Parkinson's disease subtypes identified from cluster analysis of motor and non-motor symptoms

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Abstract

Objective: To search for subtypes of Parkinson's disease (PD) using both a combination of cardinal motor features and non-motor symptoms, and non-motor symptoms only.

Methods: Two independent international cohort studies were used: (a) the validation study of the Non-Motor Symptoms Scale ($n = 411$) (Martinez-Martin et al., 2009a) and (b) baseline data from the global Non-Motor International Longitudinal Study ($n = 540$) (Ray Chaudhuri et al., 2013). *k*-means cluster analyses were performed on the non-motor and motor domains (domains clustering) and the 30 individual non-motor symptoms alone (symptoms clustering), and average-linkage hierarchical agglomerative clustering was performed to group symptoms together.

Results: Four clusters are identified from the domains clustering supporting previous studies: mild, non-motor dominant, motor-dominant, and severe. In addition, six new smaller clusters are identified from the symptoms clustering, each characterized by clinically-relevant non-motor symptoms.

Conclusions: The clusters identified in this study present statistical confirmation of the increasingly important role of non-motor symptoms in PD heterogeneity.

Introduction

Parkinson's disease (PD) is classically considered a motor disorder, with resting tremor, rigidity, and bradykinesia as its core features. However, the concept of PD has changed considerably in the last few years, now prompting a revision of its diagnostic criteria to include non-motor symptoms (NMS).[1,2] There has been growing recognition that NMS are caused by multi neurotransmitter pathway dysfunction, which involves both the central and peripheral nervous system.[3,4] The significant clinical heterogeneity of NMS in PD suggests the existence of specific non-motor subtypes.[1,9]

Previous cluster analyses have already identified motor- and non-motor-based clusters in PD patients.[5-8] Recently, it has been argued that the recent concept of non-motor endophenotypes of PD provides a stronger basis for subtyping, since these relate to the central pathophysiology of specific neurotransmitter systems and are therefore likely to remain stable over time.[1] As such, several studies have explored PD subtypes while considering motor subtypes and their association with non-motor aspects of the disease such as psychopathology and cognition,[10-14] REM sleep behavior disorder,[15] and visual daily activities.[16] To our knowledge, however, no studies have used cluster analysis techniques to examine subtypes present in NMS only.

This study was aimed at using cluster analysis techniques to search for PD subtypes from a large, multi-centre, international, and well-characterized cohort of patients across all stages, using a combination of motor cardinal features (bradykinesia, rigidity, tremor, axial signs) and comprehensive NMS assessed using specific validated rater-based scales. We believe this is the largest study of its size with these characteristics, and the first to focus on exclusively NMS-based phenotyping.

Materials and Methods

Design

Data from two independent international studies were used: the validation study of the Non-Motor Symptoms Scale (NMSS) ($n = 411$)[17] and baseline data from the global Non-Motor International Longitudinal Study (NILS) ($n = 540$).[18] NILS has been adopted as a national study by the National Institute of Health Research in the UK (UKCRN No: 10084) and is a 5-year follow-up study addressing the range, nature, and natural history of NMS in PD across all motor stages. All data in NILS are anonymised and entered into a secure database at the National Center of Epidemiology, Carlos III Institute of Health (Madrid, Spain).

Patients

PD patients diagnosed according to internationally recognized criteria[19-20] across all disease stages were included. For the NMSS study, patients were 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 with the assessment of PD; and inability to give informed consent. Patient recruitment was carried out across 15 countries in America, Asia, and Europe from 2007 to 2011.

Assessments

For all patients, 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 scale with three dimensions: A. Examination (10 items); B. Activities of daily living (7 items); and C. Complications (4 items). Each item scores from 0 (normal) to 3 (severe), the total score running from 0 to 75. This scale was derived from the Unified Parkinson's Disease Rating Scale and showed high correlation with the original scale ($r > 0.85$) and satisfactory clinimetric attributes in validation studies.[21,22]
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 total NMSS score varies from 0 to 360,[17,23] a value representing the total non-motor "symptomatic burden".

