Cluster Analysis: Identifying Parkinson's Disease Subtypes

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1 Preprocessing

1.1 Dataset Description

951 subjects, 145 metrics, collected 15-4-2012 from Pablo Martinez Martín. Only 19 features used for clustering and/or interpretation. 50 subjects with missing values of the features to be used in clustering (brought down to 901). It was decided to not impute the data. Data was scaled to $\mu = 0, \sigma = 1$ during clustering and modeling, then unscaled for visualization.

1.2 Selected Features

Combination of non-motor scale (NMS) symptoms and standard motor symptoms. PIGD was deleted after 2015-07-16 meeting.

Name	Type	Description
nms_d1	byte	cardiovascular
nms_d2	byte	sleep/fatigue
nms_d3	byte	mood/cognition
nms_d4	byte	percep/hallucinations
nms_d5	byte	attention/memory
nms_d6	byte	gastrointestinal
nms_d7	byte	urinary
nms_d8	byte	sexual function
nms_d9	byte	miscellaneous
tremor	float	tremor
bradykin	float	bradykinesia[1]
rigidity	float	rigidity
axial	float	axial[2]

Table 1: Selected Features and Details

2 Clustering

k-means clustering with $k = 4$ was tried. Statistics for determining the optimal number of clusters were used, but were inconclusive: results in Figure 3. This probably indicates that the data is not very well clustered. $k = 2, 3$ provided models that were too simplistic. $k = 5$ did not provide any new information, but rather just fragmented existing groups.

[1] Impaired ability to adjust the body's position.

[2] Issues affecting the middle of the body.

Name	μ	σ	min-max
nms_d1	1.73	3.35	0-24
nms_d2	8.75	8.70	0-48
nms_d3	8.68	11.55	0-60
nms_d4	1.64	3.86	0-33
nms_d5	5.42	7.43	0-36
nms_d6	5.53	6.79	0-36
nms_d7	8.08	8.94	0-36
nms_d8	3.52	5.97	0-24
nms_d9	7.13	7.79	0-48
tremor	2.59	2.58	0-12
bradykin	2.40	1.41	0-6
rigidity	2.24	1.36	0-6
axial	3.25	2.68	0-12

Table 2: Descriptive Statistics

Criterion	Optimal k
Minimum ASW	2
BIC	18
SSE Scree Plot	Inconclusive
Gap Statistic	4
Affinity Propagation	8

Table 3: Results of various techniques for determining k

2.1 Decision tree

Decision tree for $k = 4$ created via recursive partitioning is available in Figure 1. More discussion about the decision tree is located in Section 2.2.4.

2.2 Interpretation of Clusters

2.2.1 Cluster summaries

Available in Figure 2. Error bar is standard error.

2.2.2 Interpretation

k-means clustering ($k = 4$) found four clusters. With a brief description, they are:

1. ($n = 406$) Mildly affected in all domains.
2. ($n = 189$) Severely affected in nonmotor domains; mildly affected in motor domains.
3. ($n = 221$) Severely affected in motor domains; mildly affected in nonmotor domains.
4. ($n = 88$) Severely affected in all domains.

2.2.3 Statistical Significance Tests, $k = 4$

For each variable i and cluster means $\mu_i^1, \mu_i^2, \mu_i^3, \mu_i^4$, we use one-way ANOVA for multiple means and reject the null hypothesis that $\mu_i^1 = \mu_i^2 = \mu_i^3 = \mu_i^4$ with $p < 0.05$ for every variable except pdonset.

Post-hoc analysis using Tukey's HSD to examine statistically significant differences between individual means is available in Table 4. For brevity, only statistically insignificant relations are provided; all other relations are significant with $p < 0.05$.

Variable	Cluster Relation	p
age	2-1	0.428
	3-2	0.724
sex	2-1	0.0918
	3-1	0.216
	4-1	0.827
	4-2	0.849
	4-3	0.161
pdonset	2-1	0.859
	3-1	0.700
	4-1	0.305
	3-2	0.370
	4-2	0.147
	4-3	0.803
durat_pd	3-2	0.562
cisitot	3-2	0.522
nms_d1	3-1	0.333
nms_d4	3-1	0.557
nms_d5	3-1	0.856
nms_d8	3-1	0.122
nms_d9	3-1	0.0735
	4-2	0.730
tremor	2-1	0.360

Table 4: Tukey's HSD Insignificant Differences

2.2.4 Feature importance

Features ranked by information gain with respect to cluster are available in Table 5. Also, in the 4-cluster decision tree in Figure 1, features are ranked implicitly by importance in determining clusters. We see, quite naturally, that standard measures of motor symptoms rank very highly (ranks 1, 2, 4, 5) in information gain *except* tremor (12). Similarly, bradykinesia (1) is used as the root node of the 4-cluster decision tree, although other motor symptoms are used further down the tree, since immediately successive motor symptom decision nodes would, due to their determination of clusters, be redundant.

The most informative nonmotor symptoms are nms_d2 (sleep/fatigue) at 2, along with nms_d3 (mood/cognition). As discussed later in Section 4.1 these features become critical in one-versus-all decision trees for distinguishing various subtypes. The importance of these nonmotor symptoms confirms the longitudinal study by Fereshtehnejad et al. [2] who cites a 3-cluster PD subtype identification based primarily on nonmotor symptoms including cognitive impairment, rapid eye movement sleep disorder (RBD), anxiety, and depression, conditions that align closely with nms_d2 and nms_d3 as tested in this dataset. More analysis needs to be done on whether there are parallels between Fereshtehnejad's 3-cluster longitudinal study and the clusters found in both this investigation and van Rooden.

Interestingly, demographic information, including durat_pd, age, sex, and pdonset, plays almost no role in the determination of these clusters. That the time of onset of PD or sex is largely irrelevant provides an important negative answer to clinically-relevant questions about the demographic sources of these different subtypes.

2.2.5 Correlation Plots

The interplay between specific symptoms in each of the four clusters was examined in Figure 5. There are two points of note. The first is that there is a higher correlation in cluster 4 (severe) between overall severity (cisitot) and bradykinesia and rigidity, illustrated in Figure 3. Second, there exists a somewhat higher correlation between bradykinesia, rigidity, and nms_d6 (gastrointestinal) in cluster 4, illustrated in Figure 4. These differences are statistically significant; correlation tests are located in Table 6. I am unsure

rank	variable	information gain
1	bradykin	0.316
2	rigidity	0.296
3	nms_d2	0.242
4	cisitot	0.229
5	axial	0.228
6	nms_d3	0.205
7	nms_d9	0.158
8	nms_d7	0.153
9	nms_d5	0.145
10	nms_d6	0.140
11	nms_d1	0.132
12	tremor	0.109
13	nms_d4	0.107
14	nms_d8	0.100
15	durat_pd	0.0288
16	age	0.0235
17	sex	0.000
18	pdonset	0.000

Table 5: Features ranked by information gain

of the significance or proper interpretation of these results.

