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Publication Date

2019-08-01

DOI

10.1016/j.parkreldis.2019.06.017

Peer reviewed

HHS Public Access

Author manuscript

Parkinsonism Relat Disord. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

Parkinsonism Relat Disord. 2019 August ; 65: 178–183. doi:10.1016/j.parkreldis.2019.06.017.

Motor Phenotype Classification in Moderate to Advanced PD in BioFIND Study

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Financial Disclosure/Conflict of Interest: The authors report no conflicts of interest.

Financial Disclosure for All Authors in Past 12 months: None.

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Abstract

Background: Three motor phenotypes have been described in PD: postural instability and gait difficulty (PIGD) dominant, tremor-dominant (TD), and indeterminate (IND) subtype. These phenotypes have been associated with different cognitive trajectories, motor outcomes, and biomarkers profiles. However, whether motor subtype classifications change with treatment and disease progression is not well established.

Methods: To evaluate motor subtype ratio changes, we used the chi-square test for the *off* and *on* state motor subtypes for 115 PD participants in the BioFIND study and used repeated-measures analyses to evaluate longitudinal changes in 162 PD participants with five-year follow-up in the PPMI study.

Results: PIGD and TD subtypes in moderate to advanced PD participants change with dopaminergic agents. For those who shifted subtypes, improvement in tremor accounted for the transition of 15 (25.4%) TD participants, while the lack of tremor improvement along with minimal changes in PIGD score resulted in changes for eight (19.0%) PIGD individuals. Analyses of PPMI data revealed that all three subgroups had a significant decrease in subtype ratio with disease progression and a significant decline in subtype ratio occurred only in the TD subgroup with dopaminergic agents. The impact of dopaminergic medication effect on subtype shift for each visit was also more notable with disease advancement.

Conclusions: Motor subtypes are not fixed but change with progression of the disease *and* with treatment. Improvement in tremor was the main contributor to motor phenotype transitions in the BioFIND cohort. A more stable classification system for subtypes based on underlying biological differences is desirable.

Keywords

levodopa; motor phenotype; Parkinson's disease; subtypes

1. Introduction

Parkinson's disease (PD) is a clinically heterogeneous neurodegenerative disease characterized by four cardinal motor features: bradykinesia, rigidity, rest tremor, and postural instability. Although there have been many attempts to identify motor subtypes of

PD in order to classify potentially different disorders within the broad category of PD, it is not clear if these motor phenotypes actually represent different underlying biological groups with heterogeneous pathogeneses [1]. The most widely used classification defines two distinct motor subtypes of PD originally described in the DATATOP study by Jankovic and colleagues: tremor-dominant (TD) and postural instability and gait difficulty (PIGD) dominant [2]. These motor subtypes, described in early untreated PD cases, have been associated with different clinical courses. Compared to the TD subtype, PIGD phenotype is associated with greater risk of cognitive impairment, poorer response to dopaminergic treatment, and lower levels of CSF alpha-synuclein, raising a possibility of biological differences between these motor subtypes [3-8]. Other schemas used non-motor features and cognitive changes to classify PD subtypes [9-12]. Additionally, longitudinal studies have also shown that with disease progression PD may change from TD to the PIGD subtype, suggesting that the motor subtype classification is not stable over time [1,4]. Furthermore, dopaminergic therapy may have a differential effect on motor features and could contribute to the shift in subtype classifications. Axial features such as postural instability are less responsive to levodopa than other motor features [13-15]. Therefore, we utilized the BioFIND (Fox Investigation for New Discovery of Biomarkers in PD) study data containing motor examination during *on* and *off* states to explore this question [16]. In order to analyze longitudinal changes in motor subtypes, we evaluated early PD participants using data from Parkinson's Progression Markers Initiative (PPMI) and compared them to moderate to advanced PD participants in BioFIND.

