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Motor subtype changes in early Parkinson's disease

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Abstract

Introduction—Distinct motor subtypes of Parkinson's disease (PD) have been described through both clinical observation and through data-driven approaches. However, the extent to which motor subtypes change during disease progression remains unknown. Our objective was to determine motor subtypes of PD using an unsupervised clustering methodology and evaluate subtype changes with disease duration.

Methods—The Parkinson's Progression Markers Initiative database of 423 newly diagnosed PD patients was utilized to retrospectively identify unique motor subtypes through a data-driven, hierarchical correlational clustering approach. For each patient, we assigned a subtype to each motor assessment at each follow-up visit (time points) and by using published criteria. We

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examined changes in PD subtype with disease duration using both qualitative and quantitative methods.

Results—Five distinct motor subtypes were identified based on the motor assessment items and these included: Tremor Dominant (TD), Axial Dominant, Appendicular Dominant, Rigidity Dominant, and Postural and Instability Gait Disorder Dominant. About half of the patients had consistent subtypes at all time points. Most patients met criteria for TD subtype soon after diagnosis. For patients with inconsistent subtypes, there was an overall trend to shift away from a TD phenotype with disease duration, as shown by chi-squared test, $p < 0.001$, and linear regression analysis, $p < 0.05$.

Conclusion—These results strongly suggest that classification of motor subtypes in PD can shift with increasing disease duration. Shifting subtypes is a factor that should be accounted for in clinical practice or in clinical trials.

Keywords

Parkinson's disease; clustering; subtypes

Introduction

It is widely accepted that Parkinson's disease (PD) is a clinically heterogeneous disease with several different motor phenotypes [1,2]. Accurately characterizing the heterogeneity that occurs in PD is important for assessing prognosis, enrolling in clinical trials, and for screening for possible co-morbidities [3]. Properly subtyping patients is also a critical step for determining inclusion in both preclinical [4,5] and clinical studies, particularly those involving individualized treatment plans based on motor symptoms [6-8].

PD subtype categories were originally based on clinical observation of motor symptoms [1,9]. Commonly recognized subtypes of PD include a tremor dominant (TD) group and a postural instability and gait disorder/difficulty/dominant (PIGD) group [2]. Some clinicians and researchers also recognize an ill-defined intermediate or indeterminate type (IT) classification for patients that do not fit the TD or PIGD phenotype. Recently, studies have proposed additional subtypes based on data-driven cluster analysis approaches using other clinical characteristics including age of onset, speed of disease progression, cognitive measures, and behavioral measures [10-14]. Aside from establishing subtypes, several studies have attempted to clarify whether subtypes are fixed or whether they represent different stages of disease progression [15,16].

In this study, our goal was to use a data-driven approach to discover distinct motor subtypes in PD, and to apply these subtypes to longitudinal motor assessment data to look for shift in category over time. To accomplish this task, we used hierarchical correlational clustering on motor assessment data from 423 early PD patients included in the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data).

Methods

Data Source

Data used in this study were obtained from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.ppmi-info.org. Further details on the PPMI project have been previously published [17]. The study was approved by the Institutional Review Board (IRB) at all participating institutions. The PPMI database offers unique access to longitudinal data from 423 early PD patients. Participants were required to enroll within two years of PD diagnosis and be untreated for at least the first year of participation. Participants were also required to have abnormal 123-I Ioflupane dopamine transporter (DaTscan™) results, a Hoehn and Yahr stage of I or II at baseline, and be at least 30 years old. Exclusion criteria were in part used to exclude patients with atypical parkinsonism disorders, and included previous MRI with clinically significant neurological disorder. Patient follow-up, including motor assessment, occurred at various times after enrollment. All 423 PD patients and all follow-up visits were included in the present study.