3. The Hoehn and Yahr (HY) scale.[24]
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 ranging from 0 to 24.[25,26]

Standard Protocol Approvals, Registrations, and Patient Consents

The NMSS validation study received ethical approval from the Carlos III Institute of Health, Madrid, Spain and local research ethics committees.[17] The NILS is included in the UK Department of Health portfolio of approved studies (UK CRN portfolio Nr. 10084) and has been approved at all relevant institutions and corresponding ethics committees/institutional review boards. Patients signed their informed consent before inclusion.

Statistical analysis

SCOPA-Motor examination items were aggregated to obtain four "cardinal motor signs": tremor (items 1 and 2), bradykinesia (item 3), rigidity (item 4), and axial signs (items 5 to 10). Additionally, an aggregate "motor complications" variable was obtained from the sum of items 18 to 21. 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 data: the first clustering on the nine aggregate non-motor symptom domains, the four cardinal motor signs (tremor, bradykinesia, rigidity, axial), and motor complications, henceforth the "domains clustering", and the second on the 30 individual non-motor symptoms of the NMSS only, henceforth the "symptoms clustering". Average-linkage hierarchical agglomerative clustering on the 30 non-motor symptoms, 4 motor signs, and motor complications was also performed to observe the grouping of the variables.

Various formal measures were used to determine the optimal number of clusters for the dataset. For the domains clustering, the optimal k according to the Gap Statistic and the 1-standard-error method[27] was $k = 4$ (Figure e-1A). Other cluster determination methods suggested $k = 2, 3, 4$, where $k = 2, 3$ simply divided the data uninformatively into groups with varying levels of overall disease severity. Thus $k = 4$ was selected to offer a good combination of model fit and parsimony. The same method was applied for the symptoms clustering, where the number of clusters was $k = 6$ (Figure e-1B).

Comparative subgroup analysis

For each variable in both clusterings, we used one-way ANOVA and χ^2 tests to respectively check the equality of variable means and proportions across the clusters found, using Bonferroni correction for multiple testing with corrected $p < 0.05$ considered significant. Differences among pairwise clusters were tested post-hoc using Tukey's range test for continuous means, or pairwise χ^2 tests for proportions, with Bonferroni correction both for the within-variable pairwise tests and the multiple variable comparisons.

To compare the domains and symptoms clusterings, we depicted cluster alignment with a contingency table, and computed the adjusted rand index (ARI)[28] to evaluate similarity between the two clusterings.

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

Results

Study sample

Out of the 951 patients in the study, we used listwise deletion to exclude 47 patients due to missing measurements, resulting in 904 remaining patients. There were no significant differences between the included and excluded groups with respect to age, sex, disease duration, and HY ($\chi^2 \geq 0.19$). The characteristics of the sample included for analysis ($n = 904$) are displayed in Table e-1. Patients were predominantly male (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.

Domains clustering

Results from the k-means clustering on the nine non-motor domains, the four cardinal motor signs, and motor complications are reported in Table 1 along with additional variables not used in the analysis (heatmap in Figure 1; boxplots in Figure e-2). Cluster means for all variables were found to be statistically different except for age at disease onset and sex (adjusted $p < 0.05$). Specific pairwise differences are noted in the table.

Cluster 1 (D1, $n = 428$) patients were mildly affected in all domains. This cluster was characterized by relatively lower disease durations and ages.

Cluster 2 (D2, $n = 180$) 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 expressed significantly higher scores for non-motor domains than clusters 1 and 3, especially in the sleep/fatigue, mood/apathy, urinary, and miscellaneous domains. In motor complications uniquely, scores were not statistically different from cluster 3.

Cluster 3 (D3, $n = 232$) 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-PD scores of clusters 2 and 3 were not statistically significantly different, and no differences were observed in cluster 2 and cluster 3 age or disease duration.

Cluster 4 (D4, $n = 64$) 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 disease duration and oldest ages, but did not have a significantly different age of disease onset.