2. Methods

2.1. Study design

a. BioFIND—BioFIND is a multicenter, biomarker study of moderate to advanced PD participants and age- and sex-matched healthy controls recruited from eight sites in the United States between 2012 and 2015. Details of the study were described by Kang et al [16]. Briefly, we recruited PD participants between ages 50-75 with at least five years of motor symptoms and a well-established response to dopaminergic agents and/or amantadine. They were examined using the International Parkinson and Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [17] in a practically defined *off* state (approximately 12 hours after the last dose of PD medications the night before) and *on* state (1-3 hours after the last dose of PD medications) [16]. Levodopa equivalent daily dosages (LEDD) were calculated based on the algorithm from Tomlinson et al [18]. All recruitment and study protocols were approved by the institutional review boards for the University of Rochester Clinical Trials Coordination Center (CTCC) and individual sites and written informed consent was obtained from all participants in the study.

b. PPMI—PPMI is a multicenter study, consisting of untreated PD participants at enrollment. Details of the study were provided in a prior publication [19]. At the study onset, all PD participants were required have a positive 123-I Ioflupane dopamine transporter (DatScan®) imaging, recently diagnosed with idiopathic PD, be untreated, and have an asymmetric resting tremor or asymmetric bradykinesia or at least two of the

following: bradykinesia, rigidity, and resting tremor [19]. MDS-UPDRS was performed at every study visit in the *off* state (defined as medication naive condition or more than six hours after the last dose of dopaminergic therapy for those taking levodopa or dopamine agonists) or the *on* state (defined as an hour after the last dose of dopaminergic therapy or other PD medications) or both [17,19]. Individuals taking non-dopaminergic therapy, such as monoamine oxidase inhibitors, amantadine, or anti-cholinergics, were only examined in the *on* state [19]. *On* evaluations are done at the next study visit after the initiation of PD medications and performed yearly thereafter [19]. All PPMI sites received approval from an ethical standards committee on human experimentation and obtained written informed consent from all participants [19].

2.2. Motor Subtype Assignment

In order to classify participants' motor subtypes, tremor scores and PIGD scores were calculated using an algorithm from Stebbins et al [20]. Overall tremor score was determined by averaging eleven items: one tremor score from part II and ten tremor scores from part III (2.10, 3.15-3.18) [20]. PIGD score was calculated by averaging five items: walking/balance and freezing scores from part II; gait, freezing of gait, and postural instability scores from part III (2.12, 2.13, 3.10-3.12) [20]. Subjects were grouped based on their tremor score to PIGD score ratios: PIGD if the ratio was < 0.90, indeterminate (IND) if the ratio was >0.90 and <1.15, or TD if the ratio was > 1.15 [20].

2.3. Statistical Analyses

Demographics and clinical information for all three subtypes were compared using Chi-square and ANOVA tests for all the normally distributed variables and Kruskal-Wallis H test for non-normal variables within both cohorts. Post hoc analyses were performed using either Bonferroni or the Mann-Whitney U tests.

a. BioFIND—Chi-square tests were used to examine whether there was a significant difference in the percentage of subjects who changed motor classification from the *off* to *on* states within BioFIND cohort. Group comparisons for PIGD shifters, PIGD non-shifters, TD shifters, and TD non-shifters in BioFIND were performed using ANOVA followed by Bonferroni adjustments. Independent samples t-tests were used to perform comparisons between TD and PIGD shifters as well as TD and PIGD non-shifters. Shifters were individuals who changed subtypes after the administration of dopaminergic agents, while non-shifters remained within the same subtype post-medication. In order to analyze effect of dopaminergic agents on specific PD motor features within BioFIND, we calculated the average change in tremor, postural instability and gait, bradykinesia, and rigidity for all subjects. The average change in tremor scores was calculated using the difference between the averages of ten tremor items from part III (3.15-3.18) for *off* and *on* visits. The average change in postural instability and gait scores was computed using the difference between *on* and *off* averages of gait, freezing of gait, and postural instability scores from part III (3.10-3.12). The average change in bradykinesia scores was found by taking the difference between the two averages of ten bradykinesia items from part III (3.4-3.8). The average change in rigidity scores was calculated in a similar fashion using five rigidity items from part III (3.3a-e) for both visits.

