, and computed the adjusted rand index (ARI; Hubert and Arabie, 1985) and *v*-measure (Rosenberg and Hirschberg, 2007), to evaluate similarity between the two clusterings. Both measures range from 0 (no similarity) to 1 (identical), and respectively take a contingency table-based and information-theoretic approach to measuring clustering similarity.

Lastly, to explore the relationship between symptom/domain severity and disease duration, we computed the correlation coefficient for each variable with PD duration and fitted smoothed loess curves to the data both globally and for each cluster found in the domains clustering.

# Results

**Include sample description.** There were not significant differences between the included and excluded groups in regard to sex, PD duration, and HY (), being difference in age in the limit of statistical significance **??** ( vs. ; Mann-Whitney, ). The characteristics of the sample included for analysis () are displayed in Table 1. Patients were predominantly males (62.17%). 13.38% were in HY stage 1; 43.36% in stage 2; 29.65% in stage 3; 11.50% in stage 4; and 2.10% in stage 5.

Table 1. Description of the sample.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Mean | SD | Median | Range |
| Age at study | 64.28 | 9.86 | 65 | 34 – 89 |
| Age at onset of Parkinson’s disease (PD onset) | 56.27 | 10.72 | 57 | 25 – 89 |
| Duration of the disease (PD duration) | 8.01 | 5.80 | 7 | 0 – 40 |
|  |  |  |  |  |
|  |  |  |  |  |
| Non-Motor Symptoms Scale total score | 50.45 | 41.72 | 39 | 0 – 225 |
| Cardiovascular  Sleep/Fatigue  Mood/Apathy  Perceptual problems/Hallucinations  Attention/Memory  Gastrointestinal  Urinary  Sexual function  Miscellaneous | 1.74  8.76  8.67  1.64  5.40  5.53  8.07  3.53  7.12 | 3.26  8.71  11.54  3.86  7.42  6.78  8.93  5.98  7.78 | 0  6  4  0  2  3  5  0  4 | 0 – 24  0 – 48  0 – 60  0 – 33  0 – 36  0 – 36  0 – 36  0 – 24  0 – 48 |
| Cardinal features \*  Tremor  Bradykinesia  Rigidity  Axial | 2.59  2.40  2.23  3.25 | 2.58  1.41  1.36  2.67 | 2  2  2  3 | 0 – 12  0 – 6  0 – 6  0 – 12 |
| SCOPA-Motor Total score | 21.07 | 12.06 | 19 | 1 – 72 |
| A. Examination  B. Activities of daily living  C. Complications | 11.54  6.80  2.73 | 6.56  4.19  3.01 | 10  7  2 | 0 – 41  0 – 21  0 – 12 |
| ­­­­Clinical Impression of Severity Index | 8.29 | 4.61 | 8 | 0 – 24 |
| SD: Standard deviation. SCOPA: Scales for Outcomes in Parkinson’s Disease.  \* Scores derived from items of the SCOPA-Motor A. Examination. | | | | |

## Domains clustering

Results from the clustering on the nine non-motor domains and the five cardinal motor signs, as well as additional variables not used in the analysis, are reported in Table 2, with boxplots in Fig. 1. Cluster means for all variables were found to be statistically different except for PD onset and sex ( after correcting for the comparisons of the 19 variables). Specific pairwise differences are noted in the table.

Cluster 1 () patients were mildly affected in all domains. This cluster was characterized by relatively lower disease durations and ages.

Cluster 2 () patients were severely affected in non-motor domains but mildly affected in motor domains. This cluster had a severity of motor variables relatively similar to the cluster 1 (mild) subtype especially in tremor, but generally expressed significantly higher scores for non-motor domains than clusters 1 and 3, especially in the sleep/fatigue, mood/apathy and miscellaneous domains. In motor complications uniquely, scores were not statistically different from cluster 3.

Cluster 3 () patients were severely affected in motor domains but mildly affected in non-motor domains. Mean motor scores were greater than the means of clusters 1 and 2, with the exception of motor complications. Additionally, mean motor scores were less than 4, with the exception of tremor, which was especially high. Importantly, CISI scores of clusters 2 and 3 were not statistically significantly different, and no differences were observed in cluster 2 and cluster 3 age or PD duration.

Cluster 4 () patients were severely affected in all domains, having the greatest symptom mean out of all four clusters with the exception of tremor. Consequently, patients in Cluster 4 had the longest average PD duration and oldest ages, but did not have a significantly different age of PD onset.