Symptoms clustering

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

Cluster1 (S1, $n = 456$), the largest cluster representing 50% of the group, was similar to domains cluster 1, and was composed of patients relatively mildly affected in all NMS. Cluster 2 (S2, $n = 201$) 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 mild/moderate cluster.

Although clusters 3-6 increased in motor and overall disease severity, they varied significantly in their non-motor expression and expressed a unique set of NMS. These groups of non-motor symptoms aligned well with the established non-motor domains. Cluster 3 (S3, $n = 100$) mainly expressed domain 7 (urinary), while cluster 4 (S4, $n = 73$) was affected severely in domain 3 (mood/apathy). Cluster 5 (S5, $n = 54$) showed severe impact in most non-motor symptoms but especially in domain 5 (attention/memory). Similarly, cluster 6 (S6, $n = 20$) revealed severe effects across all non-motor symptoms and motor features, but was most severely affected in cardiovascular, perception/hallucination, and gastrointestinal NMSS domains. Overall, the symptoms clustering fragmented the domains clusters into smaller groups, as explored in the next section.

Comparison between clusterings

Alignment of the D and S clusters is visualized in Table 2. While S1 grouped patients from D1 (mild) and D3 (motor-dominant), and D4 (severe) showed a dominant contribution from S5 (severe non-motor) and S6 (severe motor and non-motor), the remaining clusters were fragmentarily distributed, as indicated by the low similarity between the clusterings ($ARI = 0.32$) For the domains clustering, patients in clusters mildly affected in non-motor domains (D1, D3) were distributed among the milder symptoms clusters (S1-S4, skewed left). Conversely, patients in clusters with severe non-motor symptoms (D2, D4) were split among the various specific non-motor-dominant clusters (S2-S6), suggesting that the symptoms clustering is clinically more precise than the domains clustering.

Hierarchical clustering on variables

Hierarchical clustering on the 30 non-motor symptoms and the four cardinal motor signs is depicted in Figure 3. Symptoms belonging to the same domain of the NMSS tended to cluster together, with some exceptions. Diplopia (domain 4) was grouped loosely with domain 8 (sexual) symptoms. RLS (domain 2) was grouped loosely with domain 9 (miscellaneous) symptoms. Similarly, drowsiness (domain 2) was grouped with domain 5 (attention/memory) symptoms. Notably, tremor was the most isolated symptom, occupying a single branch at the top of the tree.

Correlation analysis

Most variables had little to no correlation with disease duration (Figure e-3). Scatterplots for CISI Total, Tremor, Anxiety, and Depression appear in Figure e-4.

Discussion

We believe that this is the largest cluster analysis-based study of PD-related motor and non-motor symptoms from a large, international, multi-centre cohort. Previous cluster-analysis based studies have either focused on early/untreated Parkinson's disease[7,8] or lack detailed assessments based on the severity and frequency of non-motor domains and symptoms[5]. Additionally, we believe this is the first study to perform cluster analysis exclusively on NMS to reveal NMS-specific subtypes.

The domains clustering produced 4 clusters (Figure 1) which closely correspond with several previous studies,[5-8] especially those reported by van Rooden *et al*.[5] Both Clusters D1 (mild) and D4 (severe) are groups which are present in most PD studies, but unlike van Rooden, our data show that mean differences in disease duration do exist between mild and severe subtypes. Cluster D2 represents a non-motor dominant phenotype also described in many clinical phenotype-driven studies,[9] while Cluster D3 corresponds to the traditional motor-dominant view of PD. However, the high incidence of tremor in D3 (higher than D4) is interesting and appears to reflect not only the motor-dominant subtype of van Rooden but also the tremor-dominant/slow-progression cluster as described by Ma *et al*.[6]

