RESEARCH ARTICLE

# Distinct progression patterns across Parkinson disease clinical subtypes

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## Abstract

**Objective**: To examine specific symptom progression patterns and possible disease staging in Parkinson disease clinical subtypes. **Methods**: We recently identified Parkinson disease clinical subtypes based on comprehensive behavioral evaluations, "Motor Only," "Psychiatric & Motor," and "Cognitive & Motor," which differed in dementia and mortality rates. Parkinson disease participants ("Motor Only": $n = 61$, "Psychiatric & Motor": $n = 17$, "Cognitive & Motor": $n = 70$) and controls ($n = 55$) completed longitudinal, comprehensive motor, cognitive, and psychiatric evaluations (average follow-up = 4.6 years). Hierarchical linear modeling examined group differences in symptom progression. A three-way interaction among time, group, and symptom duration (or baseline age, separately) was incorporated to examine disease stages. **Results**: All three subtypes increased in motor dysfunction compared to controls. The "Motor Only" subtype did not show significant cognitive or psychiatric changes compared to the other two subtypes. The "Cognitive & Motor" subtype's cognitive dysfunction at baseline further declined compared to the other two subtypes, while also increasing in psychiatric symptoms. The "Psychiatric & Motor" subtype's elevated psychiatric symptoms at baseline remained steady or improved over time, with mild, steady decline in cognition. The pattern of behavioral changes and analyses for disease staging yielded no evidence for sequential disease stages. **Interpretation**: Parkinson disease clinical subtypes progress in clear, temporally distinct patterns from one another, particularly in cognitive and psychiatric features. This highlights the importance of comprehensive clinical examinations as the order of symptom presentation impacts clinical prognosis.

## Introduction

Parkinson disease (PD) presents as heterogeneous clinical manifestations with different combinations of motor, cognitive, and psychiatric symptoms. Differences in symptom profiles and progression patterns suggest the existence of PD subtypes, and thus potentially different clinical prognoses. Clinical subtypes have been explored previously, however, these attempts focused on motor symptoms[1,2]

or used broad metrics for cognitive function[3,4] or psychiatric function.[3,5,6] Furthermore, only a handful of studies provide follow-up beyond four years,[1,7–9] limiting prognostic utility. Therefore, prior subtypes do not account for the diversity of symptom presentation or longitudinal progression.

We recently identified three distinct PD clinical subtypes[10]: "Motor Only," featuring mild motor deficits, "Psychiatric & Motor," featuring increased psychiatric

symptoms, and "Cognitive & Motor," featuring decreased cognitive function. While cognitive and psychiatric features distinguished the subtypes and prior longitudinal studies demonstrate that cognitive,[9,11–13] motor,[12,13] and psychiatric function[14,15] worsen over time in PD, the rate of decline and pattern of symptom progression among PD clinical subtypes have not been thoroughly explored. Additionally, though our subtypes differed in mortality and dementia rates,[10] our subtypes may represent disease stages as suggested by other severity-based subtypes.[2,16,17]

This study aims to investigate longitudinal symptom progression within PD clinical subtypes and differences in symptom progression among subtypes. We hypothesize that each subtype will decline faster in its characteristic symptoms (e.g., "Cognitive & Motor" subtype will decline faster in cognitive function). Furthermore, we hypothesize that the subtypes will show distinct clinical progression patterns rather than represent sequential stages of disease severity.

## Methods

### Study protocol approvals, registrations, and patient consents

The Washington University in St. Louis Human Research Protection Office approved this study, and all participants provided written informed consent.

### Participants

All participants come from a larger, longitudinal study[10,18] examining Parkinson disease progression. For inclusion in the larger study, all participants needed to be at least 50 years old, have a minimum of 12 years of education, and agree to brain donation. PD participants needed a clinical diagnosis of PD based on the modified UK PD Society Brain Bank clinical diagnostic criteria,[19] with clear motor response to levodopa. For the larger study, the exclusion criteria included: (1) other neurologic diagnoses, (2) head injury with loss of consciousness >5 min or neurologic sequelae, and (3) schizophrenia or bipolar disorder. In addition, control participants had to have no first-degree family history of PD, a normal neurological exam, and intact cognition at baseline.

All PD participants in this study received a baseline subtype classification from a prior analysis[10]: "Motor Only," "Psychiatric & Motor," or "Cognitive & Motor." For inclusion in the present study, PD and controls also needed (1) a baseline evaluation between January 2006 and September 2015, (2) at least one subsequent evaluation from their baseline visit, and (3) a Clinical Dementia Rating evaluation (CDR)[20] <1 at baseline (i.e., not demented). Additionally, controls needed a $\beta$-amyloid (Pittsburgh compound B; PiB) PET mean cortical binding potential <0.18[21] for inclusion, reducing the risk for preclinical Alzheimer disease.

The original subtyping analysis[10] included 162 PD participants. For this study, 14 participants did not have usable data after the baseline visit (Fig. 1). Thus, these longitudinal analyses include 148 PD participants ("Motor Only": $n = 61$, "Psychiatric & Motor": $n = 17$, "Cognitive & Motor": $n = 70$) and 55 controls who met all inclusion criteria.