Table 2. Domains clustering summary. Unless otherwise specified, statistics are reported as mean (sd).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Cluster | 1 | 2 | 3 | 4 |
|  | *n* (%) | 428 (47%) | 180 (20%) | 232 (26%) | 64 (7%) |
| Non-motor | 1. Cardiovascular | 0.7 (1.5)24 | 3.2 (3.7)134 | 1.1 (2.1)24 | 6.9 (6.4)123 |
| domains | 2. Sleep/fatigue | 4.5 (5.0)234 | 16 (8.7)134 | 7.5 (6.6)124 | 21.7 (9.7)123 |
|  | 3. Mood/apathy | 3.4 (4.8)234 | 19.2 (15.0)13 | 6.6 (8.0)124 | 21.7 (13.5)13 |
|  | 4. Perception/hallucination | 0.5 (1.7)24 | 2.7 (4.3)134 | 0.8 (1.8)24 | 9.7 (6.9)123 |
|  | 5. Attention/memory | 3.0 (4.5)24 | 10.5 (9.2)134 | 3.3 (4.4)24 | 14.5 (11.0)123 |
|  | 6. Gastrointestinal | 2.9 (4.1)234 | 8.5 (7.1)134 | 4.7 (5.3)124 | 17.4 (9.2)123 |
|  | 7. Urinary | 4.7 (6.2)24 | 14.0 (9.9)134 | 6.2 (6.7)24 | 20.3 (9.7)123 |
|  | 8. Sexual function | 1.7 (3.4)234 | 7.3 (7.8)13 | 2.4 (4.1)124 | 9.0 (9.9)13 |
|  | 9. Miscellaneous | 4.0 (4.8)234 | 13.2 (8.7)13 | 6.2 (6.8)124 | 14.5 (10.1)13 |
| Motor symptoms | Axial | 1.7 (1.5)234 | 3.6 (2.2)134 | 4.5 (2.3)124 | 8.2 (2.7)123 |
|  | Bradykinesia | 1.6 (0.9)234 | 2.2 (1.1)134 | 3.5 (1.0)124 | 4.5 (1.3)123 |
|  | Rigidity | 1.5 (0.9)234 | 1.8 (1.2)134 | 3.3 (1.0)124 | 4.2 (1.2)123 |
|  | Tremor | 2.0 (1.9)34 | 1.5 (1.8)34 | 4.1 (2.8)12 | 4.1 (4.1)12 |
|  | Motor complications | 1.4 (2.1)234 | 3.1 (2.9)14 | 3.7 (2.9)14 | 7.0 (3.6)123 |
| Variables not | Sex (% male) | 64 | 54 | 67 | 58 |
| used in analysis | CISI-PD total | 5.5 (3.0)234 | 9.6 (3.8)14 | 10.1 (3.5)14 | 16.4 (4.6)123 |
|  | Age | 62.5 (9.7)4 | 65.2 (9.4)4 | 64.9 (10.1)4 | 71.1 (7.9)123 |
|  | PD onset | 56 (10.5) | 56.6 (10.6) | 56.3 (11.3) | 56.7 (10.6) |
|  | PD duration | 6.5 (4.7)234 | 8.6 (5.7)14 | 8.6 (5.7)14 | 14.4 (8.0)123 |
| 1 Significant difference with cluster 1 (corrected )  2 Significant difference with cluster 2 (corrected )  3 Significant difference with cluster 3 (corrected )  4 Significant difference with cluster 4 (corrected ) | | | | | |

## Symptoms clustering

*k*-means performed on the 30 individual non-motor symptoms found 6 clusters, which were subsequently ordered according to increasing CISI-PD score (Table 3, heatmap in Fig. 2). Means of all symptoms were found to differ across clusters except for PD onset, sex, and tremor, with pairwise differences again noted in the table.

Cluster 1 (), the largest cluster representing 50% of the group, was similar to domains cluster 1, and was composed of patients relatively mildly affected in all domains. Cluster 2 () had higher mean symptom scores than Cluster 1’s in several cases, including restless legs syndrome (RLS), swallowing, and the miscellaneous domain, but could nonetheless be classified as a relatively average cluster.