From the symptoms clustering (Figure 2), six smaller clusters were identified. S1 was similar to D1. S2 to S6, while increasing in motor severity, expressed specific NMS, thus supporting the clinical concept of NMS-based subtyping. Cluster S2, with principal components including RLS, swallowing, pain, and others, may be a new finding from this study. Cluster S3, with significant urinary dysfunction, fits the descriptions by Erro *et al*.,[7] highlighting the relevance of this symptom as a specific marker in non-motor dominant clusters and disease progression. Cluster S4, characterized by high mood/apathy symptoms, is consistent with the sleep and apathy clinical phenotypes described by other studies.[9] Clusters S5 and S6 are of clinical interest, as in these clusters NMS are dominant, overshadowing motor symptoms with an emphasis on cognitive impairment in S5 and autonomic (cardiovascular and gastrointestinal) symptoms in S6. Overall, many of these subtypes are newly reported and their characteristics support clinical endophenotyping of non-motor subtypes not reported in previous studies.

The comparison between the domains and symptoms clustering shown in the contingency table (Table 2) suggests that the broader subset of S1, a mild non-motor dominant cluster, essentially expresses two NMS subtypes, one of them with motor symptoms. The low numbers observed in some cells do not allow consistent clinical interpretation. The dendrogram (Figure 3) indicates that the symptoms grouping in the NMSS dimensions works as expected, as most items in each domain group together.

Notable differences in disease progression for each cluster can be seen by the graphs in Figure e-4. NMS dominant cluster D2 starts at higher scores for anxiety and depression, and decreases with increasing disease duration, thus indicating that these patients' subtypes can be determined early after disease onset. Similar improvements in NMS and depression and anxiety scores have been reported recently in a 2-year follow-up study of an untreated PD cohort.[29]

What are the clinical implications of these clusterings? First, our analysis represents statistical conformation of NMS-dominant presentation of PD. The specific expression of several NMS domains such as mood/anxiety, sleep/fatigue, cognition, and urinary function suggests that these subgroups may have different patterns of neurodegeneration involving the brain's various non-dopaminergic pathways, possibly in excess of dopaminergic degeneration, as suggested by several authors.[3] Second, clinical recognition of subtypes using ad hoc criteria would allow for the development of truly subtype-specific treatment packages for PD.[1] Third, clinical characterisation of these groups will allow studies of natural history of specific subtypes.

Due to the data collection methods of the two studies used in this analysis, selection due to prevalence bias, i.e. overrepresentation at the study sample of patients with higher survival, would not likely explain this clustering. In contrast, clustering at clinical early stages might have been undermined by neglect of symptoms poorly recorded prior to diagnosis. The clinical non-specificity of D1, S1, D4, and S6, with extremely different disease duration and severity, contrasts with the identification of clinically characterized S3, S4, and S5, clusters with dominant expression of urinary, mood/apathy and attention/memory symptoms, respectively, at intermediate stages of the disease course. This pattern is in line with the notion of "phenotypic convergence" proposed by Warren *et al*.[30] as a key clinical feature of the spread of neurodegenerative disorders due to abnormal protein aggregates. The identified clusters may represent distinct footprints of large-scale network disintegration whose translation to clinical management is required.

Like any cohort-based, cluster-analysis driven study, there are several limitations of this analysis. First, we did not report a control group, although our intention was not to describe the symptoms as discriminant from normal subjects. Second, NMS profiles in advanced PD could also be influenced by patterns of dopaminergic therapy, particularly hallucinations and orthostatic problems. However, these symptoms did not emerge as key drivers of any of the domains identified in either of our clusterings. Conversely, our study has several notable strengths: (1) the sample size, which to our knowledge is the largest international sample in this kind of study; (2) inclusion of patients in all disease stages; and (3) the use of detailed assessments both for motor and non-motor symptoms.

In conclusion, we present statistical confirmation of the growing recognition of NMS-dominant presentation of PD and its heterogeneity. The specific expression of several NMS domains such as mood/anxiety, sleep/fatigue, cognition, and urinary function suggests differential patterns of neurodegeneration involving non-dopaminergic pathways, as suggested from neuropathology studies.[3] The clinical recognition of subtypes as reflected by the domains clusters could allow for treatments to be tailored and could be the beginning of subtype-specific treatment packages for PD.[1] In the future, clinical characterisation of these groups will allow for studies of natural history of the various non-motor dominant clusters identified in this paper. Translating results to clinical management or experimental designs would require the identification of inclusion and exclusion criteria of patients into specific subgroups.