b. PPMI—To analyze changes in motor subtype ratio longitudinally within PPMI, three motor subtypes were defined in the *off* state at year one (V4) and then repeated-measures analyses were performed on subsequent PPMI visits for each of the three subtypes using the 162 participants who completed the study until the end of year five (V12). Dopaminergic medication effects on subtype ratios were also evaluated using repeated-measures analyses for all PPMI visits with *on* and *off* state scores for years one through five (V4, V6, V8, V10, V12). IBM SPSS software version 23 and SAS version 9.3 (SAS Institute, Cary, NC) were used to perform all calculations.

c. PPMI and BioFIND—After combining both cohorts, linear regression analyses were performed for subtype ratio and each of the demographic and clinical variables, specifically, age, sex, *off* motor MDS-UPDRS score, disease duration, and cohort (PPMI or BioFIND). A multiple linear regression analysis was subsequently conducted including only predictors with $p < 0.25$ from the univariate analyses. PPMI demographic variables for the first year of the study were used in the analyses.

3. Results

3.1. Cohort demographics.

a. BioFIND.—BioFIND study enrolled 119 PD subjects but final analyses consisted of 115 individuals who had complete clinical data. During the *off* state in BioFIND, there were 42 (36.5%) PIGD, 14 (12.2%) IND, and 59 (51.3%) TD subtypes. Subjects in each of the three groups during the *off* state were comparable in their age at enrollment, sex, ethnicity, race, level of education, disease duration, *off* motor UPDRS scores, and Montreal Cognitive Assessment (MoCA) [21] scores, but significantly different in their H&Y stage (PIGD 2.6±0.8, IND 1.9±0.5, TD 2.0±0.4, $p<0.001$) and LEDD (PIGD 873.4±382.1 mg, IND 662.0±413.6 mg, TD 664.6±361.7 mg, $p=0.02$). Post-hoc comparison showed that PIGD subtype had significantly higher H&Y stage when compared to either IND ($p=0.002$) or TD subtypes ($p<0.001$) and had higher LEDD when compared to TD subtype ($p=0.02$) (Supplementary Table 1).

b. PPMI.—At baseline, PPMI study enrolled 423 individuals but final analyses comprised of 162 individuals who completed all five years of the study and had complete demographic information. There were 25 (15.4%) PIGD, 20 (12.3%) IND, and 117 (72.2%) TD participants and the three subtype groups were comparable in their age, sex, ethnicity, race, education level, disease duration, *off* motor MDS-UPDRS scores, and MoCA scores, but were significantly different in their H&Y stages (PIGD 1.7±0.6, IND 1.9±0.4, TD 1.5±0.5, $p=0.001$). Post-hoc comparisons revealed that the TD group had significantly lower H&Y stage compared to either the IND group ($p=0.001$) or the PIGD group ($p=0.045$) (Supplementary Table 2).

3.2. Effect of disease progression on tremor to PIGD score ratio.

a. PPMI changes with four years follow-up.—Taking into account all 423 individuals at baseline, after one year, there were 86 (23.4%) PIGD, 40 (10.9%) IND, and 241 (65.7%) TD individuals. After five years, there were 53 (30.5%) PIGD, 16 (9.2%) IND,

and 105 (60.3%) TD patients (Figure 1). For all three subtypes, there were were significant changes in tremor to PIGD score ratio for each consecutive *off* visit from year one to year five with an average decrease of 0.51 for all three groups (PIGD β=−0.51, SE=0.08, $p<0.0001$; IND β=−0.51, SE=0.08, $p<0.0001$; TD β=−0.51, SE=0.08, $p<0.0001$).

b. PPMI vs BioFIND.—When comparing the PPMI cohort at year one to the BioFIND cohort in order to gauge differences in motor phenotype in early vs. moderate stages of PD, we found a higher percentage of participants classified as PIGD (23.4% PPMI vs. 36.5% BioFIND) and a lower percentage of participants classified as TD (65.7% PPMI vs. 51.3% BioFIND) in the BioFIND cohort. Our multiple linear regression model included four demographic and clinical variables from the univariate analyses: enrollment age ($p=0.08$), *off* motor MDS-UPDRS ($p=0.0015$), disease duration ($p=0.0006$), group ($p<0.0001$). The cohort in BioFIND had 0.85 points lower average tremor to PIGD score ratio compared to the PPMI cohort (BioFIND: 1.59, PPMI: 2.44) and the cohort effect is significantly associated with tremor to PIGD score ratio ($p=0.0002$) after adjusting for the enrollment age ($p=0.88$), disease duration ($p=0.12$), and *off* MDS-UPDRS motor score ($p=0.40$).