3 Nonmotor-predominant subtype analysis

3.1 k-means sub-subdivision on Cluster 2

In an attempt to understand further the properties of the nonmotor-dominated subtypes, k-means analysis was run again on specifically this subtype to examine any possible patterns.

The same k-determining tests were run on subtype 2 and are displayed in Table 7.

Boxplots for k-means run for $k = 2, 3, 4$ can be seen in Figures 6, 7, and 8. Clusters are ordered by increasing cisitot.

3.2 Interpretation

An interesting set of subtleties occurs when $k = 2$ and 3. When $k = 2$, the two groups are divided generally by PD severity (see cisitot and especially axial). The specific symptoms of the two groups follow this trend, except nms_d3 and tremor, which are actually decreasing, and other symptoms like rigidity, nms_d4, and nms_d9, which are more indeterminate.

When $k = 3$, the symptoms that continue show a non-monotonically increasing trend are nms_d2, tremor, and rigidity scores, where patients in the 3rd subtype exhibit lower severities. nms_d4 and nms_d9 differences turn out to be not as pronounced.

4 Further modeling

One further step of this investigation was to produce accurate, practical models that could be used in a clinical setting to predict the subtype of PD based on previous clustering results. Cluster assignments obtained from previous k-means investigation were treated as labels in a supervised classification problem in an attempt to produce useful and easily interpretable models.

[3] $\lambda = 0.98$, q = 0, maxits = 1000, convits = 100

Cluster	Variables	95% CI	p
1	bradykin, cisitot	[-0.0225, 0.171]	0.131
	rigidity, cisitot	[-0.000406, 0.192]	0.0510
	bradykin, nms_d6	[-0.0634, 0.131]	0.493
	rigidity, nms_d6	[-0.101, 0.0932]	0.934
2	bradykin, cisitot	[0.0786, 0.351]	$0.00248^{(**)}$
	rigidity, cisitot	[-0.215, 0.069]	0.310
	bradykin, nms_d6	[-0.152, 0.133]	0.897
	rigidity, nms_d6	[-0.123, 0.163]	0.781
3	bradykin, cisitot	[0.0995, 0.350]	$0.000620^{(***)}$
	rigidity, cisitot	[0.0687, 0.322]	$0.00298^{(**)}$
	bradykin, nms_d6	[0.0350, 0.292]	$0.0134^{(*)}$
	rigidity, nms_d6	[-0.0846, 0.179]	0.478
4	bradykin, cisitot	[0.454, 0.724]	$3.97 \times 10^{-10^{(***)}}$
	rigidity, cisitot	[0.375, 0.675]	$4.99 \times 10^{-08^{(***)}}$
	bradykin, nms_d6	[0.297, 0.624]	$2.60 \times 10^{-06^{(***)}}$
	rigidity, nms_d6	[0.278, 0.611]	$6.43 \times 10^{-06^{(***)}}$

Table 6: Correlation tests. (*) $p < 0.05$, (**) $p < 0.01$, (***), $p < 0.001$

Criterion	Optimal k
Minimum ASW	2
BIC	1 (?)
SSE Scree Plot	Inconclusive
Gap Statistic	3
Affinity Propagation[3]	5

Table 7: Results of various techniques for determining k, applied to subtype 2

4.1 One-versus-all decision trees

While the decision tree in Figure 1 is useful, it could be considered overly complicated. Additionally, a model is not necessarily needed to make simpler diagnoses such as classifying a patient as mildly affected (subtype 1) or severely affected (subtype 4). One-versus-all (OVA) decision trees were thus considered, in order to isolate the classification problem and look at possible distinguishing characteristics of individual subtypes. These OVA decision trees for all 4 subtypes are located in Figures 9, 10, 11, and 12. Trees are pruned by selecting the version of tree with the minimum 10-fold cross-validated error.

4.1.1 1 (mild)

The tree for the mild subtype classifies mainly based on negative responses to nodes asking whether the patient has a relatively severe manifestation of a symptom. The majority of examples are classified by following the bradykinesia < 2.5, which subsequently tests the severity of several nonmotor symptoms. Most of subtype 1 patients that score relatively mildly on these scales are classified this way. There are also small populations of patients who 1) score higher on bradykinesia but lower with axial, tremor, rigidity, and nms_d2 and 2) score higher in nms_d2 (sleep) but lower with nms_d7 (urinary).

4.1.2 2 (nonmotor-predominant)

The decision tree for the nonmotor-predominant subtype is quite simple. Interestingly, although nms_d9 (miscellaneous) is not the most important nonmotor symptom, since the information gain is less than nms_d2 and nms_d3 and it does not appear very high in the 4-class decision tree, it is used as the root node of this decision tree, classifying over half of the negative examples based on whether the subject has a low severity of miscellaneous symptoms (nms_d9 < 7.5)[4]. This could be an indication that nonmotor-predominant PD patients do indeed have a wide manifestation and variety of nonmotor symptoms. After classifying on nms_d9, the tree then classifies negatiave examples as having rigidity ≥ 3.5, an example of how subtype 2 patients have relatively low motor symptoms. Finally, the tree classifies on the nonmotor symptom with the most information gain, nms_d2, where patients ≥ 7.5 are classified as falling into subtype 2.

4.1.3 3 (motor-predominant)

This tree classifies overwhelmingly on severity of bradykinesia, with 476 negative examples when bradykinesia is less than 2.5. The resulting tree is quite complex, but generally, nodes check again for severity of motor symptoms (tremor is the next node) and end up classifying positive examples based on both mildness of nonmotor symptoms and severity of motor symptoms. For example, in the furthest right branch, once nms_d2 (as we know, an important feature) is established to be relatively mild (< 12), the test for subtype 3 involves several more nodes verifying the severity of rigidty, tremor, and axial, and the mildness of nms_d7 (urinary).

4.1.4 4 (severe)

The OVA tree for patients severely affected in all areas is predictable, testing entirely on whether or not symptoms (both motor and nonmotor) are relatively severe. Positive nodes always appear to the right (no) of less-than checks. Interestingly, however, nms_d4 (percep/hallucinations), previously not of note, is used twice as the root node of a tree and again further down. As the boxplot display in Figure 2 shows, nms_d4 is perhaps the most distinguishing symptom of subtype 4 against nonmotor-predominant subtype 2 in particular, as subtype 2 has relatively mild percep/hallucination symptoms, in contrast to the comparable levels of severity for other nonmotor symptoms in both groups. This shows that issues with perception and hallucinations generally occur in only the most severe cases of PD, and are relatively rare when a patient exhibits a nonmotor-predominant form of PD.

4.2 Different angles of exploration: 2 and 4, 2 and 3 vs rest

There are many more interesting questions to be asked when examining the relationship between these clusters. One thing that may be helpful in understanding the relationship between the clusters is exploring different groupings of clusters for decision trees. The trees in Figure 13 and 14 are preliminary examples of this kind of exploration.