### Data collection

All participants completed an initial baseline evaluation and longitudinal follow-up assessments every 1–3 years (average number of follow-up visits = 3.7, average time in study = 4.6 years, range = 1–12 years). At each study visit, participants completed comprehensive motor, cognitive, and psychiatric evaluations as described below.
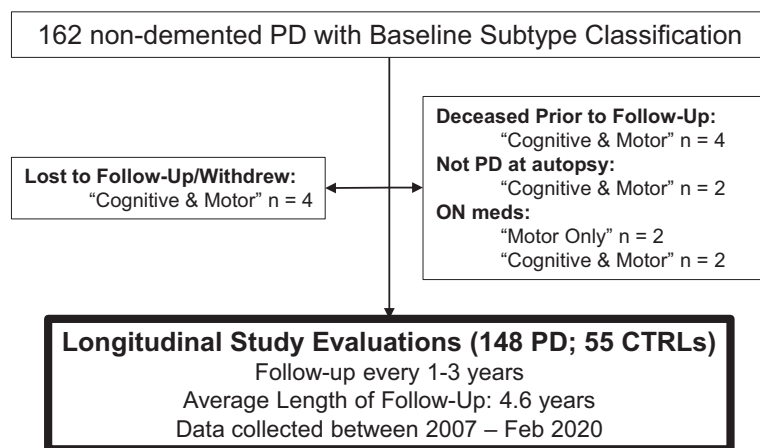


Figure 1. Consort diagram.

For the motor assessment, testing occurred in the practical "OFF" medication state, defined as overnight withdrawal from PD medications. A movement disorder specialist rated the Unified Parkinson Disease Rating Scale motor subscale III (UPDRS3-Total)[22] at the study visit or from video recording.[23,24] The specialist's UPDRS3-Total rating was broken down into tremor (items 1–7), rigidity (items 8–12), bradykinesia (items 13–20), and postural instability and gait disturbance (PIGD; items 23–26) scores. Importantly, all rigidity scores come from the day of the study visit from either the specialist or the trained tester. Raters were trained by a movement disorder specialist (JSP) to properly score rigidity for consistency across all testing. This maximized the amount of usable data.

For cognitive evaluations, participants completed a comprehensive battery of neuropsychological tests for each cognitive domain: executive function (Trail Making Test[25]; Verbal Fluency- Switching[26]; Color-Word Interference[26]), visuospatial function (Judgement of Line Orientation[27]; Spatial Relations Test[28]), memory (California Verbal Learning Test- II, short form[29]; Logical Memory[30]), attention (Digit span[31]; Digit Symbol[31]), and language (Boston Naming test).[32] PD participants completed cognitive assessments while 'OFF' medications to avoid potential medication confounds on performance (i.e., this provides a more accurate assessment of the participant's cognitive function). Additionally, trained raters completed the CDR with each participant and a collateral source and scored the CDR sum of boxes (CDR-SB) to provide a global measure of cognitive function and functional abilities. All CDR interviews were completed 'ON' medications.

For the psychiatric assessments, participants completed self-report measures of depression (Geriatric Depression Scale [GDS])[33] and apathy (Frontal Systems Behavior Scale- Apathy subscale [FrSBe-A]).[34] With the participant's collateral source, participants also completed the Neuropsychiatric Inventory Questionnaire (NPIQ)[35] as an overall measure of psychiatric symptoms and severity. All psychiatric assessments were completed 'ON' medications since the assessments measure function over a period of time rather than just at the time of the study visit.

## Data processing

Standardized scores were computed for each participant at each visit using the mean and standard deviation of baseline raw scores (e.g., z-scores) across all participants in our sample (PD and Control), providing insight into how each group changes from baseline as well as how PD subtypes differ from controls. For participants who developed severe cognitive impairment and could not complete the entire cognitive battery (e.g., CDR ≥1 at the study visit, failed the practice portion, or were unable to complete the task), missing test scores were imputed as the lowest (worst) score possible. All other missing scores remained blank (i.e., missing). In total, each visit had eleven assessment domains (Motor: bradykinesia, tremor, rigidity, PIGD; Cognitive: attention, memory, language, visuospatial, and executive function; Psychiatric: depression, apathy), representing the original indicator variables used to define the subtypes[10] and three global domains for motor (UPDRS3 Total), cognitive (CDR-SB), and psychiatric function (NPIQ), making fourteen domains in total.

## Baseline subtypes

PD participants were categorized into one of three subtypes, previously described in detail in Campbell et al. (2020).[10] Briefly, a latent class analysis (LCA)[36] identified clinical subtypes within PD. LCA is a data-driven, person-centered analysis that classifies individuals based on score patterns, rather than classifying individuals based on relationships among variables. The baseline motor, cognitive, and psychiatric function scores served as inputs, with age, sex, and education covariates. Based on the results of the LCA, three distinct PD clinical subtypes were evident: (1) "Motor Only," characterized by mild motor deficits with intact cognitive and psychiatric function, (2) "Psychiatric & Motor," characterized by prominent apathy and depression and moderate motor deficits, and (3) "Cognitive and Motor," characterized by impaired cognitive and motor function but relatively normal psychiatric function.

## Statistical analyses

We used hierarchical linear growth models (HLM) to investigate longitudinal changes in behavior for PD and control participants. This class of statistical models accounts for both individual and group variance. For these analyses, intercept and slope varied across individuals (i.e., random effects), with group status as a predictor of intercept and slope. Additionally, HLM do not require participants to have the same number of data points (visits) nor the same length of time between visits. This increases flexibility with participant inclusion, providing a more complete picture of between group differences. All analyses were run in R,[37] using the lme4 package,[38] and all figures were generated with ggplot2.[39] HLM examined longitudinal performance changes and between group differences ("Motor Only", "Psychiatric & Motor", and "Cognitive & Motor", controls) for each of the 11 assessment and three global domains. Time between visits was

calculated as time from a participant's baseline visit using the lubridate package.[40] Intercept was defined as initial assessment and time was modeled in years for all fourteen domains. Similarly, age and symptom duration were calculated as age and years of motor symptoms at baseline visit. Covariates for all models included: age, sex, and symptom duration; for the cognitive assessment models, years of education and number of testing exposures (i.e., visits) acted as additional covariates to mitigate potential practice effects. All controls received a symptom duration of zero. The key test was the time by group subtype interaction. After running models for all assessments, slopes were extracted from the models using ggeffects[41] to assess the magnitude of change over time for each assessment and global domain. After extracting each domain's slopes from the models, the slopes were converted from standardized units back to domain specific raw units (e.g., actual change in UPDRS3-Total score per year) for CDR-SB, all motor domains, and all psychiatric domains.