3.3. Effects of antiparkinsonian treatment on tremor to PIGD score ratio.

a. Changes in PPMI with dopaminergic treatment.—For both the PIGD and IND subtypes, there were no significant differences in the tremor to PIGD score ratio between *off-on* states within each visit from year one through five (PIGD β=0.23, SE=0.13, $p= 0.071$; IND β=0.04, SE=0.19 $p=0.823$). The TD subgroup had a significant change in tremor to PIGD score ratio within each visit when comparing all five *off-on* visits with an average decrease of 0.30 (β=−0.30, SE=0.06, $p<0.0001$).

b. Changes in BioFIND with dopaminergic treatment.—During the *off* state, there were 42 (36.5%) PIGD, 14 (12.2%) IND, and 59 (51.3%) TD subtypes. There was a significant proportion of participants who shifted their subtype from the *off* to *on* state ($p=0.001$) (Supplementary Table 3). Of those that were classified as TD during the *off* state, 15 (25.4%) changed to another subtype during the *on* state, with six individuals switching to PIGD and nine others transitioning to the IND subtype. 44 (74.6%) TD participants remained within the same category. Of those that were classified as PIGD, eight (19.0%) subjects shifted to another subtype, including two individuals who transitioned to TD subtype and six individuals who transitioned to the IND subtype. 34 (81.0%) PIGD participants remained the same subtype after administration of dopaminergic therapy. Ten (71.4%) IND individuals transitioned to either the PIGD or the TD subtype while four (28.6%) remained within the IND category post medication.

3.4. Changes in motor subscores with treatment in BioFIND.

In order to elucidate the driving forces responsible for motor subtype shifts after administration of dopaminergic medication, we analyzed the improvement in each of the four motor features of PD and found a significantly greater improvement in tremor in the TD group who shifted their subtype (0.56±0.48) than the TD non-shifters (0.12±0.37, $p=0.001$), PIGD non-shifters (0.15±0.22, $p=0.006$), or PIGD shifters (−0.02 ±0.27, $p=0.005$). For the PIGD shifters, the improvement in PIGD score (0.33±0.18) was similar when compared to

the PIGD non-shifters (0.24±0.31, p=1.00) and the TD shifters (0.09±0.26, p=0.15). Specifically, the two PIGD shifters who changed to the TD subtype showed similar improvement of PIGD scores (0.20±0.00) compared to the PIGD non-shifters (0.24±0.31, p=0.45). However, they also experienced an accompanying increase in their tremor scores (−0.14±0.19), as opposed to an improvement in tremor seen in the PIGD non-shifters (0.15±0.22, p=0.08). Therefore, the subtype change was driven by a combination of increased tremor score in the numerator and decreased PIGD score in the denominator. All four groups, (TD shifters, PIGD shifters, TD non-shifters, and PIGD non-shifters) had similar improvement in their bradykinesia and rigidity scores (bradykinesia: TD shifters 0.52±0.50, PIGD shifters 0.49±0.76, TD non-shifters 0.36±0.57, PIGD non-shifters 0.51±0.57, p=0.63; rigidity: TD shifters 0.41±0.51, PIGD shifters 0.40±0.64, TD non-shifters 0.36±0.45, PIGD non-shifters 0.38±0.55, p=0.99) (Figure 2).