4.2.1 2 and 4 vs rest

In this tree, the node classifying examples as subtype 4 is localized to the furthest right branch. Predictably, examples in this node have scored relatively higher in rigidity (≥ 3.5). Interestingly, a classification decision that is replicated in the 4 versus all decision tree is the decision to use nms_d7 (urinary) as a node, where subtype 4 is classified as having relatively high nms_d7 components (≥ 12). Indeed, as shown in Figure 2, the mean of nms_d7 severity is similar to nms_d4 in that it is especially higher in cluster 4 than in cluster 2.

4.2.2 2 and 3 vs rest

In this tree, classification of patients in subtype 3 is primarily dependent on asserting bradykin ≥ 2.5 then splitting on tremor < 3.5 is considered. Interestingly, the two nonmotor symptoms that differentiate cluster 3 are nms_d5 (attention/memory) and nms_d7 (urinary). Additionally, nms_d2, a quite important symptom, does not appear in the classification tree for this task.

[4] Recall that $0 <$ nms_d9 < 48.

4.3 Bayesian Networks

4.3.1 On all data

I decided to discretize the data into three uniform-width groups based on the scales of each symptom. In other words, each symptom was discretized into a mild, moderate, and severe bin. Continuous data was unreliable on my computer, and updating intricately connected nodes like nms_d2 resulted in slowdowns and crashes on my computer.

Two bayesian network algorithms were tried: the default Bayesian score-search algorithm and the PC conditional independence tests algorithm. I couldn't find the exact name of the Bayesian search implementation, but it was the default method used by GeNIe. GeNIe files will be attached electronically.

I assume these models are to be looked at by Dr. Martín. I have not done too much investigation myself, as I'm not exactly sure what I'm looking for.

4.3.2 On nms-dominated data

I tried to construct Bayesian networks based on the nms-dominated subtype, but the data was too sparse to create a very informative network, even when leaving the information continuous. However, I'm not sure this is necessary. If it is, I can work on this problem more.

5 Preliminary Conclusions

5.1 Overall clustering

k-means clustering on this Parkinsons' Disease data set reveals clusters that confirm previous computationally-based findings in the field, mainly van Rooden et al. [5] and the identification of four subtypes of Parkinson's disease: mild, nonmotor-predominant, motor-predominant, and severe. van Rooden's work was done with a separate dataset using a different modeling method (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 (nonmotor/motor predominated) subtypes are insignificant (Table 4), suggesting different developmental paths of the disease.

Overall, little information was found in pdonset, durat_pd, or current age, according to Tables 4 and 5. Mean ages were similar for subgroups 1, 2, and 3 ($p > 0.05$, but different for the severe subtype 4, which makes sense given that patients in 4 also have longer disease durations. Specifically, clusters 1 and 4 seem to be phenotypically quite similar, except at different stages of disease progression, given cluster 4's higher age and durat_pd scores.

However, clusters 2 and 3 clearly show different disease progression, one in the motor direction, and one in the nonmotor. Both groups have similar age, pdonset, and durat_pd scores, but differ wildly in symptomatic expression. Cluster 2 is dominated by a high prevalence of nonmotor symptoms, such as nms_d2, nms_d3, nms_d7, and nms_d9. Cluster 3, however, is dominated by a high prevalence of motor symptoms, while most motor symptoms are similar to the mild cluster 1. Of note is that the tremor population mean is the highest cluster mean, even higher than the severe subtype 4. This motor-dominant cluster may thus overlap with Ma's tremor dominant/slow progression cluster [3].

Generally, given stable pdonset scores and predictably increasing durat_pd scores for clusters 1 and 4, Ma et al's rapid disease progression/late onset and tremor dominant/slow progression clusters [3] were mostly not found in this dataset, save for the tremor-dominant motor cluster.

The most important nonmotor symptoms in determining these clusters were nms_d2 (sleep) and nms_d3 (mood/cognition), which echo findings of Fereshtehnejad's longitudinal study [2] and are similar to Sauerbier's identification of sleep dominant and cognitive dominant clinical NMS subtypes [4]. Compared to Erro et al. [1], nonmotor/motor dominant subtypes were indeed found, but an additional subgroup with relatively severe levels of both motor and nonmotor symptoms were found. Erro's benign subtype groups possibly overlap with the mild cluster 1 found in this investigation.

5.2 Nonmotor subtype: clustering and modeling

Nonmotor symptoms nms_d2 and nms_d3 became critical not only in classification trees distinguishing between the various symptoms but in the nonmotor-predominant subgroup itself. In k-means subdivision of the nonmotor-dominant subtype where $k = 2$ and $k = 3$, opposite trends were confirmed with nms_d2 and nms_d3 symptoms. Similarly, in the 2 and 4 vs rest decision tree (Figure 13), nms_d2 and nms_d3 nodes were used to differentiate various categories of nomotor-dominant patients. When $k = 3$, the subtype with the highest nms_d2 scores and lowest nms_d3 scores had by far the highest axial scores, nms_d6 (gastrointestinal) scores, and nms_d7 (urinary) scores. Thus subtype 3 of the nonmotor-dominated group could include patients falling into the cognitive/depression-dominant or autonomic dominant subtypes.

Despite the variety in symptomatic expression in this nonmotor group, what seems most consistent is the presence of nms_d9 (miscellaneous) nonmotor symptoms, as it is used as the root node of the 2 vs all decision tree (Figure 10) and the 2 and 4 vs rest decision tree (Figure 13).

It remains to be seen whether these classification models, especially the one-vs-all decision trees, are useful in clinical practice.

References

[1] Erro et al (2013). The Heterogeneity of Early Parkinsons Disease: A Cluster Analysis on Newly Diagnosed Untreated Patients

[2] Fereshtehnejad et al (2015). New Clinical Subtypes of Parkinson Disease and Their Longitudinal Progression

[3] Ma et al (2015). Heterogeneity among patients with Parkinson's disease: Cluster analysis and genetic association

[4] Sauerbier et al (2015). Non motor subtypes and Parkinson's disease.