To investigate potential disease staging, we ran the same growth models (excluding controls) with an added three-way interaction term for symptom duration, time, and subtype. We also ran the HLM models with an added three-way interaction term for age at baseline, time, and subtype. This additional term tests whether symptom duration (or age), as indicators of disease severity, significantly impacts how the subtypes change over time in a given domain. To reduce the number of analyses, only growth models with a significant subtype by time interaction were run with the additional three-way interaction.

## Data availability

Data presented in this report will be made available to research investigators upon request to the corresponding author.

## Results

Consistent with our prior research,[10] groups differed on all baseline demographic and behavioral variables (Table 1), delineating the differences between the subtypes.

## Longitudinal changes

Table 2 contains the slopes, converted into the domain specific raw units, for each assessment domain. For complete HLM results for each motor, cognitive, and psychiatric assessment and global domain, including comparisons to controls, see Tables S1–S3, respectively, and Figure S1. As expected, all subtypes worsen in motor, cognitive, and psychiatric function compared to controls.

## Motor domains

Across subtypes, few differences in motor changes over time existed (Table 2; Fig. 2A). Of note, the "Motor Only" subtype worsened significantly faster in rigidity than the "Cognitive & Motor" subtype, whereas the "Cognitive & Motor" subtype worsened significantly faster in PIGD than "Motor Only." The "Psychiatric & Motor" subtype did not significantly differ from the other two subtypes on any other motor domains. All three subtypes worsened in overall motor function (UPDRS3 Total) at similar rates.

## Cognitive domains

The "Cognitive & Motor" subtype worsened significantly faster than the "Motor Only" and "Psychiatric & Motor" subtypes in executive function, visuospatial function, and memory (Table 2; Fig. 2B). For attention, the "Cognitive & Motor" subtype worsened faster than the "Motor Only" subtype. The "Cognitive & Motor" subtype also worsened in overall cognitive function (CDR sum of boxes) significantly faster than "Motor Only" and "Psychiatric & Motor" subtypes. No other subtype comparisons were significant.

## Psychiatric domains

The "Psychiatric & Motor" subtype significantly differed from the other two subtypes on depression ratings (GDS), showing *improvement* over time while the other subtypes reported increased symptoms (Table 2; Fig. 2C). Furthermore, the "Psychiatric & Motor" subtype reported relatively stable apathy scores, while apathy ratings increased for both the "Motor Only" and "Cognitive & Motor" subtypes. There were no significant subtype differences in overall psychiatric function (NPIQ) changes over time.

## Medications

To explore the "Psychiatric & Motor" subtype's improved depression (GDS) ratings, we compiled antidepressant medication data for the baseline visit and categorized participants based on antidepressant usage (Yes/No). There was a significant group difference ($\chi^2$ (3,203) = 10.6, $p = .01$) in antidepressant use at baseline, with more participants from the "Psychiatric & Motor" subtype taking antidepressants ($n = 9$ of 17) than the "Motor Only" subtype ($n = 14$ of 61; $\chi^2$ (1,78) = 4.4, $p = .04$) as well as compared to controls ($n = 8$ of 55; $\chi^2$ (1,72) = 8.6, $p = .003$). The "Psychiatric & Motor" subtype and "Cognitive & Motor" subtype did not significantly differ