Motor Scores

The PPMI schedule of events includes motor assessments every 3 months after enrollment up to month 12, followed by motor assessments every 6 months up to month 60, followed by motor assessments every 12 months up to month 96. However, exact time points varied across patients (see Results). We compiled together all OFF and ON-medication scores from the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III assessment as well as items 2.10, 2.11, 2.12, and 2.13 from MDS-UPDRS Part II. Per the PPMI protocol, OFF-medication scores were obtained after patients withheld dopaminergic medication for up to 12 hours and ON-medication scores were obtained at least 1 hour after dosing. MDS-UPDRS items with a “left” and “right” component were summed into a single score, and different body parts were scored separately (e.g., rigidity scores for neck, right upper extremity, left upper extremity, right lower extremity, and left lower extremity were analyzed as three scores: neck rigidity, upper extremity rigidity, and lower extremity rigidity). This approach resulted in 22 individual scores for each motor assessment time point.

Clustering

Cluster analysis is a widely-used machine learning technique for uncovering groups of data points that are similar [18,19]. It is a form of unsupervised learning, meaning that the underlying structure of the data is initially unknown. While several types of clustering algorithms are used in practice, we chose to use hierarchical clustering because this type of clustering approach does not require the number of clusters as input [18]. In a hierarchical approach, data points may belong to a cluster, which in turn, might be part of a larger cluster.

All ON and OFF-medication scores from each motor assessment time point were used as input to a hierarchical clustering using squared spearman correlation coefficients as similarity measures [20]. This procedure treated each motor score from the same patient at different time points as separate entries into the algorithm. This ensured that a representative

range of possible entries for MDS-UPDRS scores were included in the algorithm. No *a priori* models were used. We named each identified cluster based on the MDS-UPDRS items that the cluster included.

Subtyping

For each patient, we assigned each OFF and ON-medication motor assessment time point to a subtype from the identified clusters. To do this, we summed together the values from the MDS-UPDRS items included in each cluster to obtain subtype scores. Final subtype designation was determined based on ratios of subtype scores. We followed previous guidelines for assigning these subtypes based on motor scores [21]. That is, we summed the MDS-UPDRS items within each subtype to obtain a subscore for each subtype. If $TD_{\text{subscore}}/PIGD_{\text{subscore}}$ was greater than 1.15, we assigned the subtype TD, and if it was less than 0.9, we assigned the subtype PIGD [21]. If neither of these criteria were met, we then checked for IT subtypes. Since Appendicular-Dominant (ApD) and Rigidity-Dominant (RD) categories were within a distinct subgroup within the overall IT group (Figure 1), separate from the Axial-Dominant (AxD) group, we computed the ratio $AxD_{\text{subscore}}/(ApD_{\text{subscore}}+RD_{\text{subscore}})$. If this value was greater than 1, we assigned the subtype AxD. Otherwise, if $ApD_{\text{subscore}}/RD_{\text{subscore}}$ was greater than 1, we assigned the subtype ApD, and if it was less than 1, we assigned the subtype RD. Note that in this protocol, it is possible that a motor assessment would result in an unassigned subtype, usually in the case of two subtype scores being equivalent, and hence leading to a ratio of 1.0.

Next, we examined changes in OFF-medication motor subtype over time within subjects and across subjects. We assigned the categorical subtypes ordinal values for quantitative analysis.

Statistical Analysis

All data analyses for the present study were completed in R software (www.cran.r-project.org). Subtype frequency changes over time were analyzed using Chi-square and linear regression tests.

Results

The number of total motor score assessments available in the PPMI database varies between 2 and 14 for each patient ($M = 6.81$, $SD = 2.40$). Follow-up visits for the sample as a whole occurred between 0 and 7.84 years after diagnosis ($M = 1.63$, $SD = 1.46$). The vast majority (96.4%) of time points were within 5 years of diagnosis. A total of 2866 motor score assessments were used for clustering, which resulted in three overall clusters: TD, IT, and PIGD. Within IT, three specific clusters emerged: AxD, ApD, and RD (Figure 1). Subtypes were named based on the MDS-UPDRS items they included (Table 1).

Using all available motor score assessment data (OFF and ON-medication) at all time points, the following frequencies of subtypes were observed: 70.4% TD, 1.1% AxD, 4.7% ApD, 20.3% PIGD. 0.7% of cases were not assigned a subtype. However, these values are irrespective of disease duration.

Next we evaluated for any changes in subtypes during the duration of data collection. We examined OFF-medication subtype changes over time for each patient to study natural disease progression. We found that 232 patients (54.8%) maintained a stable motor subtype designation at all follow-up visits. Of these patients, 91.4% were classified as TD and 8.6% were classified as PIGD. The remaining 191 (45.2%) patients met criteria for at least two different motor subtype designations throughout the duration of the study. We were interested in whether or not there were trends in the subtype designation within this group specifically.