[5] van Rooden et al (2010). The Identification of Parkinson's Disease Subtypes Using Cluster Analysis: A Systematic Review

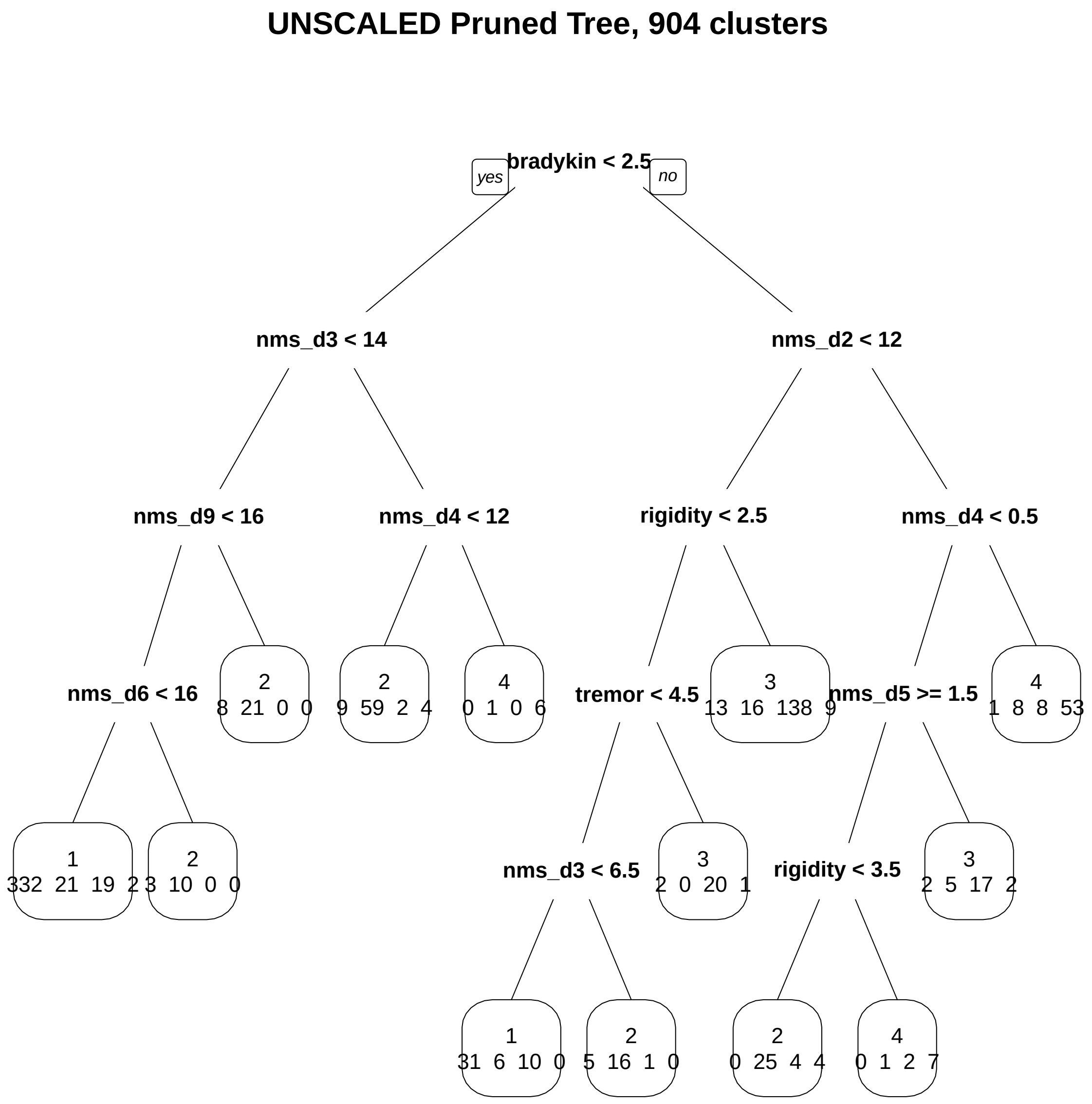


Figure 1: Decision Tree from k-means clustering, 4 clusters

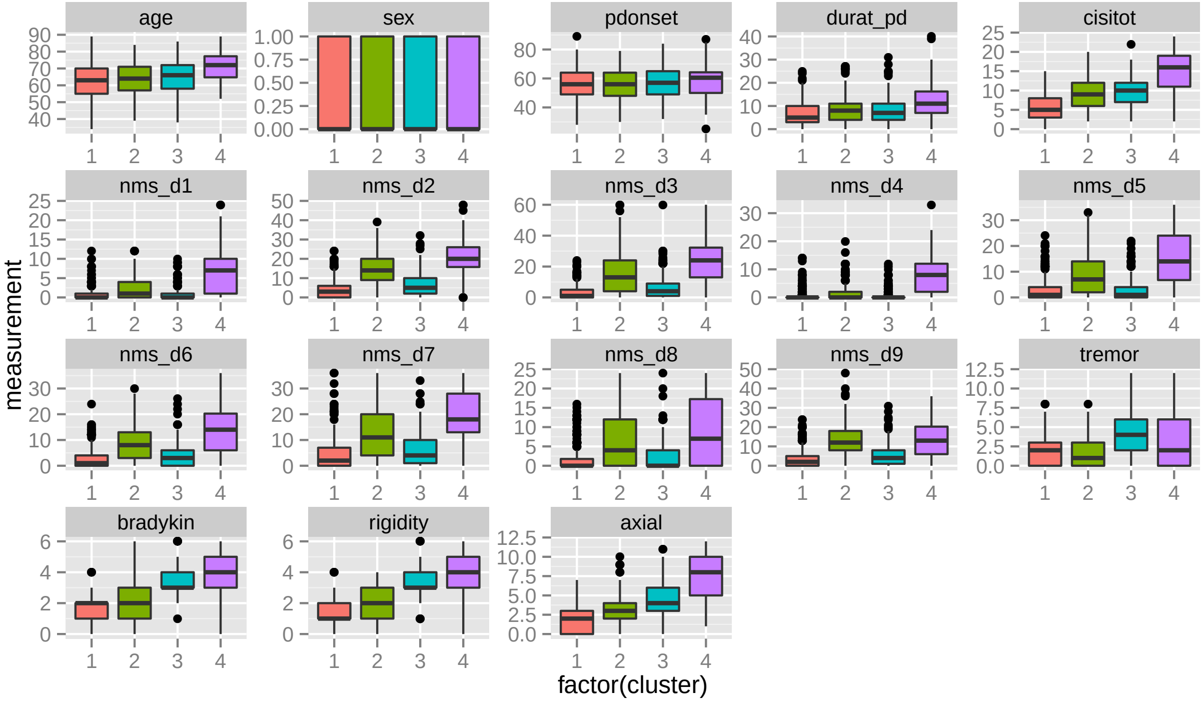
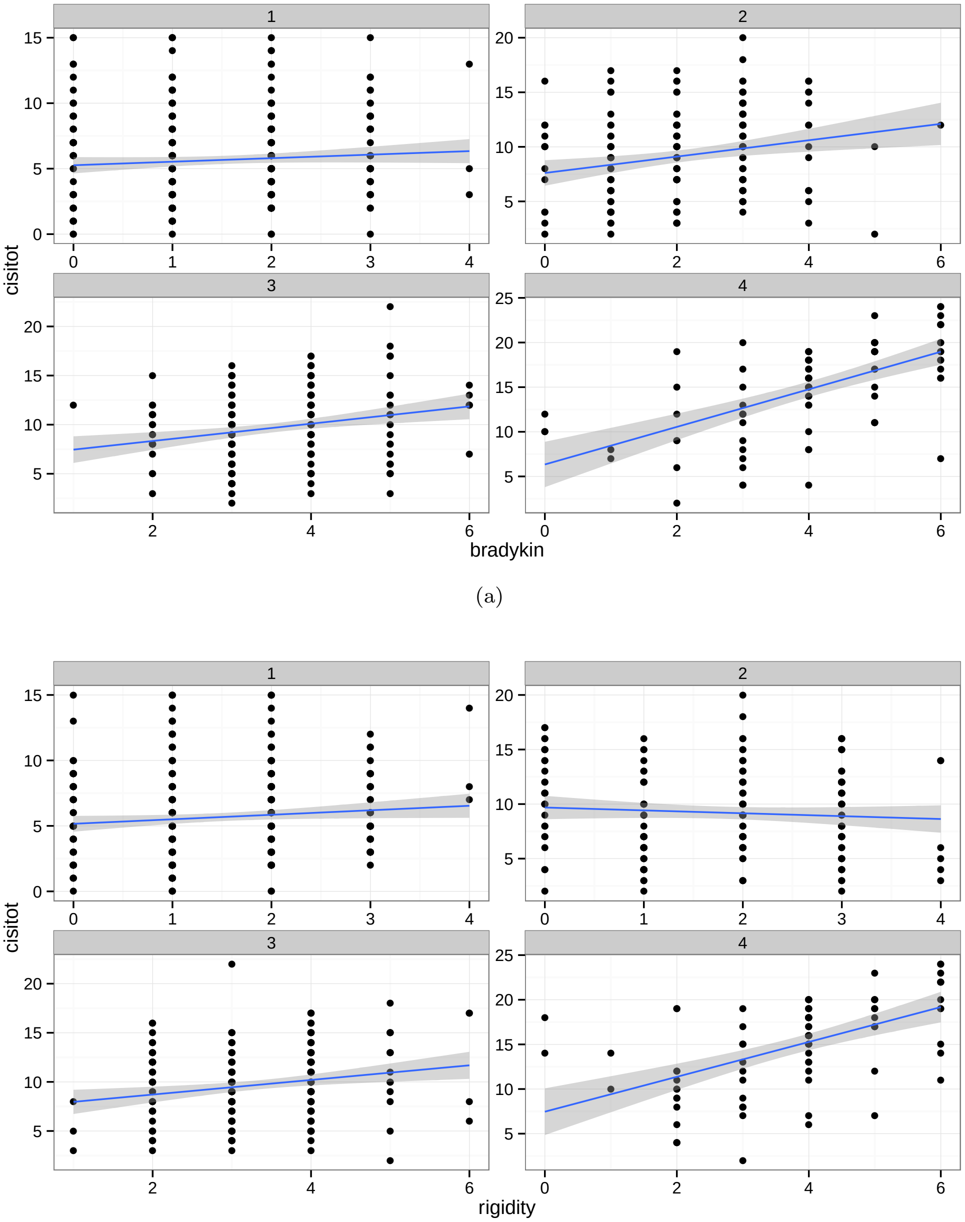