Although clusters 3–6 increased in motor and overall PD severity, they varied significantly in their non-motor expression and generally expressed a specific set of non-motor symptoms unique to the cluster. These characterizing groups of non-motor symptoms aligned well with the established non-motor domains. Cluster 3 () was dominated by domain 7 (urinary), while cluster 4 () was affected severely in domain 3 (mood/apathy). Cluster 5 () was affected in most non-motor symptoms but especially in domain 5 (attention/memory). Similarly, cluster 6 () was also affected across non-motor symptoms, but was most severely affected in domains 1 (cardiovascular), 4 (perception/hallucination), and 6 (gastrointestinal). Overall, the symptoms clustering appeared to fragment several of the domains clusters into smaller groups, as demonstrated in the next section.

Table 3. Symptoms clustering summary. Unless otherwise specified, statistics are reported as mean (sd).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | Cluster | 1 | 2 | 3 | 4 | 5 | 6 |
|  | *n* (%) | 456 (50%) | 201 (22%) | 100 (11%) | 73 (8%) | 54 (6%) | 20 (2%) |
| 1. | Lightheadedness | 0.5 (1.1)23456 | 1.7 (2.5)156 | 2.5 (3.4)16 | 1.9 (2.5)16 | 3.3 (3.7)126 | 7.7 (3.6)12345 |
| Cardiovascular | Fainting | 0.1 (0.6)6 | 0.3 (1)6 | 0.1 (0.5)6 | 0.5 (1.2)6 | 0.1 (0.5)6 | 6.3 (2.9)12345 |
| 2. Sleep/ | Drowsiness | 0.9 (1.8)23456 | 2.4 (2.9)156 | 2.3 (2.9)156 | 2.2 (3)156 | 6.6 (4.2)1234 | 5.2 (3)1234 |
| fatigue | Fatigue | 1.2 (1.9)23456 | 4.2 (3.7)145 | 4.5 (4)15 | 5.9 (4.2)12 | 8 (3.5)123 | 6.9 (3.1)1 |
|  | Insomnia | 1.1 (2.2)23456 | 3 (3.8)14 | 3.1 (4.2)14 | 5.3 (4.8)123 | 4.7 (4.8)1 | 5 (2.4)1 |
|  | RLS | 0.5 (1.3)2456 | 2.4 (3.5)136 | 1 (2.4)256 | 1.8 (3.2)16 | 3.2 (4.2)13 | 4.9 (2.6)1234 |
| 3. Mood/ | Loss interest | 0.4 (0.9)2456 | 1.1 (1.8)1456 | 0.6 (1.3)456 | 6.6 (3.9)1235 | 4.5 (3.7)1234 | 5.3 (2.8)123 |
| apathy | Loss activities | 0.6 (1.3)2456 | 1.9 (2.7)1456 | 1 (2)456 | 7.8 (3.5)12356 | 6 (4.5)1234 | 4.7 (2.9)1234 |
|  | Anxiety | 0.8 (1.6)2456 | 2.2 (2.9)1456 | 1.6 (2.9)456 | 5.8 (4.3)123 | 6.4 (4.4)123 | 4.7 (3)123 |
|  | Depression | 0.7 (1.4)2456 | 2.7 (3.2)13456 | 1.4 (2.3)2456 | 7.4 (4)123 | 5.8 (4.3)123 | 5.3 (3.2)123 |
|  | Flat affect | 0.3 (1)2456 | 1.1 (2.1)145 | 0.8 (2.1)456 | 4.8 (4.3)1235 | 2.9 (3.7)1234 | 3 (2.1)13 |
|  | Loss pleasure | 0.3 (1.1)456 | 1 (1.8)456 | 0.8 (1.8)456 | 7.3 (3.8)12356 | 4.6 (4.2)1234 | 3.6 (2.8)1234 |
| 4. Perception/ | Hallucination | 0.2 (0.9)56 | 0.6 (1.7)56 | 0.7 (1.9)56 | 0.6 (1.8)56 | 2.7 (3.3)12346 | 4.8 (3.3)12345 |
| hallucination | Delusion | 0.1 (0.6)456 | 0.3 (1.4)456 | 0.1 (0.6)456 | 1.3 (3)1236 | 2 (3.5)1236 | 4.7 (3.4)12345 |
|  | Diplopia | 0.2 (0.8)56 | 0.6 (1.4)56 | 0.4 (1.6)56 | 0.8 (2.2)56 | 3.1 (4.4)1234 | 3.6 (2.7)1234 |