**Table 1.** Demographic and baseline behavioral data.

| Variable | Control | Motor Only | Psychiatric & Motor | Cognitive & Motor |
|---|---|---|---|---|
| N | 55 | 61 | 17 | 70 |
| Baseline age (years) | 64.07 (9.76)[#] | 63.44 (6.23)[¥] | 65.08 (8.70) | 69.08 (7.66)[#,¥] |
| Education (years) | 14.67 (2.63)[*,#] | 16.48 (2.38)[*,¥] | 15.41 (2.35) | 15.59 (2.63)[#,¥] |
| Sex, f/m (%f) | 38/17 (69%)[^,#] | 32/29 (52%)[¥] | 4/13 (31%)[^] | 20/50 (29%)[#,¥] |
| Symptom duration (years) | – | 5.93 (4.49)[&,¥] | 8.46 (4.4)[&] | 7.68 (4.23)[¥] |
| Number of testing exposures | 3.09 (1.04)[*,#] | 4.25 (1.84)[*] | 3.41 (1.12) | 4.23 (1.93)[#] |
| Executive function | 0.32 (0.5)[#] | 0.38 (0.52)[¥] | 0.05 (0.7)[§] | −0.62 (0.9)[#,¥,§] |
| Visuospatial function | 0.24 (0.6)[#] | 0.32 (0.67)[¥] | −0.01 (0.91)[§] | −0.51 (0.98)[#,¥,§] |
| Memory | 0.32 (0.75)[^,#] | 0.19 (0.64)[¥] | −0.15 (0.5)[^] | −0.38 (0.61)[#,¥] |
| Attention | 0.15 (0.75)[*,#] | 0.5 (0.64)[*,¥] | 0.2 (0.5)[§] | −0.62 (0.61)[#,¥,§] |
| Language | 0.29 (0.62)[^,#] | 0.24 (0.83)[&,¥] | −0.36 (1.49)[^,&] | −0.35 (1.11)[#,¥] |
| CDR-SB | 0.0 (0.07)[#] | 0.11 (0.28)[¥] | 0.44 (0.46) | 0.89 (0.96)[#,¥] |
| Bradykinesia | .32 (0.67)[*,^,#] | 8.15 (4.04)[*,&,¥] | 10.34 (3.96)[^,&] | 12 (3.52)[#,¥] |
| Tremor | .18 (0.69)[*,^,#] | 1.82 (2.10)[*] | 2.53 (2.08)[^,§] | 1.57 (1.65)[#,§] |
| Rigidity | 0.10 (0.49)[*,^,#] | 3.72 (2.23)[*,&,¥] | 5.75 (2.61)[^,&] | 6.43 (2.92)[#,¥] |
| PIGD | 0.22 (0.63)[*,^,#] | 1.67 (1.36)[*,&,¥] | 2.89 (1.45)[^,&] | 3.44 (1.51)[#,¥] |
| UPDRS3-total | 0.89 (1.46)[*,^,#] | 16.71 (7.09)[*,&,¥] | 22.84 (6.03)[^,&] | 25.64 (7.13)[#,¥] |
| GDS | 1.51 (2.11)[^,#] | 1.10 (0.95)[&,¥] | 9.31 (2.33)[^,&,§] | 2.63 (1.78)[#,¥,§] |
| FrSBe-A | 23.69 (5.87)[^,#] | 22.02 (5.12)[&,¥] | 35.31 (6.26)[^,&,§] | 30.19 (6.45)[#,¥,§] |
| NPIQ | 0.57 (.93)[*,^,#] | 1.79 (2.49)[*,&,¥] | 3.94 (3.79)[^,&] | 3.5 (3.6)[#,¥] |
| LEDD | – | 666 (502)[&] | 945 (688)[&] | 794 (435) |
| Baseline antidepressant, Yes/No (%yes) | 8/47 (15%)[^] | 14/47 (23%)[&] | 9/8 (53%)[^,&] | 18/52 (25%) |

Values represent mean (SD) except where indicated. CDR-SB, Clinical Dementia Rating evaluation, sum of boxes; PIGD, postural instability and gait disturbance; UPDRS3-Total, Unified Parkinson Disease Rating Scale, part 3 motor subscale; GDS, Geriatric Depression Scale; FrSBe-A, Frontal Systems Behavior scale, apathy subscale; NPIQ, Neuropsychiatric Inventory questionnaire; LEDD, Levodopa Equivalent Daily Dose.

All $\alpha < 0.05$.

*Significant difference between Controls and "Motor Only".

^Significant difference between Controls and "Psychiatric & Motor".

#Significant difference between Controls and "Cognitive & Motor".

&Significant difference between "Motor Only" and "Psychiatric & Motor".

¥Significant difference between "Motor Only" & "Cognitive & Motor".

§Significant difference between "Psychiatric & Motor" and "Cognitive & Motor."

($n = 18$ of 70; $\chi^2$ (1,87) = 3.6, $p = .06$). Despite these differences in baseline antidepressant usage, the "Psychiatric & Motor" subtype reported significantly higher depression symptoms at baseline (see Table 1).

Next, we analyzed the change in antidepressant usage, based on data from the baseline and last visit, for the "Psychiatric & Motor" subtype. There was no significant change in antidepressant usage between the two time points (McNemar chi-square: $\chi^2$ (1,17) = 1.8, $p = .18$). Furthermore, GDS slopes for each individual in the "Psychiatric & Motor" subtype were extracted and then compared, showing no significant difference in GDS slopes based on change in antidepressant medication usage (Wilcoxon signed-rank: $W = 26$, $p = .42$; Fig. 3).

We also explored the impact of dopaminergic medication on depression in the "Psychiatric & Motor" subtype as it can impact mood.[42–44] Levodopa equivalent daily dose (LEDD) for baseline and final visits were calculated.[45] LEDD between baseline and last visits did not significantly change (paired-sample Wilcoxon: $W = 54$, $p = .30$). An interaction between subtype and change in LEDD (last visit–baseline) was added to the GDS growth model, showing no significant effect on change in GDS score over time ($p = .23$).

## Disease staging

To address the possibility that the subtypes reflect more severe stages of PD, we examined the impact of symptom duration and baseline age—as proxies for disease severity—on symptom progression. A three-way interaction for time, subtype, and symptom duration (or separately, baseline age) was added to growth models, testing whether disease severity impacts a subtype's symptom progression. Tests for potential effects of disease severity failed to find any significant effects across motor, cognitive, and psychiatric domains (Table 3). Similarly, the three-way interaction with age was only significant for

**Table 2.** Domain specific slopes.

| Cognitive domains | Executive function[¥,§] | Visuospatial function[¥,§] | Memory[¥,§] | Attention | Language | CDR-SB[¥,§] |
|---|---|---|---|---|---|---|
| Motor Only | −0.101 | −0.125 | −0.024 | −0.053 | −0.013 | 0.192 |
| Psychiatric & Motor | −0.195 | −0.011 | −0.036 | −0.095 | 0.033 | 0.558 |
| Cognitive & Motor | −0.383 | −0.271 | −0.168 | −0.118 | −0.057 | 1.087 |

| Motor domains | Bradykinesia | Tremor | Rigidity[¥] | PIGD[¥] | UPDRS3-total |
|---|---|---|---|---|---|
| MOTOR ONLY | 0.568 | 0.293 | 0.400 | 0.326 | 2.086 |
| Psychiatric & Motor | 0.563 | 0.217 | 0.313 | 0.330 | 2.105 |
| Cognitive & Motor | 0.502 | 0.299 | 0.037 | 0.566 | 1.952 |

| Psychiatric domains | GDS[&,§] | FrSBe-A | NPIQ |
|---|---|---|---|
| Motor Only | 0.184 | 1.025 | 0.178 |
| Psychiatric & Motor | −0.391 | 0.366 | 0.065 |
| Cognitive & Motor | 0.301 | 1.074 | 0.344 |