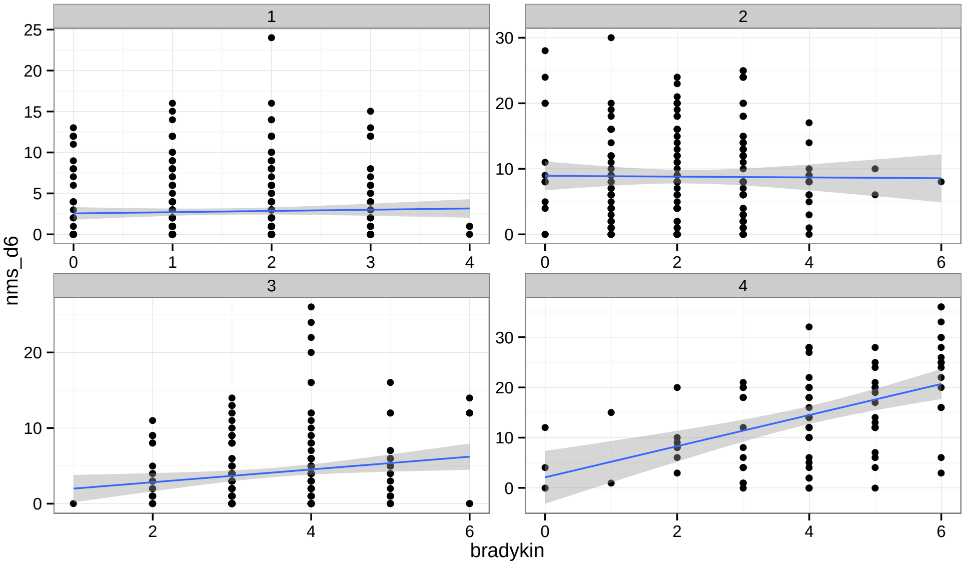
Figure 2: Cluster Summaries, $k = 4$



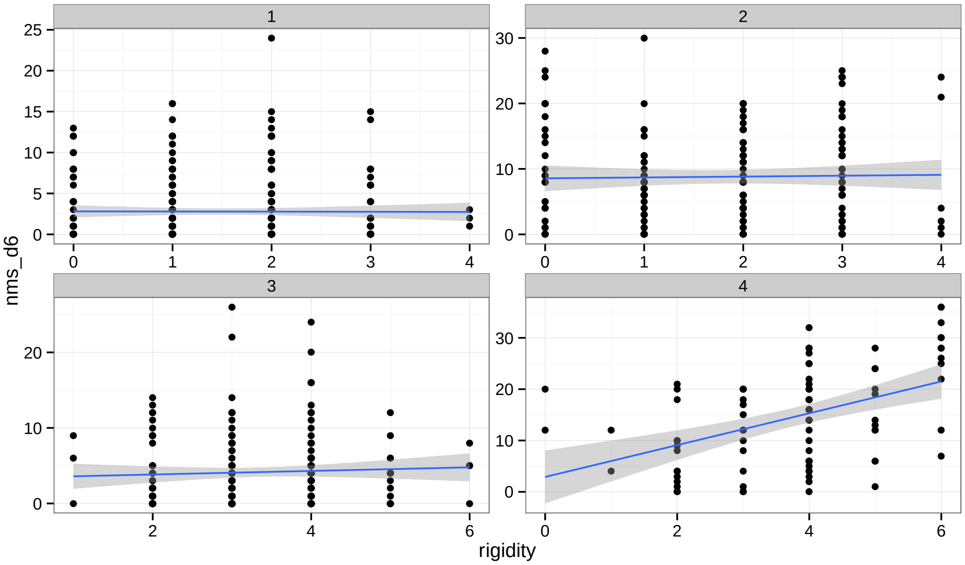
(a)

(b)

Figure 3: Relationship between (a) bradykinesia, (b) rigidity and overall severity (cisitot). Shaded band is 95% confidence interval.