| 5. Attention/ | Loss concentration | 0.7 (1.5)23456 | 2.6 (2.9)156 | 2.2 (3.4)156 | 2.9 (2.9)15 | 7.5 (3.9)1234 | 5.1 (2.8)123 |
| memory | Forget explicit | 0.7 (1.3)23456 | 2.2 (2.7)156 | 2.2 (3)156 | 2.1 (2.5)156 | 8.5 (3.2)12346 | 4.8 (2.9)12345 |
|  | Forget implicit | 0.5 (1.2)23456 | 1.9 (2.6)156 | 1.5 (2.7)156 | 1.8 (2.2)156 | 7.6 (4.1)12346 | 5.1 (3.2)12345 |
| 6. | Drooling | 0.6 (1.5)23456 | 2.3 (3.3)156 | 3.3 (4.1)16 | 3.3 (4.2)16 | 4.2 (4.8)12 | 6.2 (3.3)1234 |
| Gastrointestinal | Swallowing | 0.3 (0.8)2356 | 2 (3)16 | 1.2 (2)16 | 1.2 (2)6 | 2.3 (2.9)16 | 6.5 (4.2)12345 |
|  | Constipation | 1.5 (2.7)23456 | 3 (3.8)16 | 3.8 (4.4)16 | 3.7 (4.4)16 | 4.5 (4.9)16 | 8.8 (4.4)12345 |
| 7. Urinary | Urinary urgency | 0.9 (1.7)23456 | 1.8 (2.4)1356 | 6.6 (3.8)124 | 2.4 (3.4)1356 | 7.7 (4.3)124 | 6.2 (3.5)124 |
|  | Urinary frequency | 0.9 (1.8)3456 | 1.3 (1.9)3456 | 7.7 (3.5)124 | 3.1 (3.6)12356 | 6.2 (4.5)124 | 6.7 (3.1)124 |
|  | Nocturia | 1.7 (2.3)3456 | 2.6 (2.9)3456 | 8.5 (3.5)124 | 4.6 (4.2)1235 | 6.9 (4.4)124 | 7.1 (3.4)12 |
| 8. Sexual | Sex drive | 0.7 (1.7)23456 | 1.9 (3.4)15 | 3 (4.1)15 | 3.6 (4.4)15 | 6 (5.3)1234 | 3.9 (5.3)1 |
|  | Sex dysfunction | 0.7 (2)3456 | 1.8 (3.3)35 | 3.4 (4.3)12 | 2.3 (4.2)15 | 5 (5.2)124 | 3.8 (5.6)1 |
| 9. | Unexplained pain | 0.7 (1.8)23456 | 2.6 (3.9)1 | 2.4 (4)1 | 2.3 (3.6)1 | 4.3 (5)1 | 4.3 (2.2)1 |
| Miscellaneous | Gustation/olfaction | 1.2 (2.5)2456 | 4 (4.2)1 | 2.5 (3.6) | 3 (3.9)1 | 4 (4.7)1 | 5.5 (4.7)1 |
|  | Weight change | 0.8 (1.4)2456 | 1.9 (3.1)15 | 1.8 (3)5 | 2.1 (2.8)1 | 3.6 (4.3)123 | 4 (3.9)1 |
|  | Sweating | 0.6 (1.6)23456 | 2.5 (3.9)1 | 2.4 (3.9)1 | 2.1 (3.6)1 | 2.8 (3.9)1 | 3.9 (3.4)1 |
| Motor | Axial | 2.3 (2)23456 | 3.5 (2.6)156 | 4 (2.8)16 | 4.4 (2.7)16 | 5.3 (3.3)126 | 8.5 (2.3)12345 |
| symptoms | Bradykinesia | 2.1 (1.2)456 | 2.5 (1.4)6 | 2.5 (1.4)6 | 2.9 (1.4)16 | 3 (1.6)16 | 4.5 (1.7)12345 |
|  | Rigidity | 2 (1.2)6 | 2.3 (1.5)6 | 2.3 (1.4)6 | 2.5 (1.3)6 | 2.6 (1.5)6 | 4.7 (1)12345 |
|  | Tremor | 2.6 (2.4)6 | 2.5 (2.4)6 | 2.1 (2.5)6 | 2.5 (2.6)6 | 2.4 (2.8)6 | 5.8 (5.3)12345 |
|  | Motor comp | 1.9 (2.5)2456 | 3.5 (3)16 | 2.7 (2.7)6 | 3.7 (3.3)16 | 3.9 (3.7)16 | 8 (3.7)12345 |
| Variables not | Sex | 67 | 57 | 64 | 49 | 63 | 50 |
| used in analysis | CISI PD total | 6.4 (3.5)23456 | 9.3 (4.1)156 | 9.4 (4.1)16 | 10.7 (4.6)16 | 11.8 (5.5)126 | 18.4 (4.2)12345 |
|  | Age | 62.8 (10)356 | 63.8 (10)5 | 68.3 (7.5)1 | 63.1 (9.2) | 69.7 (9.2)12 | 72.1 (7.7)1 |
|  | PD onset | 56.2 (10.8) | 55 (10.7) | 58.2 (10) | 54.8 (10.3) | 58.8 (11.7) | 59.2 (8.6) |
|  | PD duration | 6.6 (4.8)2356 | 8.8 (5.9)1 | 10.1 (6.7)1 | 8.3 (4.9) | 11 (8.5)1 | 12.8 (6.5)1 |
| *n* Significant difference with cluster *n* (corrected ) | | | | | | | |