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Tables

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

[1] Significant difference with cluster D1 (corrected $p < 0.05$)

[2] Significant difference with cluster D2 (corrected $p < 0.05$)

[3] Significant difference with cluster D3 (corrected $p < 0.05$)

[4] Significant difference with cluster D4 (corrected $p < 0.05$)

Table 2. Contingency table describing cross-categorization of individuals in the domains and symptoms clusters.

Domains clusters \ Symptoms clusters	S1	S2	S3	S4	S5	S6	Total
D1	335	64	26	3	0	0	428
D2	0	54	46	49	31	0	180
D3	121	77	22	12	0	0	232
D4	0	6	6	9	23	20	64
Total	456	201	100	73	54	20	

Figure legends

Figure 1. **Domains clustering heatmap**. Heatmap of variables for each cluster, separated by white lines according to 9 non-motor domains, 4 cardinal motor features, motor complications, and 4 variables not included in the analyses. Since symptoms have different scales, cluster means for each symptom are displayed as standardized scores relative to each overall symptom mean.

Figure 2. **Symptoms clustering heatmap**. Heatmap of variables for each cluster, separated by white lines according to 30 individual non-motor symptoms, 4 cardinal motor features, motor complications, and 4 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.

Supplemental legends

Table e-1. **Description of the sample.**

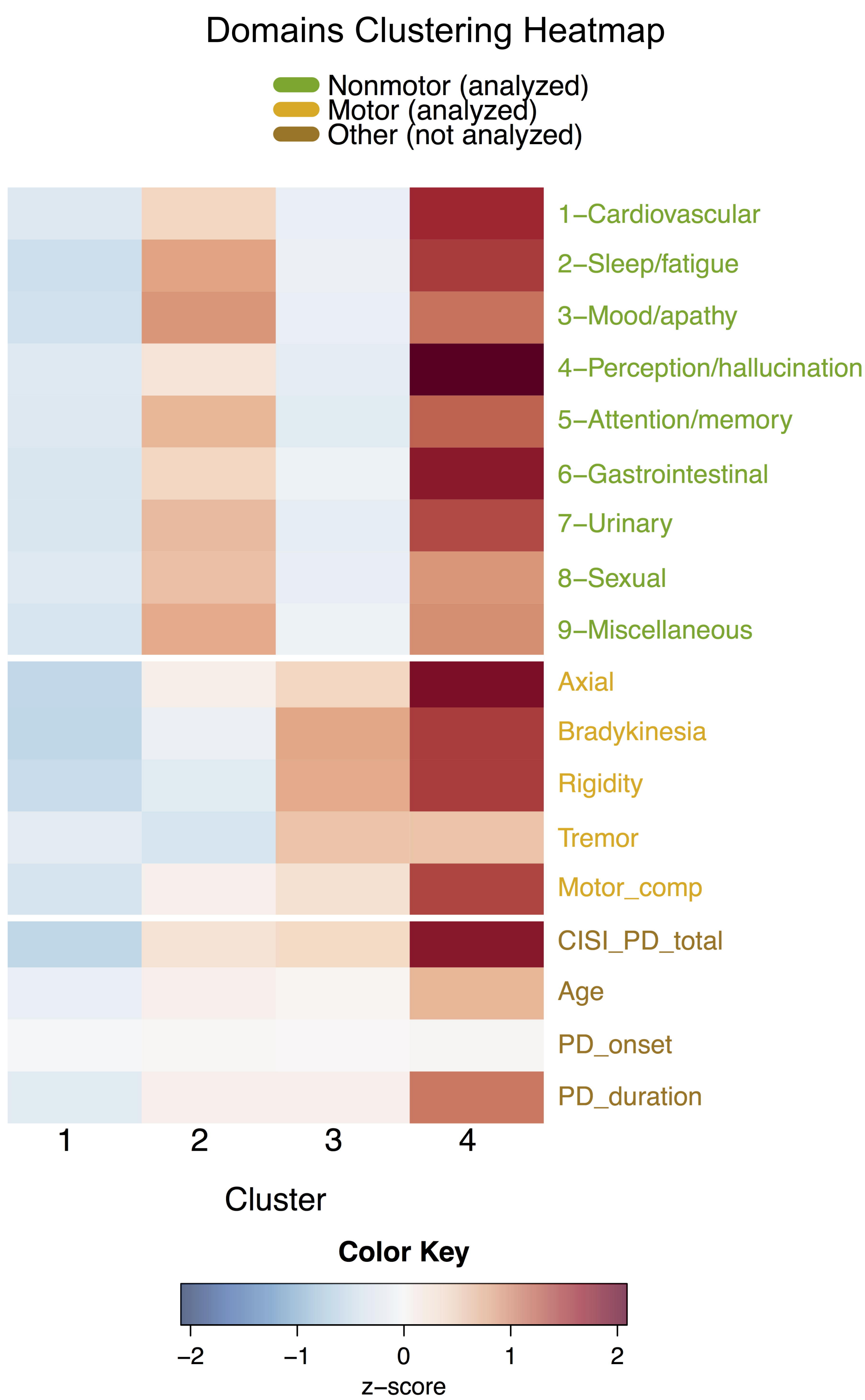
Table e-2. **Symptoms clustering summary.** Unless otherwise specified, statistics are reported as mean (sd).