(a)



(b)

Figure 4: Relationship between (a) bradykinesia, (b) rigidity and nms_d6 (gastrointestinal). Shaded band is 95% confidence interval.

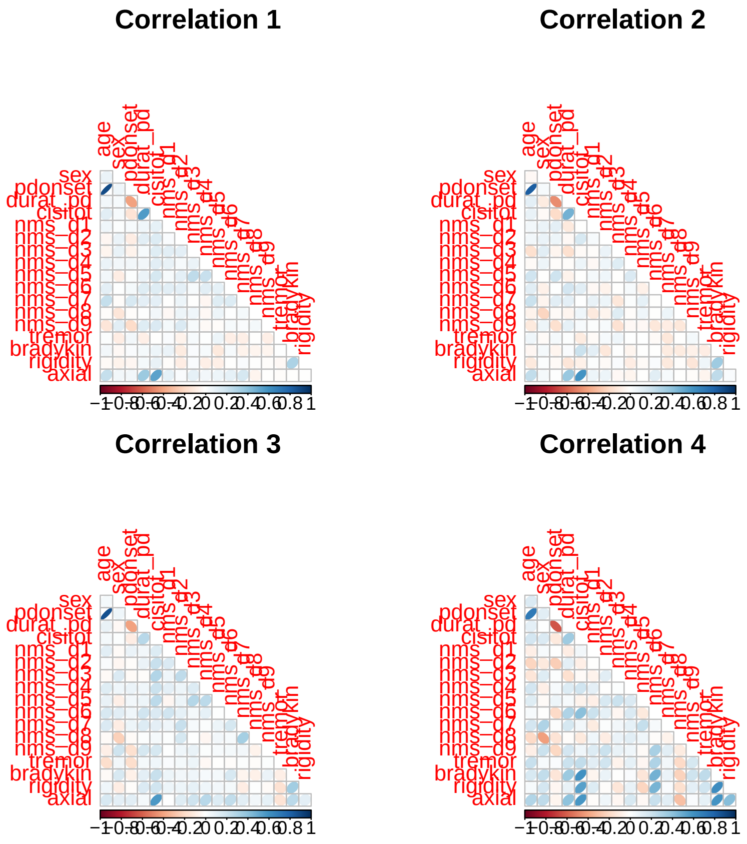


Figure 5: Correlation plots

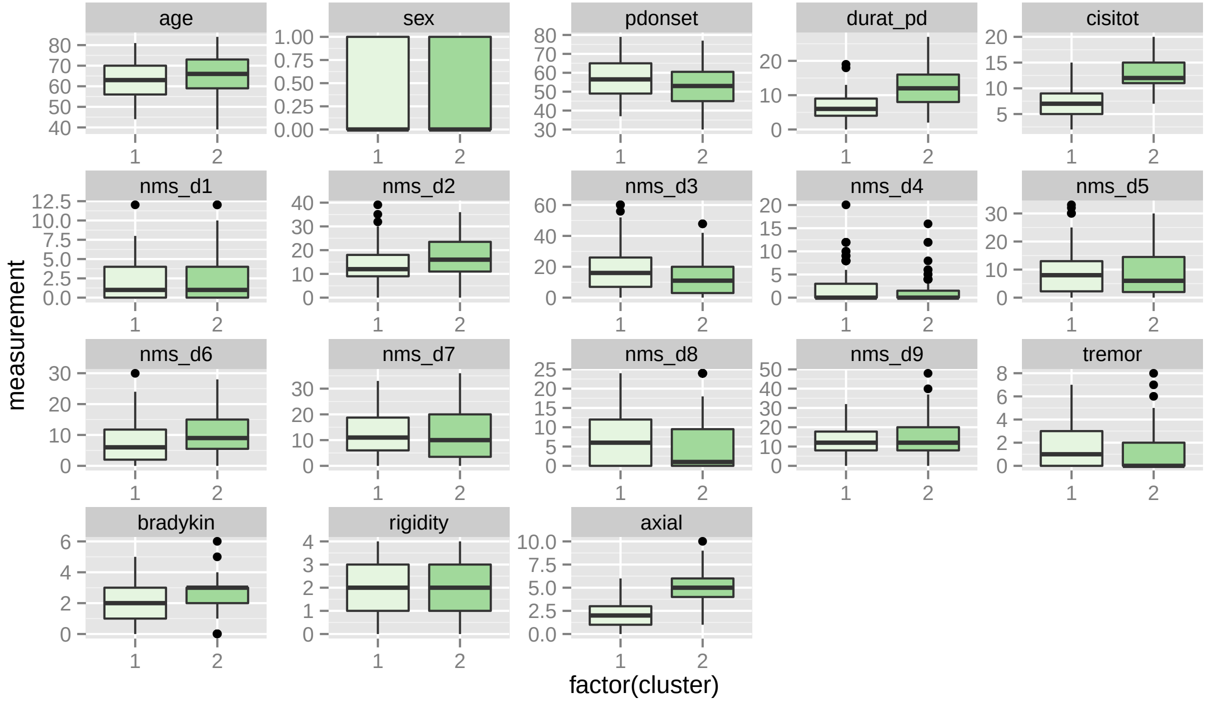


Figure 6: Clustering on nonmotor group: $k = 2$

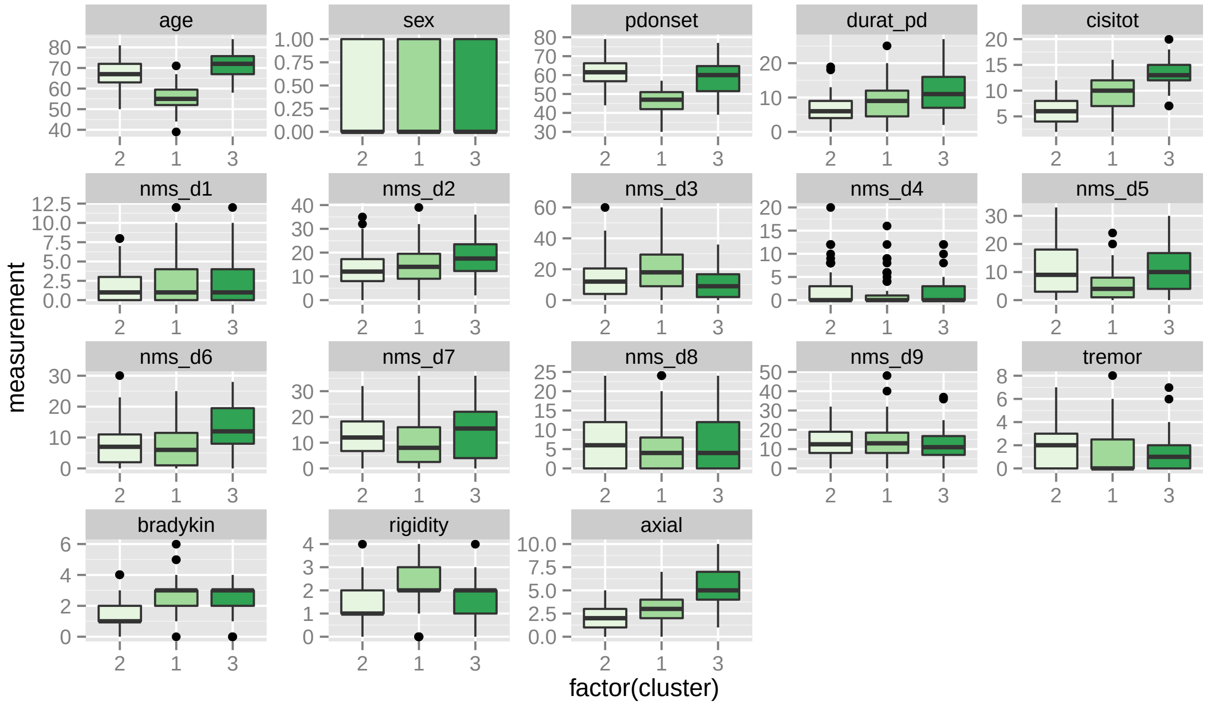