All patients with inconsistent subtypes were subsequently examined together to produce sample-level summary data. Using 6-month bins between 0 and 5 years (yrs) after diagnosis, we totaled the number of time points assigned to each subtype. For analysis, we dropped bins that had less than 25% of patients included (2.5-3.0 yrs, 3.5-4.0 yrs, and 4.5-5.0 yrs). Chi-square test between 0-0.5 yrs and 4-4.5 yrs suggested that subtype frequencies change over time, $\chi^2(4) = 18.34$, $p < 0.01$ (Figure 2).

To better understand this change over time, we examined the proportion of subtypes continuously with increasing disease duration (Figure 3). Using a stacked area plot, for visualization we ordered the subtypes from TD to PIGD, with intermediate subtypes in between. We chose this designation based on previous work suggesting that TD could represent the earliest stages of PD, whereas PIGD may represent later stages [22,23]. We chose to place AxD following TD since it has an overall decreased prevalence in the time range we considered (Figure 2). And while ApD and RD both have an overall increased prevalence with disease duration (Figure 2), we noticed that RD increased relatively more, hence we placed RD after ApD and before PIGD. When considering all time points, there remained a significant change in subtype frequencies over time, $\chi^2(24) = 54.80$, $p < 0.001$. Post-hoc comparisons revealed no differences within the first 2 years of diagnosis: 0.5 vs 1 yr after diagnosis, $\chi^2(4) = 7.17$, $p = 0.13$, 0.5 vs 1.5 yrs after diagnosis, $\chi^2(4) = 4.66$, $p = 0.32$, and 0.5 vs 2 yrs after diagnosis, $\chi^2(4) = 2.57$, $p = 0.63$. However, beginning at 2 yrs after diagnosis, we observed significant changes in subtype frequencies for the remaining follow-up periods: 2 vs 2.5 yrs, $\chi^2(4) = 12.19$, $p < 0.05$, 2 vs 3.5 yrs, $\chi^2(4) = 10.78$, $p < 0.05$, and 2 vs 4.5 yrs, $\chi^2(4) = 20.48$, $p < 0.001$.

Given the significant differences observed beginning at 2 years after diagnosis, we used a linear regression to quantify the stepwise change in subtype frequencies between 2 and 4.5 years after diagnosis. In this time range, TD frequency decreased by 0.086 per year ($p < 0.01$) and PIGD frequency increased by 0.097 per year ($p < 0.01$).

Discussion

Our results identified an additional AxD, ApD, and RD subtypes of PD, in addition to the previously reported TD, IT, and PIGD subtypes [2]. Our methods employed a novel, unsupervised machine learning approach to isolate different motor subtypes in newly diagnosed PD by using MDS-UPDRS motor assessment data. These results also suggested that early PD sub-classification was stable for some patients, but quite unstable for others. Around 60% of patients are classified as TD and 20% as PIGD within 6 months of

diagnosis. By five 5 after diagnosis, these values shifted to 40% and 35%, respectively. That is, there was an overall shift away from TD. These results strongly suggest that motor subtype designation may be influenced by disease duration.

Previous studies using data-driven techniques differ from the present study in several ways. This was the first clustering-based investigation to specifically utilize the MDS-UPDRS assessment, which therefore resulted in subtypes that have direct motor clinical correlation. In contrast, several previous clustering studies have resulted in groups such as “good motor control”[13], which may be difficult to interpret or difficult to apply to patients in the clinical setting. Some of the prior clustering routines relied on previously defined models [24] or variables such as a tremor score [25], while our methodology used no *a priori* information. Also, our study uses a particularly large sample size ($n = 423$). For comparison, a recent systematic review of cluster analysis in PD noted studies with sample sizes ranging from 44 to 176 [26]. Finally, our approach utilized longitudinal data, distinguishing it from most data-driven clustering studies, with relatively low sample sizes [26], that usually rely on single time points, allowing us to identify subtype changes over time and more precisely categorize subtype shifting.