4. Discussion

This is one of the few studies analyzing the effect of dopaminergic agents and disease duration on motor subtype classification in moderate to advanced PD. The major advantage to utilizing the BioFIND database is the high diagnostic specificity of PD since the study enrolled participants who met all three motor signs for PD with sufficient duration of disease to screen out those with atypical parkinsonian syndromes. We found that a significant proportion of participants shifted their motor subtypes when examined *off* versus *on* meds in both the moderate to advanced PD cohort within BioFIND and also with disease progression after analyzing the longitudinal data from PPMI. Compared to a previous study about the stability of motor subtypes in PPMI within the first year [22], our result offers extended analyses of the PPMI cohort focused on the PPMI participants who initiated therapy from year one through year five and shows an interesting trend for increasing proportion of shifters with PD progression. In addition, the TD group was more likely than the PIGD to transition to another subtype after the administration of dopaminergic agents within BioFIND. Likewise, in PPMI, the rate of shift from the TD subtype with the administration of dopaminergic agents increased whereas the rate of shift from the PIGD subtype decreased with disease progression. The relative lack of influence of dopaminergic therapy on PD motor subtypes from baseline to year one of the PPMI study as previously reported by Simuni and colleagues may be due to their milder motor deficit and the long-duration response to levodopa that limits the differences between *on* and *off* states with less than a day of withdrawal from medication [22-26]. Additionally, the increasing number of the subjects with PIGD classification over time could reflect worsening of non-dopaminergic lesions and poor response of PIGD symptoms to dopaminergic medications.

To further explore the driving forces influencing the changes in motor classification, we compared the PIGD shifters to the TD shifters in BioFIND and discovered that the TD shifters had a significantly greater change in their average tremor scores, or the numerator of the TD/PIGD ratio, compared to the change in their PIGD scores indicating improvements in tremor may be the catalyst behind transitions in the TD group. On the other hand, the tremor to PIGD score ratio increase for the PIGD shifters was partially driven by the lack of improvement in tremor (Figure 2). Motor subtype transitions depend on the change in ratio of the average tremor score to the average PIGD score. If the improvement in tremor

(numerator) outweighs the improvement in PIGD then the ratio will become smaller, resulting in an overall shift towards PIGD subtype. Conversely, if the improvement in PIGD (denominator) is greater than the improvement in tremor then the ratio will become larger, resulting in a transition towards TD subtype. A ratio introduces a non-linear relationship in some situations when a small change in denominator can introduce a large change in the ratio (Figure 3). Overall, the improvement in postural instability and gait with dopaminergic medication was smaller than the improvement in either bradykinesia or rigidity for each of the four groups, reflecting the possible involvement of non-dopaminergic pathways in postural instability and gait abnormalities in PD [15,27]. BioFIND PIGD subjects were on higher LEDD compared to TD and IND subtypes, again suggesting the differential response of postural instability versus bradykinesia or rigidity consistent with previous studies [13-15].

Although BioFIND is a cross-sectional study, comparison with PPMI study with the same clinical and biological protocol provided some additional insight on the effect of disease severity on motor subtypes. At the beginning of the study, the PPMI cohort were on average almost seven years younger, had eight years shorter disease duration, and scored 18 points lower in their *off* state motor MDS-UPDRS scores compared to the BioFIND group [16, 22]. Although BioFIND required subjects to have all three classic motor signs of parkinsonism rather than only two motor signs for the diagnosis of PD in PPMI, there still were more individuals classified as PIGD and fewer participants classified as TD in BioFIND than compared to PPMI baseline or year 5. Similar numbers of IND participants occupy both cohorts. Consistent with findings from other published reports [1,4], our study also suggests a shift towards PIGD classification and away from TD subtype with the progression of the disease, specifically a decline in tremor to PIGD score ratio from year one to five of PPMI. In a prospective study by Alves and colleagues examining 171 PD participants from Norway, there were 53.8% PIGD and 25.1% TD at baseline, 88.1% PIGD and 6.0% TD after eight years of follow up, again pointing toward a preference for more PIGD subtype and less TD subtype with the progression of the disease [4].

Within the BioFIND study, both TD and PIGD subtypes are unstable between *off* and *on* states. Changes in the average tremor score mainly drove the transitions in the TD and PIGD groups. Comparing the *off* states for the BioFIND cohort with the PPMI cohort at baseline and year five, we found an increase in PIGD subtype with a decrease in TD subtype, in agreement with previously published reports about subtype trends in PD [1,4]. Traditionally defined motor phenotypes shift with dopaminergic medication and disease severity and may not be indicative of biologically different subgroups within PD. Therefore, previously reported conclusions about differential motor, cognitive, and occupational outcomes within each motor subtypes need to consider this possibility. Further research on biologically meaningful way of classifying subgroups within the currently defined diagnostic category of PD is a crucial next step.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We would like to thank Dr. Changyu Shen of Harvard Catalyst for his biostatistical help and the PPMI and BioFIND study teams and the volunteers who participated in the study.