Figure 7: Clustering on nonmotor group: $k = 3$

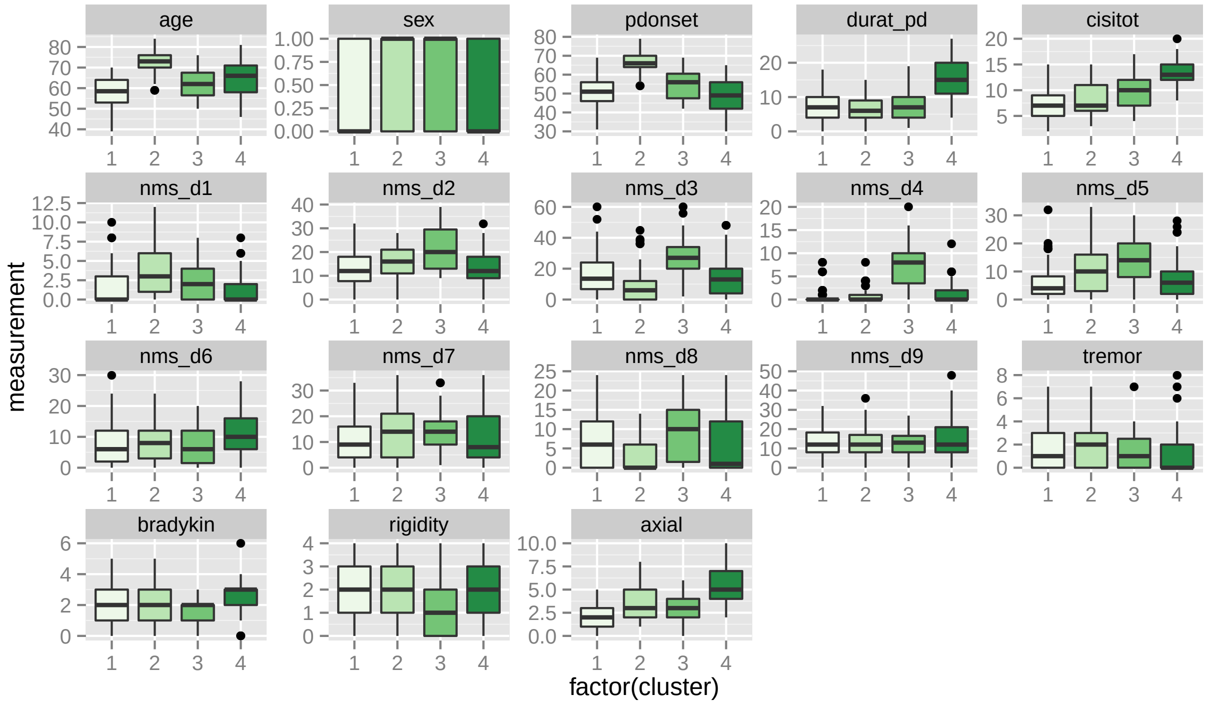


Figure 8: Clustering on nonmotor group: $k = 4$

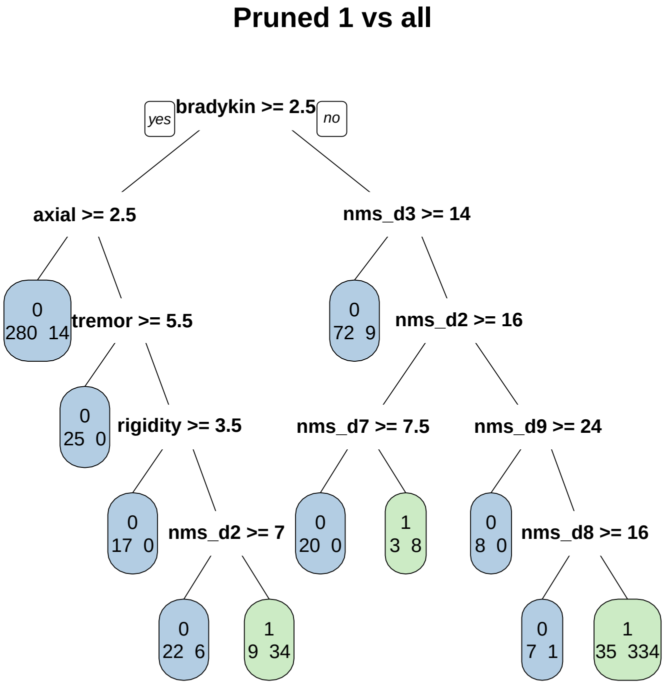


Figure 9: Cluster 1 (mild) vs all

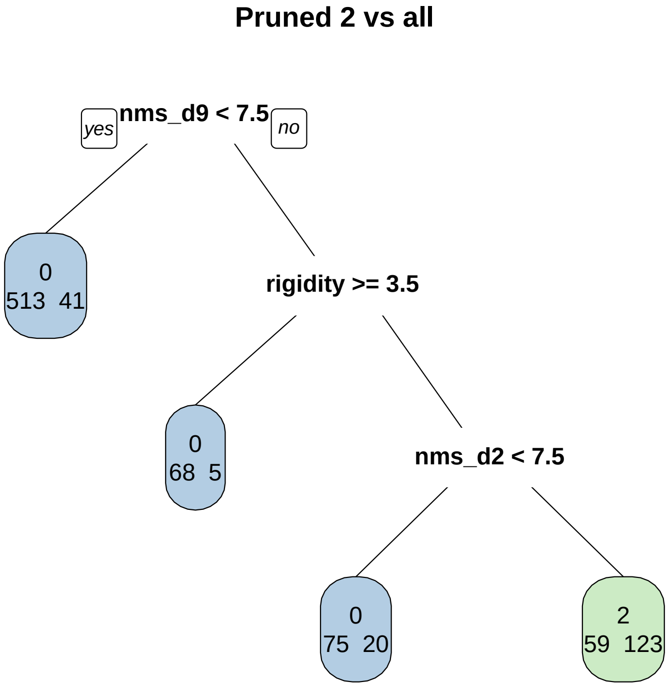


Figure 10: Cluster 2 (nonmotor-dominated) vs all

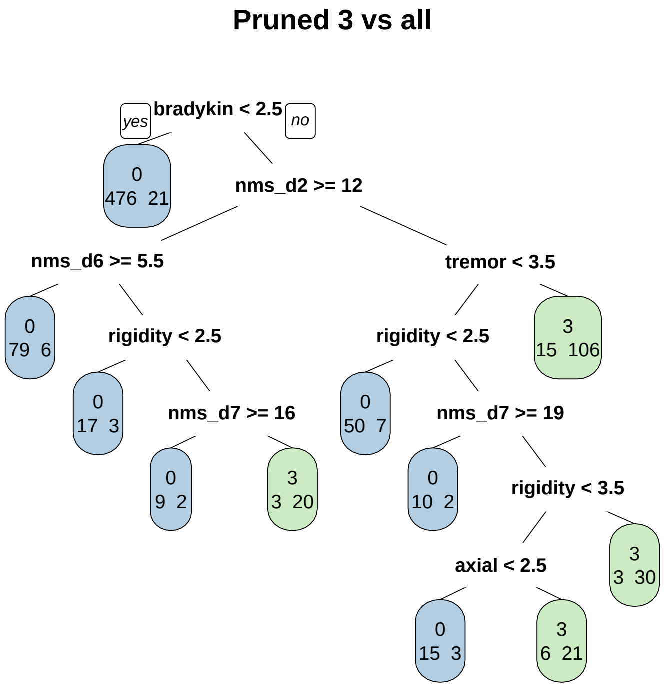

Pruned 3 vs all