Our results align well with prior studies and general clinical observation regarding identification of the most commonly recognized motor subtypes. Stebbins and colleagues used a non-data-driven approach to determine which MDS-UPDRS Part II and III items to sum when computing a TD or PIGD score in practice [21]. In our study, the MDS-UPDRS items assigned to the PD and PIGD subtype respectively were identical to those listed in Stebbins's report, with the exception of the addition of Item 2.11 (getting out of a bed, a car, or a deep chair) and 3.9 (arising from a chair) within the PIGD score. Interestingly, since we elected to use a hierarchical technique, we were able to discern a potential solution to the highly controversial IT group. That is, there appeared to be distinct AxD, ApD, and RD groups. However, these subtypes were not as prevalent, particularly the AxD and RD, though there were more cases of RD with longer disease duration. Previous authors suggested the presence of these dominant symptoms in certain PD patients [3,15]. It is unclear whether these intermediate subtypes in particular are distinct from others with regards to comorbidities and non-motor measures. Longer follow-up may elucidate whether these patients progress differently than others.

For patients with inconsistent subtypes, we discovered an overall trend to shift away from a TD phenotype and toward a PIGD phenotype. It is possible that patients with consistent subtypes may have slower disease progression (for TD patients) or faster progression (for PIGD patients), hence this may have masked changes in subtype for some patients in our cohort [15]. These findings contribute to the collective body of evidence showing that with disease duration, the prevalence of TD subtype designation decreases and that of PIGD increases [3,27-29].

Our study has several important limitations. First, the motor subtypes we identified were limited by the items included in the MDS-UPDRS assessment. Only those motor symptoms captured by this assessment could be used to arbitrarily classify motor subtype categories. Second, our ratio-based approach to setting cutoff criteria for assigning subtypes, while also

based on previous research [21], may not have been stringent enough for categorizing patients into one of several subtypes. Finally, it is important to note the number of time points for each patient and the disease duration at each time point varied considerably in this large sample. Longer and consistent follow-up will be needed to ascertain that this sample does not include any atypical parkinsonism patients.

Our findings overall suggest that there exist at least 5 distinct motor subtypes in early PD patients: TD, AxD, ApD, RD, and PIGD. Subtypes were mutable throughout disease duration with a trend that was detectable within the first 5 years. Further studies should investigate the differences between patients with consistent and inconsistent subtypes with respect to variables such as demographics, genetics, environmental, and other disease attributes. Longer patient follow-up periods may overcome some of the limitations of the present study.

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Figure 1. Schematic representation of the output from the hierarchical clustering algorithm. Taken together, we categorized Axial Dominant (AxD), Appendicular Dominant (ApD), and Rigidity Dominant (RD) as Intermediate or Indeterminate Type (IT).

Figure 2.

Frequencies of each subtype for patients with inconsistent subtypes between 0 and 0.5 years after diagnosis (a) and between 4.0 and 4.5 years after diagnosis (b). There is a significant shift away from a TD phenotype.

Figure 3.

Proportions of motor subtypes for patients with changing motor subtypes up to 4.5 years following diagnosis. Data were grouped into 6-month bins. For instance, the proportions of different subtypes between 1.5 and 2.0 years is plotted on the x-axis at the value 2.

Table 1
Motor Subtypes

Subtype Name	MDS-UPDRS Items ^a
Tremor Dominant (TD)	2.10, 3.15 (R, L), 3.16 (R, L), 3.17 (RUE, LUE, RLE, LLE, Lip/Jaw), 3.18
Intermediate Type (IT)	
Axial Dominant (AxD)	3.1, 3.2, 3.13, 3.14
Appendicular Dominant (ApD)	3.4 (R, L), 3.5 (R, L), 3.6 (R, L), 3.7 (R, L), 3.8 (R, L)
Rigidity Dominant (RD)	3.3 (Neck, RUE, LUE, RLE, LLE)
Postural Instability and Gait Disorder (PIGD)	2.11, 2.12, 2.13, 3.9, 3.10, 3.11, 3.12

^aR: Right, L: Left, UE: Upper Extremity, LE: Lower Extremity

The column on the right indicates the MDS-UPDRS items that were included in each cluster. The left column indicates the name we assigned to these clusters.