For motor domains, a positive slope indicates worsening performance. For cognitive domains, a negative slope indicates worsening performance, except for CDR-SB where, a positive slope indicates worsening cognitive dysfunction. For psychiatric domains, positive slope indicates worsening severity. For CDR-SB, all motor domains, and all psychiatric domains, the model derived slope was converted to change in domain raw units per year (e.g., in one year, the "Motor Only" subtype will increase in UPDRS3-Total score by 2.086 points). CDR-SB, Clinical Dementia Rating evaluation, sum of boxes; PIGD, postural instability and gait disturbance; UPDRS3-Total, Unified Parkinson Disease Rating Scale, part 3 motor subscale; GDS, Geriatric Depression Scale; FrSBe-A, Frontal Systems Behavior scale, apathy subscale; NPIQ, Neuropsychiatric Inventory Questionnaire. For CDR-SB, all motor domains, and all psychiatric domains, the model-derived slope was converted to domain raw units (e.g., in 1 year, the "Motor Only" subtype will increase in UPDRS3-Total score by 2.086 points).
All $\alpha < 0.05$.
[&]Significant difference between "Motor Only" and "Psychiatric & Motor".
[¥]Significant difference between "Motor Only" and "Cognitive & Motor".
[§]Significant difference between "Psychiatric & Motor" and "Cognitive & Motor".

executive function and memory, indicating age impacted change in those two domains between the "Cognitive & Motor" and "Motor Only" subtypes, likely because of the age difference between the two subtypes.

## Discussion

This study aimed to understand longitudinal symptom changes in PD clinical subtypes, as well as investigate whether these subtypes represent sequential disease stages. Our results show distinct motor differences between the "Motor Only" and "Cognitive & Motor" subtypes, where "Motor Only" worsens faster in rigidity and "Cognitive & Motor" worsens faster in PIGD. For cognitive domains, the "Cognitive & Motor" subtype declines in executive function, visuospatial function and functional abilities (CDR sum of boxes) faster than the other two subtypes. Most interestingly, results for psychiatric domains show the "Psychiatric & Motor" subtype improves in depressive symptoms, whereas the other two subtypes worsen in depressive symptoms. Use of antidepressants cannot explain this difference. Furthermore, age and symptom duration do not account for subtype differences in the longitudinal progression of behavioral features. Not only do these results provide no evidence for staging across

subtypes, but they also indicate that the three clinical subtypes progress in temporally unique patterns, such that the order of symptom manifestation distinguishes the subtypes from one another and impacts clinical prognosis.

### Subtype progression follows key features

Overall, the subtypes demonstrate similar progressions to one another in motor symptoms, despite baseline differences and even after accounting for age, sex, and symptom duration. This contrasts with prior subtypes derived from motor symptoms.[1] While the "Motor Only" subtype differentiates itself from the "Cognitive & Motor" subtype in PIGD and rigidity progression, this represents a small magnitude of change compared to cognitive and psychiatric changes.