Figure 11: Cluster 3 (motor-dominated) vs all

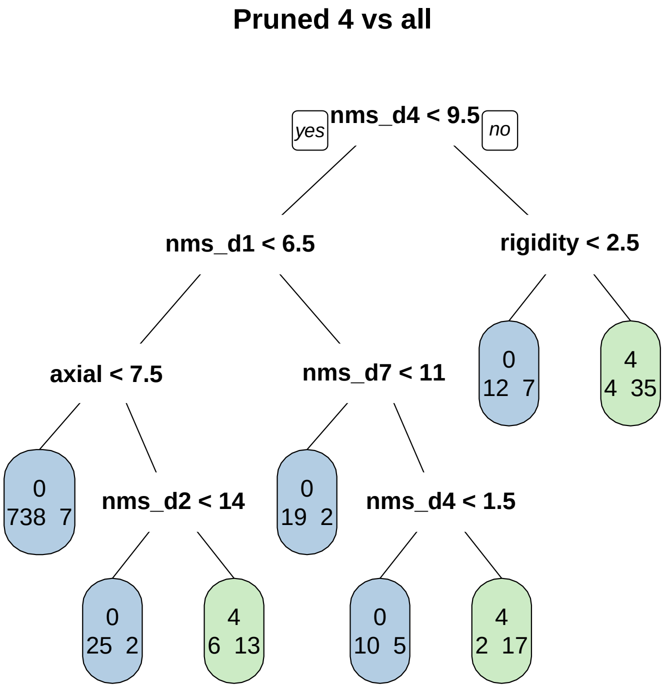

Pruned 4 vs all

Figure 12: Cluster 4 (severe) vs all

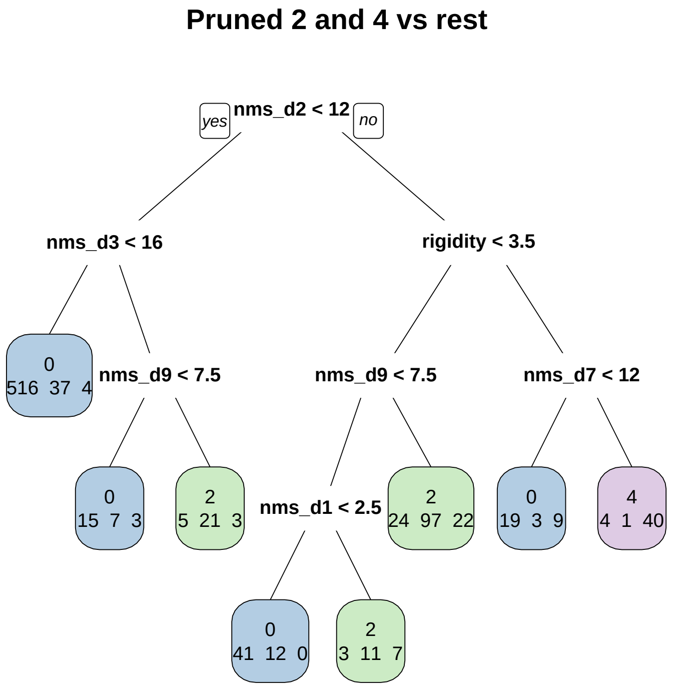


Figure 13: Clusters 2 (nms) and 4 (severe) vs rest (1 and 3)

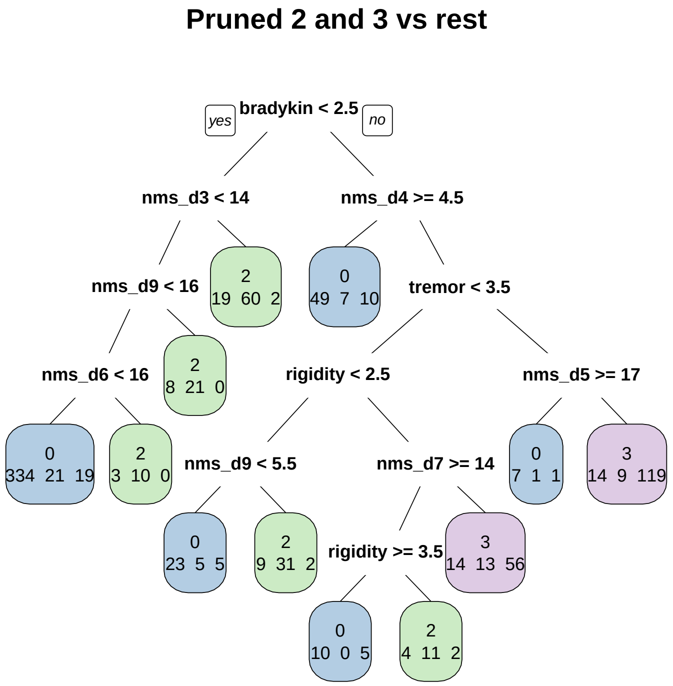


Figure 14: Clusters 2 (nms) and 3 (motor) vs rest (1 and 4)