## Comparison between clusterings

The two clusterings were not very similar (). To help compare the alignment of the two clusterings, we denoted the four clusters in the domains clustering as , and the clusters in the symptoms clustering as . Alignment of the clusters is visualized in Table 4. For the domains clustering, patients in clusters mildly affected in non-motor domains () were correspondingly distributed among the milder symptoms clusters ( skewed left). Conversely, patients in clusters with severe non-motor symptoms () were split among the various specific non-motor-dominant clusters (), evidence that the symptoms clustering found more specific disease clusters than the domains clustering.

For the symptoms clustering, clusters were composed of an overlapping mixture of patients from all for domains clusters , likely due to the ambiguity of clustering patients without regards to their motor variables. However, divided patients perfectly into (mild) and (motor-dominant), while and divided patients perfectly into (nonmotor-dominant) and (severe), representing strong agreement between the clusterings at the ends of the PD severity continuum.

Table 4. Contingency table describing cross-categorization of individuals in the domains and symptoms clusters.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Symptoms clusters | | | | | | |  |
| Domains clusters |  |  |  |  |  |  |  | Total |
|  | 335 | 64 | 26 | 3 | 0 | 0 | 428 |
|  | 0 | 54 | 46 | 49 | 31 | 0 | 180 |
|  | 121 | 77 | 22 | 12 | 0 | 0 | 232 |
|  | 0 | 6 | 6 | 9 | 23 | 20 | 64 |
| Total | | 456 | 201 | 100 | 73 | 54 | 20 |  |

## Hierarchical clustering on symptoms

Hierarchical clustering on the 30 non-motor symptoms and the four cardinal motor signs produced the dendrogram in Fig. 3. Predictably, symptoms in the same non-motor domains tended to cluster together, with some notable exceptions. Diplopia (domain 4) was grouped away from other perception/hallucination symptoms, instead categorized loosely with domain 8 (sexual). RLS (domain 2) was grouped with domain 9 (miscellaneous) symptoms, albeit at a very high point on the tree, indicating a high dissimilarity. Similarly, drowsiness (domain 2) was grouped with the attention/memory symptoms of domain 5. Notably, tremor was the most dissimilar symptom, occupying a single branch at the top of the tree.

## Correlation analysis

Due to high variance, most variables had little to no correlation with PD duration (Supplementary Fig. 2). Variables with the highest correlation near 0.5 included symptoms urinary frequency, swallowing, and drooling; domains 9 (miscellaneous), 7 (urinary), and 6 (gastrointestinal); axial and motor complications; and total CISI-PD score. Scatterplots for CISI Total, Tremor, Anxiety, and Depression appear in Supplementary Fig. 3.

# Discussion

The domains clustering reveals clusters that confirm previous findings in the field, mainly van Rooden *et al*. and the identification of four subtypes of Parkinson’s disease: mild, non-motor-dominant, motor-dominant, and severe. van Rooden’s work was conducted with a separate dataset using different rating scales and modeling methods (expectation-maximization), and this investigation independently confirms these subtype classifications. Unlike van Rooden, mean disease durations differences do exist between subtypes 1 (mild) and 4 (severe), likely due to further development of the disease, although the differences between 2 and 3 (non-motor/motor-dominant) subtypes are insignificant (Table 2), importantly suggesting different developmental paths of the disease.