Parts of the data used in the preparation of this article were obtained from the Fox Investigation for New Discovery of Biomarkers ("BioFIND") database (http://biofind.loni.usc.edu/). For up-to-date information on the study, visit www.michaelifox.org/biofind. BioFIND is sponsored by The Michael J. Fox Foundation for Parkinson's Research (MJFF) with support from the National Institute for Neurological Disorders and Stroke (NINDS). Parts of the data used in the preparation of this article were obtained from the PPMI database (www.ppmi-info.org/data). For up-to-date information on the study, visit www.PPMI-info.org. PPMI—a public-private partnership—is funded by MJFF and funding partners, including AbbVie, Avid, Biogen, Bristol-Myers Squibb, Covance, GE Healthcare, Genentech, GalaxoSmithKline, Lily, Lundbeck, Merck, Meso Scale Discovery, Pfizer, Piramal, Roche, Servier, and UCB found at www.ppmi-info.org/fundingpartners.

Funding: The BioFIND study funding was provided by The Michael J. Fox Foundation for Parkinson's Research and National Institute of Neurological Disorders and Stroke. The National Center for Advancing Translational Sciences of the National Institutes of Health at Columbia University (UL1TR000040) and Oregon Health & Science University (UL1TR000128) provided research visit space support. Fellowship funding for Dr. Luo was provided by the Parkinson's Foundation and the National Institutes of Health Training Grant T32-NS07153.

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Highlights:

- In PD, motor subtypes are not fixed but change with progression of the disease *and* with treatment.
- Changes in tremor score were the main contributor to motor phenotype transitions in the BioFIND cohort.
- Five-year longitudinal analyses of PPMI data revealed significant changes in the tremor to PIGD score ratio for all three subgroups with disease progression and a significant decrease in the tremor to PIGD score ratio for the TD subgroup after dopaminergic treatment.