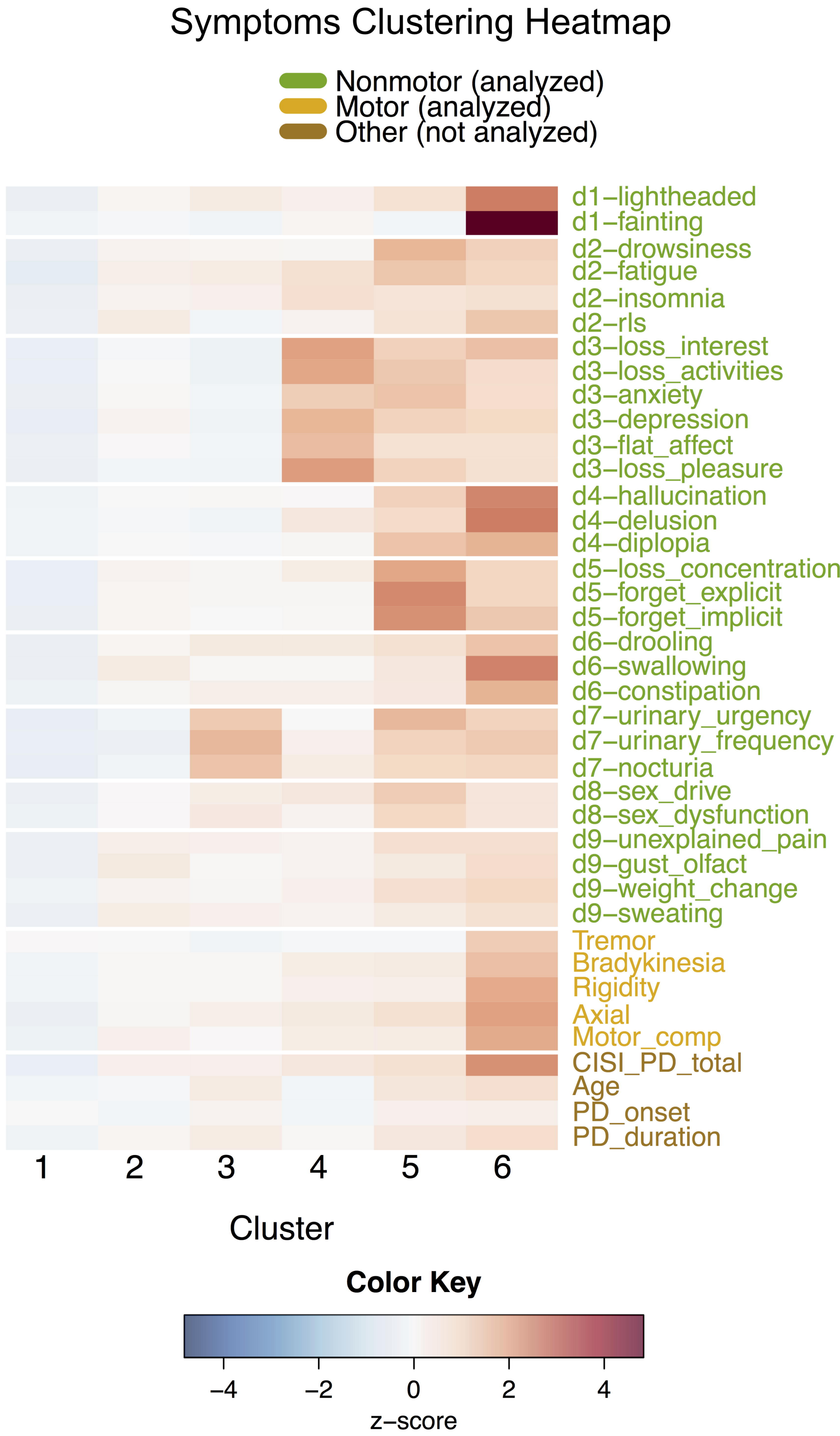
Figure e-1. **Gap statistics.** Plot of the gap statistic $\mathrm{Gap}(k)$ versus number of clusters with k-means on 500 bootstrapped samples of a) the domains clustering, and b) the symptoms clustering. Error bars represent ± 1 standard error (se). Per the one-standard error method,[25] the optimal number of clusters is the smallest k such that $\mathrm{Gap}(k) \geq \mathrm{Gap}(k+1) - \mathrm{se}_{k+1}$. For the domains clustering, $k = 4$; for the symptoms clustering, $k = 6$. The gap statistic for the optimal k and the comparison to $k + 1$ are marked with dotted lines.