Overall, little information was found in PD onset, PD duration, or current age. Mean ages were similar for domains clusters 1, 2, and 3, but different from the severe cluster 4, intuitively since cluster 4 represented a more advanced stage of the disease. Specifically, clusters 1 and 4 seemed to be phenotypically quite similar, except at different stages of disease progression, given cluster 4’s higher ages and disease durations.

However, clusters 2 and 3 clearly showed different disease progression, one in the motor direction, and one in the non-motor. Both groups have similar age, PD onset, and PD duration scores, as well as similar overall PD severity as rated by the CISI-PD scale, but differed significantly in their symptomatic expression expression. Cluster 2 was dominated by a high severity of non-motor domains, especially Sleep/fatigue, Mood/apathy, Urinary, and Miscellaneous. Cluster 3, however, was dominated by a high prevalence of motor symptoms, where most non-motor symptoms were similar to the mild cluster 1. Of note is that the tremor population mean was the highest cluster mean, even higher than the severe subtype 4. This motor-dominant cluster may thus overlap with Ma *et al*.’s tremor dominant/slow progression cluster.

Generally, given stable PD onset scores and predictably increasing PD duration scores for clusters 1 and 4, Ma *et al*.’s rapid disease progression/late onset and tremor dominant/slow progression clusters were mostly not found in this dataset, save for the tremor-dominant motor cluster.

Our symptoms clustering found 6 clusters which demonstrate the variability in the non-motor-dominant domains clusters. TODO… It’s intuitive that a Depression-Dominant group emerges from the symptoms clustering, since the Mood/apathy domain consists of 5 separate measures. Thus, any high expression of depressive symptoms is magnified in clustering, since the symptoms are highly similar (Fig. 3) and treated with equal weight. Once again reinforcing what was discovered previously, depressive symptoms have been shown to be very important in determining subtypes of PD.

Our correlation analysis gives more insight into the clusters found in the previous analyses. Due to the large variability in PD severity throughout the PD duration continuum, most symptoms are uncorrelated with PD duration (Supplementary Fig. 2), especially Mood/apathy symptoms (anxiety, depression) and tremor. The differences in disease progression for each cluster can be seen by the corresponding graphs in Supplementary Fig. 3. Cluster 2 (non-motor-dominant) starts at higher scores for anxiety and depression, and actually decreases with increasing PD duration, thus indicating that these patients’ subtype can be determined early after PD onset from the depressive symptom score. Similarly, when examining cluster 3 (motor-dominant), the mean tremor score is substantially higher from PD onset. Interestingly, cluster 4 (severe) generally starts at lower tremor and motor scores during disease, but then rises sharply, exceeding other clusters. More evidence that tremor is a unique motor symptom is located in Fig. 3, where it is the most distant symptom from all other symptoms.

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# Supplementary material

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# Figure Legends

Figure 1. **Domains clustering boxplots.** Boxplots for domains clustering for each symptom and cluster.

Figure 2. **Symptoms clustering heatmap.** Heatmapof symptoms for each cluster, separated by white lines according to motor symptoms, non-motor domains, and variables not included in the analysis.Since symptoms have different scales, cluster means for each symptom are displayed as standardized scores relative to each overall symptom mean.

Figure 3. **Hierarchical clustering on symptoms.** Average-linkage hierarchical clustering of motor (blue) and non-motor (black) symptoms. Symptoms are labeled with their name and corresponding domain number. The dendrogram is colored with 5 clusters.

Supplementary Figure 1. **Gap statistics.** Plot of the gap statistic versus number of clusters with k-means on 500 bootstrapped samples of a) the domains clustering, and b) the symptoms clustering. Error bars represent standard error (). Per the method described in Tibshirani *et al*. (2001), the optimal number of clusters is the smallest k such that For the domains clustering, ; for the symptoms clustering, . The gap statistic for the optimal and the benchmark for are marked with dotted lines.

Supplementary Figure 2. **Correlation with PD duration.** Correlation of applicable variables with PD duration. PD onset has a negative correlation with PD duration but is excluded since it provides no information about PD progression.

Supplementary Figure 3. **Symptoms against PD duration.** For clarity, scatterplot points are colored according to cluster and jittered slightly. Smoothed loess curves for each cluster are drawn in their respective cluster colors. The black curve is the curve for the entire population, and the global mean score is marked with a dotted line.