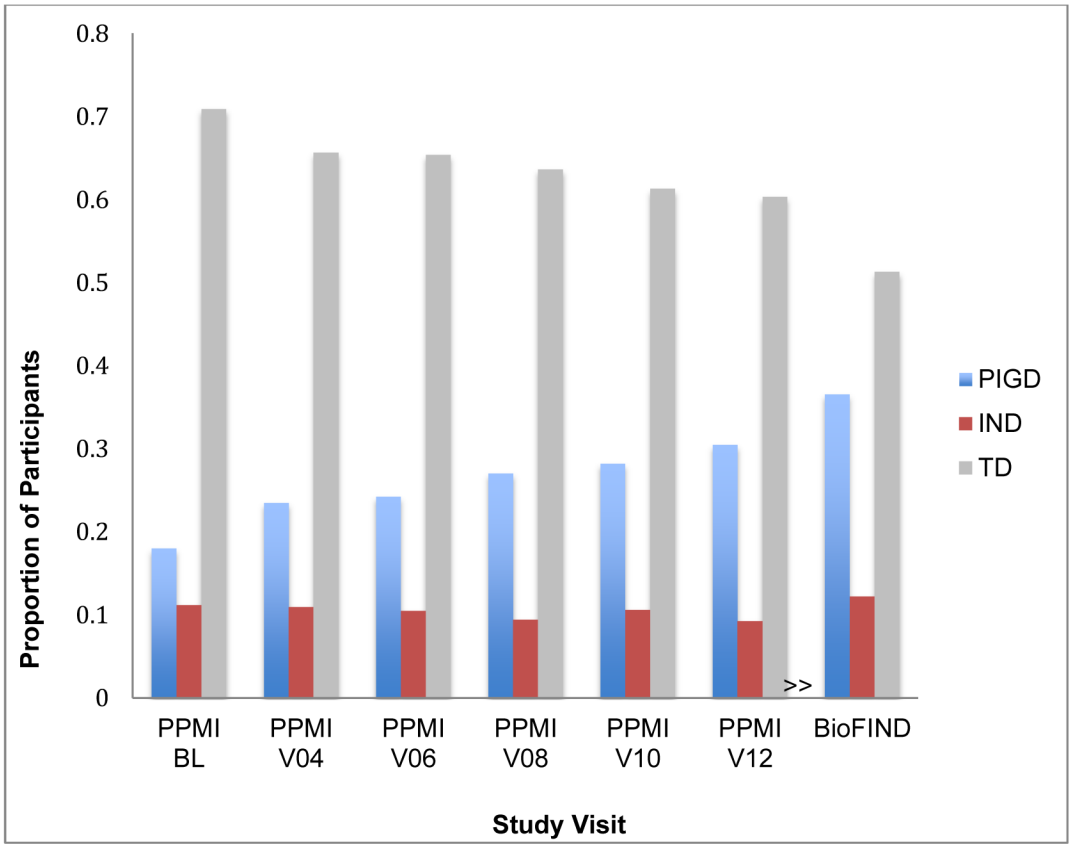

Figure 1. Longitudinal changes in motor subtype classification over time in PPMI and BioFIND cohorts.

BL= Baseline Visit, V04= 4th Visit, V06= 6th Visit, V08= 8th Visit, V10= 10th Visit, V12= 12th Visit

Blue, red, and gray bars represent the proportion of participants with PIGD, IND, and TD subtypes, respectively. Within the PPMI study, the participants at baseline had an average of six months of disease. For PPMI visits 4 and 12, they had on average 18 and 66 months of disease, respectively. BioFIND participants had on average 108 months of disease. PIGD subtype increases while TD subtype decreases over time when comparing *off* state subtypes for PPMI from baseline to year 5 and BioFIND. The proportion of IND subtype remains approximately the same over time.