Figure e-2. **Domains clustering boxplots.** Boxplots for domains clustering for each symptom and cluster.

Figure e-3. **Correlation with disease duration.** Correlation of applicable variables with disease duration.

Figure e-4. **Symptoms against disease duration.** For clarity, scatterplot points are colored according to cluster and jittered. 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.


Domains Clustering Heatmap
Nonmotor (analyzed)
Motor (analyzed)
Other (not analyzed)
1–Cardiovascular
2–Sleep/fatigue
3–Mood/apathy
4–Perception/hallucination
5–Attention/memory
6–Gastrointestinal
7–Urinary
8–Sexual
9–Miscellaneous
Axial
Bradykinesia
Rigidity
Tremor
Motor_comp
CISI_PD_total
Age
PD_onset
PD_duration
1
2
3
4
Cluster
Color Key
−2
−1
0
1
2
z−score


Symptoms Clustering Heatmap
Nonmotor (analyzed)
Motor (analyzed)
Other (not analyzed)
d1−lightheaded
d1−fainting
d2−drowsiness
d2−fatigue
d2−insomnia
d2−rls
d3−loss_interest
d3−loss_activities
d3−anxiety
d3−depression
d3−flat_affect
d3−loss_pleasure
d4−hallucination
d4−delusion
d4−diplopia
d5−loss_concentration
d5−forget_explicit
d5−forget_implicit
d6−drooling
d6−swallowing
d6−constipation
d7−urinary_urgency
d7−urinary_frequency
d7−nocturia
d8−sex_drive
d8−sex_dysfunction
d9−unexplained_pain
d9−gust_olfact
d9−weight_change
d9−sweating
Tremor
Bradykinesia
Rigidity
Axial
Motor_comp
CISI_PD_total
Age
PD_onset
PD_duration
1
2
3
4
5
6
Cluster
Color Key
−4
−2
0
2
4
z−score

Hierarchical Clustering on Symptoms