Indeed, cognitive domains show some of the most robust differences in symptom progression between subtypes. Expectedly, the "Cognitive & Motor" subtype differentiates itself from the other two subtypes in these domains, most notably in overall functional abilities (CDR sum of boxes), highlighting the subtype's overall worsening cognitive function. This aligns with our work showing increased dementia and mortality risk for the
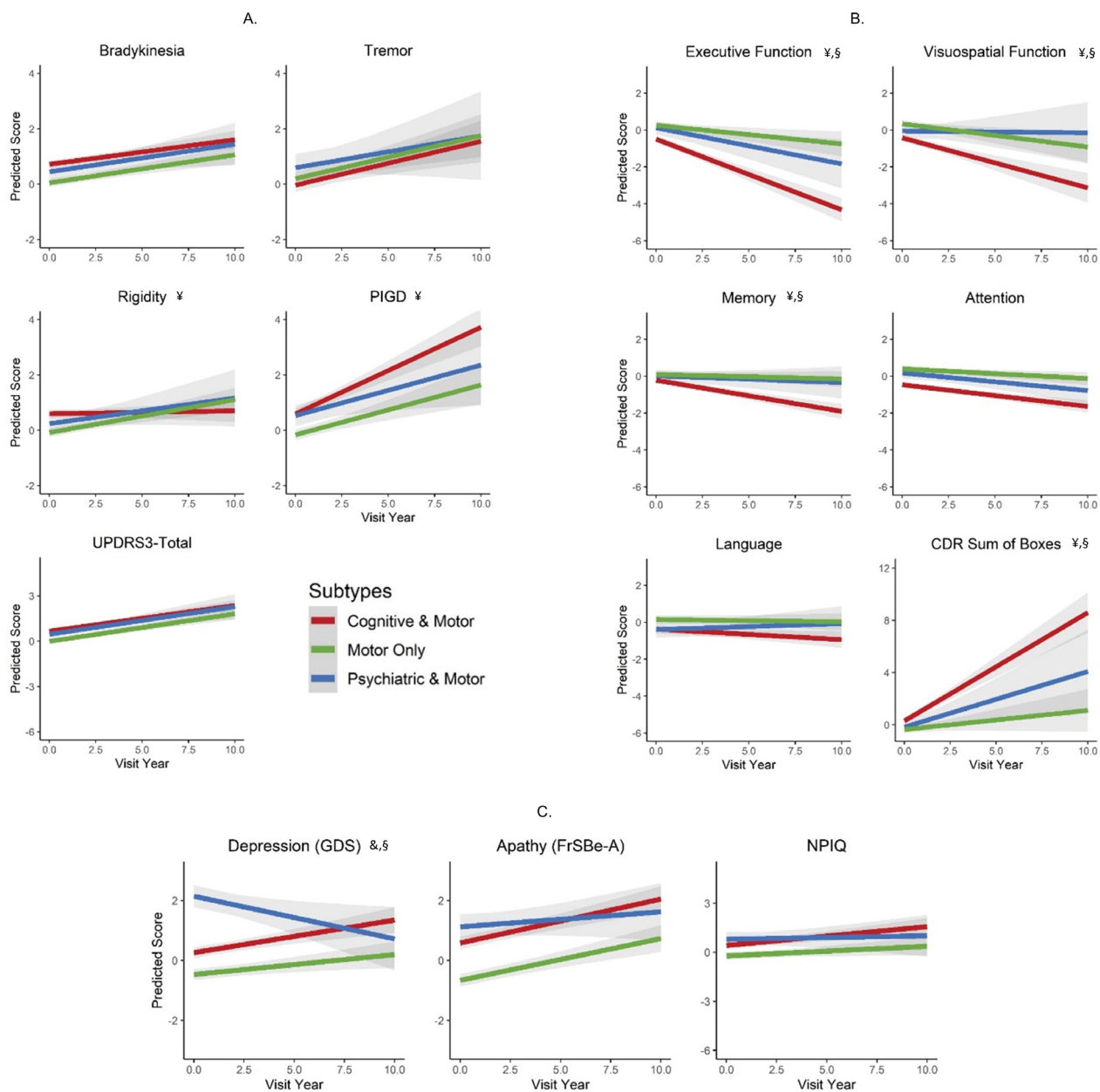
**Figure 2.** Predicted change in each domain. All predictions are based on the HLM growth models. (A) Depicts change over time for each motor domain. A positive slope indicates worsening performance. (B) Depicts change over time for each cognitive domain for each group. For CDR-SB, a positive slope indicates worsening cognitive dysfunction. For all other cognitive domains, a negative slope indicates worsening performance. (C) Depicts change over time for each psychiatric domain. A positive slope indicates worsening severity. UPDRS3-Total, Unified Parkinson Disease Rating Scale, part 3 motor subscale; CDR-SB, Clinical Dementia Rating evaluation, sum of boxes; PIGD, postural instability and gait disturbance; GDS, Geriatric Depression Scale; FrSBe-A, Frontal Systems Behavior scale, apathy subscale; NPIQ, Neuropsychiatric Inventory questionnaire. [&]significant difference between "Motor Only" and "Psychiatric & Motor"; [¥]significant difference between "Motor Only" & "Cognitive & Motor"; [§]significant difference between "Psychiatric & Motor" and "Cognitive & Motor." All $\alpha < 0.05$.

"Cognitive & Motor" subtype[10] and prior research linking cognitive decline with increased mortality.[46,47]

Surprisingly, while having stable but elevated apathy, the "Psychiatric & Motor" subtype differentiates itself from the other two subtypes in depression in an unexpected direction (i.e., the subtype's depression symptoms improve), that cannot be explained by antidepressant use at baseline, changes in antidepressant usage while in the study, or changes in LEDD. Strikingly, Figure 3 shows that all participants in the "Psychiatric & Motor"
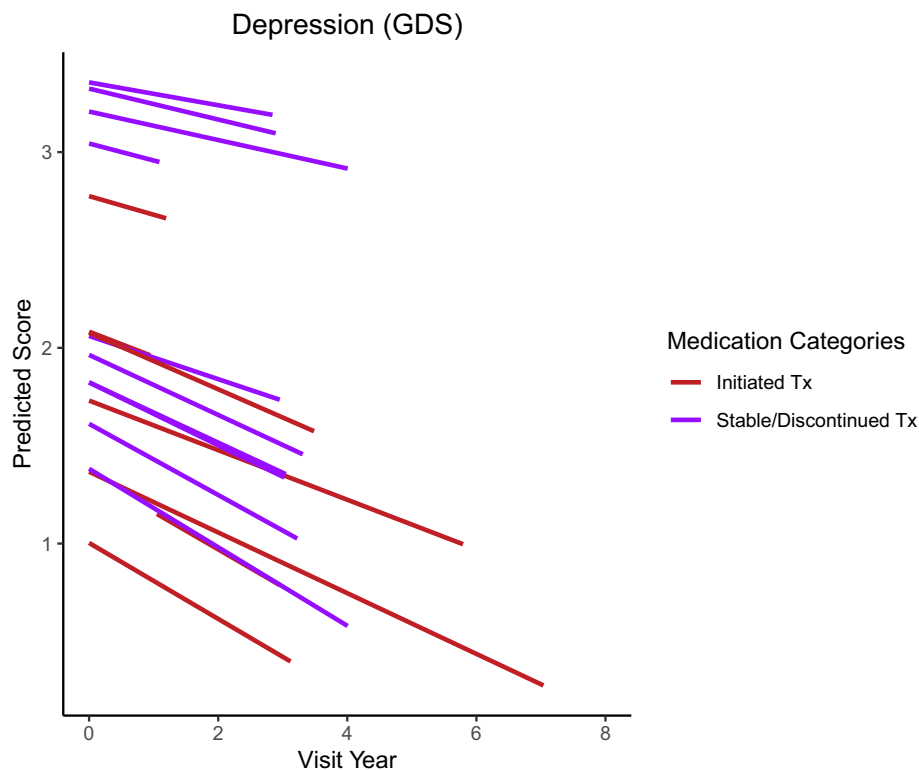
**Figure 3.** Individual depression changes in the "Psychiatric & Motor" subtype. From baseline and last visit medication information, participants were categorized as "Initiated Tx" (individuals who started to take antidepressants during the study) and "Stable-Discontinued Tx" (individuals whose antidepressant usage did not change between baseline and last visit and individuals who stopped taking antidepressants after the baseline visit). All $\alpha < 0.05$.