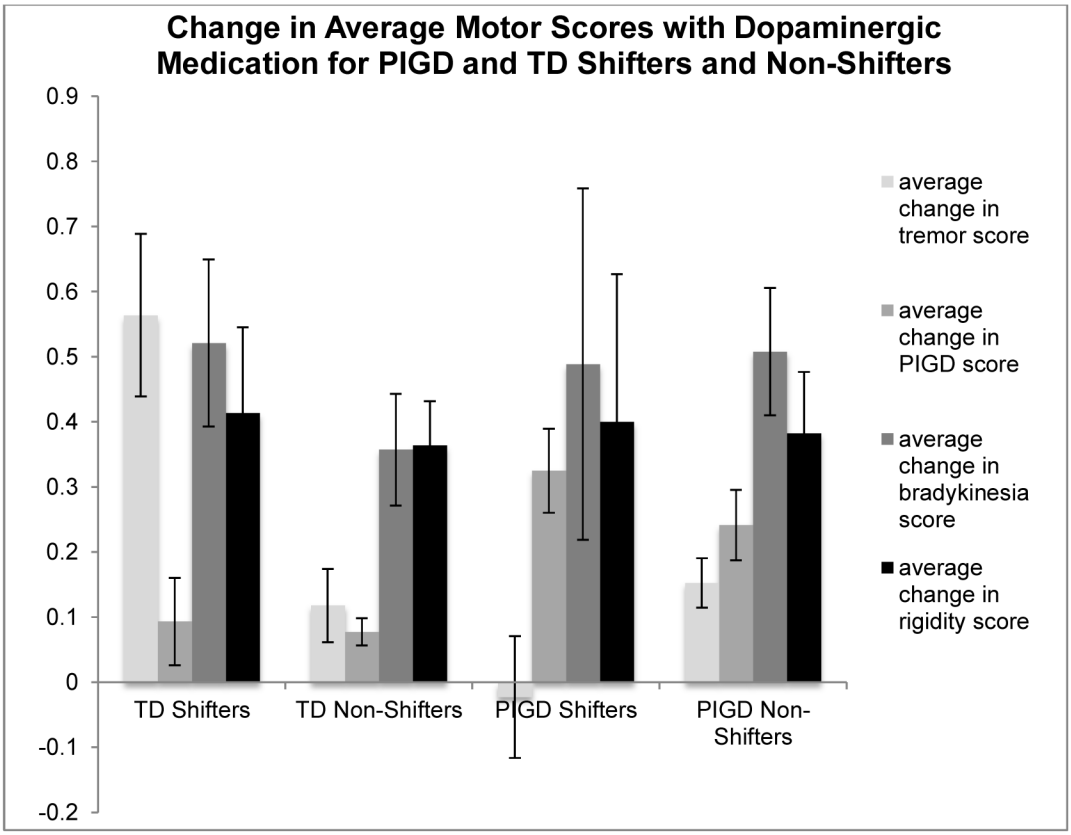

Figure 2. Changes in motor features from *off* to *on* state in PIGD and TD shifters in the BioFIND cohort.

All four groups improved in all four motor features of PD after dopaminergic medication administration except for tremor in PIGD shifters. Changes in average tremor score and PIGD score were significantly different between PIGD and TD shifters. For TD shifters, the improvement in tremor score accounted for the transition from TD to either IND or PIGD. On the other hand, the improvement in postural instability and gait accounted for the transition from PIGD to either TD or IND. Bradykinesia and rigidity improved similarly across both groups.

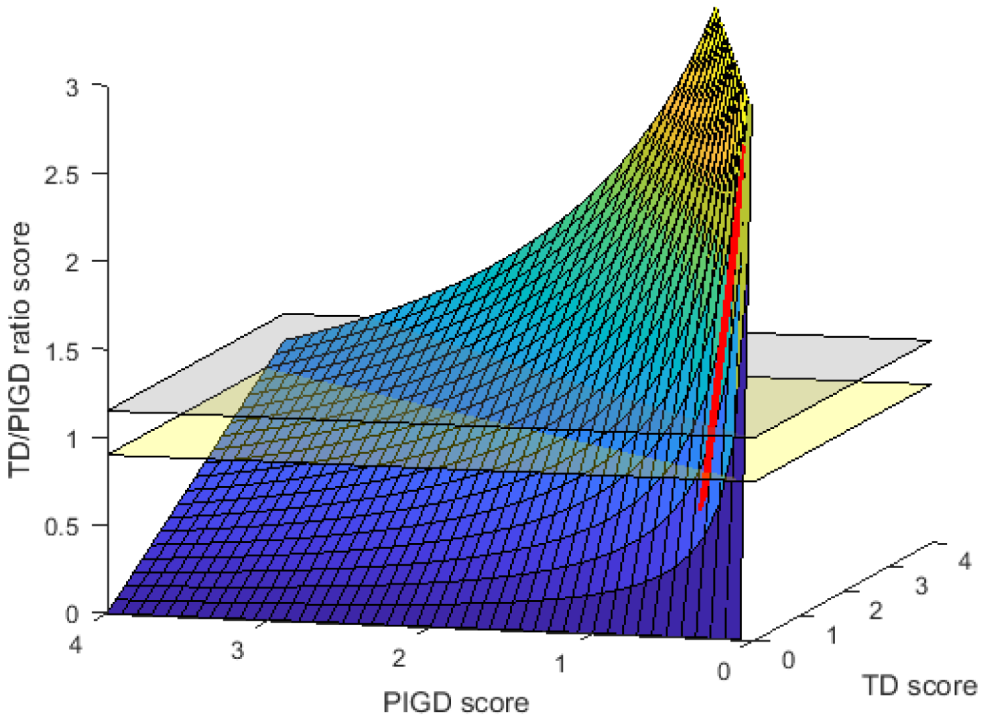

Figure 3. Ratio of the average tremor score to the average PIGD score determines motor subtype.

The relationship between TD/PIGD ratio (Z axis) vs. TD score and PIGD scores. The grey plane shows the borderline between TD and indeterminate subtypes and the yellow plane shows the borderline between the indeterminate and PIGD subtypes. The red line shows one subject who shifted from PIDG to TD subtype with small changes in TD and PIGD scores that resulted in a relatively large change in the TD/PIGD ratio.