subtype had reduced depression symptoms over time. While the depression symptom pattern held, regardless of antidepressant usage, future research should examine the influence of antidepressant class, duration of use, dosage, and other treatments (e.g., cognitive behavioral therapy) on changes in depression. Indeed, to our knowledge, there is no general consensus on dose equivalents across antidepressants. While prior research has looked into this,[48] it concedes assumptions of dose-response relationships that have not been adequately investigated in PD. Thus, though the "Psychiatric & Motor" subtype reported greater baseline antidepressant usage, baseline depression remained elevated. If anything, antidepressant usage reduced differences in baseline GDS scores between "Psychiatric & Motor" and the other groups, yet the "Psychiatric & Motor" subtype still reported elevated levels of depression.

## Age and symptom duration cannot explain subtype progression

The analyses probing disease staging yielded nonsignificant results. Neither three-way interaction with age

at baseline or symptom duration at baseline, show consistent, significant interactions between any two subtypes across a domain category (i.e., motor, psychiatric, or cognitive). While some "Motor Only" individuals may represent early stages of either of the other two subtypes, the "Motor Only" subtype had longer survival times to clinical milestones than the other two subtypes,[10] symptom duration and age do not yield meaningful interactions, and overall symptom progression profiles do not resemble those of the other two subtypes.

## Sequence of clinical manifestations differs across subtypes

The robust differences in symptom progression and the lack of evidence for disease staging suggest clear, subtype-specific temporal patterns in symptom manifestation (Fig. 4). Most importantly, while the "Motor only" and "Cognitive & Motor" subtypes report worsening depression, after 10 years, the levels do not reach that of "Psychiatric & Motor" subtype at baseline. This difference in progression further supports our hypothesis of three

**Table 3.** Disease staging.

| Domain | Interaction with | Age | | Symptom duration | |
|---|---|---|---|---|---|
| | | Beta | *p*-value | Beta | *p*-value |
| Executive function | Time × (Psychiatric & Motor vs. Motor Only) | 0.02 | 0.778 | 0.02 | 0.859 |
| | Time × (Cognitive & Motor vs. Motor Only) | −0.12 | 0.028 | −0.02 | 0.667 |
| | Time × (Cognitive & Motor vs. Psychiatric & Motor) | −0.14 | 0.062 | −0.04 | 0.693 |
| Visuospatial function | Time × (Psychiatric & Motor vs. Motor Only) | 0.02 | 0.889 | −0.01 | 0.942 |
| | Time × (Cognitive & Motor vs. Motor Only) | −0.04 | 0.568 | −0.08 | 0.294 |
| | Time × (Cognitive & Motor vs. Psychiatric & Motor) | −0.06 | 0.573 | −0.07 | 0.618 |
| Memory | Time × (Psychiatric & Motor vs. Motor Only) | 0 | 0.947 | −0.04 | 0.588 |
| | Time × (Cognitive & Motor vs. Motor Only) | −0.08 | 0.046 | 0.05 | 0.163 |
| | Time × (Cognitive & Motor vs. Psychiatric & Motor) | −0.08 | 0.132 | 0.09 | 0.2 |
| Attention | Time × (Psychiatric & Motor vs. vs. Motor Only) | −0.01 | 0.789 | 0 | 0.937 |
| | Time × (Cognitive & Motor vs. Motor Only) | −0.01 | 0.855 | 0.03 | 0.308 |
| | Time × (Cognitive & Motor vs. Psychiatric & Motor) | 0.01 | 0.877 | 0.04 | 0.548 |
| CDR-SB | Time × (Psychiatric & Motor vs. Motor Only) | −0.01 | 0.956 | −0.01 | 0.979 |
| | Time × (Cognitive & Motor vs. Motor Only) | 0.07 | 0.636 | −0.06 | 0.641 |
| | Time × (Cognitive & Motor vs. Psychiatric & Motor) | 0.08 | 0.686 | −0.06 | 0.827 |
| Rigidity | Time × (Psychiatric & Motor vs. Motor Only) | 0.03 | 0.699 | −0.15 | 0.123 |
| | Time × (Cognitive & Motor vs. Motor Only) | 0.03 | 0.55 | −0.03 | 0.507 |
| | Time × (Cognitive & Motor vs. Psychiatric & Motor) | 0 | 0.982 | 0.12 | 0.213 |
| PIGD | Time × (Psychiatric & Motor vs. Motor Only) | 0.05 | 0.6 | −0.12 | 0.334 |
| | Time × (Cognitive & Motor Vs. Motor Only) | 0.05 | 0.426 | 0.09 | 0.165 |
| | Time × (Cognitive & Motor vs. Psychiatric & Motor) | 0 | 0.999 | 0.21 | 0.095 |
| GDS | Time × (Psychiatric & Motor vs. Motor Only) | 0.12 | 0.076 | 0.09 | 0.267 |
| | Time × (Cognitive & Motor vs. Motor Only) | −0.01 | 0.859 | 0.01 | 0.709 |
| | Time × (Cognitive & Motor vs. Psychiatric & Motor) | −0.12 | 0.055 | −0.08 | 0.34 |

The three-way interactions between the different subtypes were extracted from the HLM and are shown for symptom duration and age. PIGD, postural instability and gait disturbances; GDS, Geriatric Depression Scale.

distinct clinical subtypes, suggesting that the "Psychiatric & Motor" subtype experiences psychiatric symptoms before experiencing cognitive decline whereas the opposite sequence seems true for the "Cognitive & Motor" subtypes. In contrast, the "Motor Only" subtype worsens in motor symptoms, but remains relatively unremarkable in cognitive decline and psychiatric function. Thus, the temporal sequence and rate of progression of clinical features differs across PD subtypes.

The temporal sequences also emphasize the clinical significance for these subtypes. While all subtypes show deficits across motor, cognitive, and psychiatric domains, the order in which these deficits appear impacts prognosis. The motor decline in the "Motor Only" subtype resembles motor decline in the other two subtypes, but that subtype does not have marked decline in cognitive function and only modest worsening of psychiatric symptoms. The "Psychiatric & Motor" subtype starts high in depression and apathy, but improves in depression ratings and remains relatively stable in apathy and overall psychiatric function over time. Interestingly, while research suggests that depression[49] and apathy[50] produce negative effects on cognitive function, the "Psychiatric & Motor" subtype

does not demonstrate cognitive dysfunction at baseline. Rather, despite relatively stable or improved psychiatric function, the "Psychiatric & Motor" subtype increases in overall cognitive dysfunction (CDR sum of boxes) over time. By contrast, the "Cognitive & Motor" subtype displays cognitive dysfunction at baseline that worsens over time, however, depression and apathy take >6 years to significantly increase in severity (i.e., one standard deviation) from baseline. Not only do these patterns emphasize the difference in progression, they are also incongruous with research suggesting that depression is an early indicator of dementia,[51] as the "Cognitive & Motor" subtype, not the "Psychiatric & Motor" subtype, has an increased risk of dementia.[10]

While the subtypes likely converge in motor, cognitive, and psychiatric dysfunction at end-stage disease (premorbid), the quality of life in the preceding years will be sharply impacted by symptom presentation. Therefore, it is imperative that clinicians conduct a comprehensive assessment of a patient's symptoms and their relative order of onset, as one's prognosis, particularly time to dementia and mortality, closely relates to the order in which different symptoms appear.
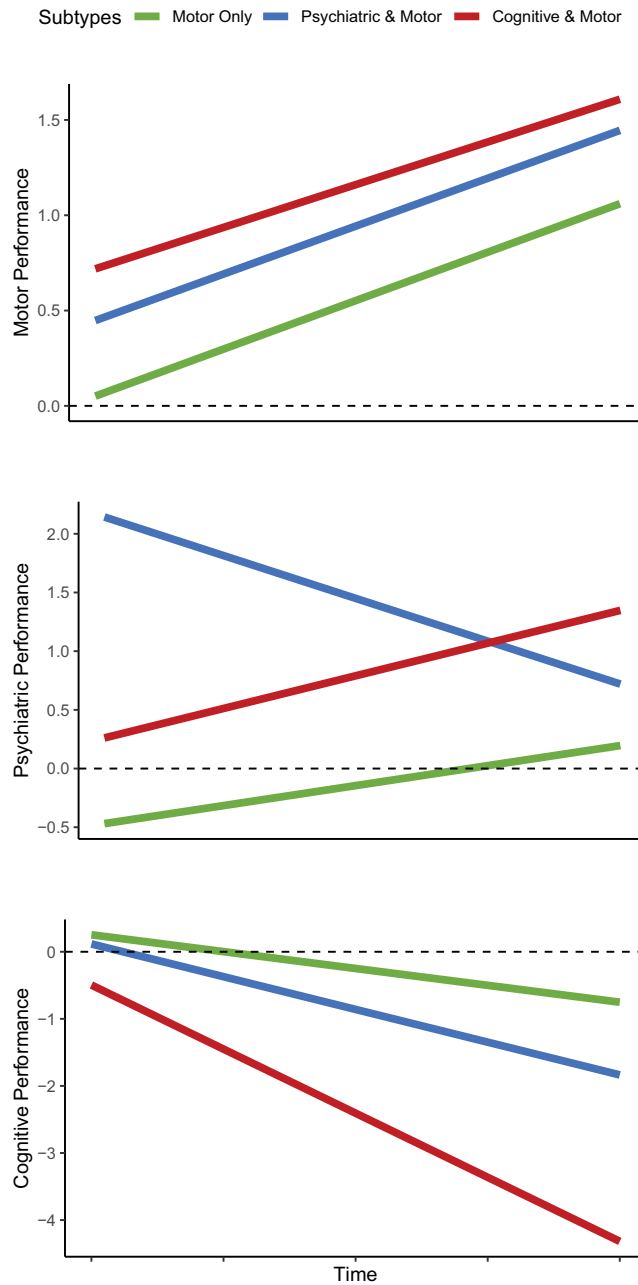
**Figure 4.** Subtype-specific symptom manifestation patterns. Based on results, motor, psychiatric, and cognitive symptom progressions are shown for each subtype, illustrating the temporal relationships of symptom manifestations. For the cognitive domain, a negative slope represents worse performance. For the motor and psychiatric domains, a positive slope represents worse performance.

## Strengths and limitations

This study presents evidence for three distinct PD clinical subtypes whose symptom progression is unique to the subtype; however, given that average symptom duration is greater than average time in the study, it remains possible that individuals could transition from one subtype to another, particularly near the end stages of the disease when symptom manifestations may converge. Despite this, our modeling highlights subtype differences. Even with the "Psychiatric & Motor" subtype's small sample size (*n* = 17), which limits overall power, we see robust differences between subtypes. Future research should use an independent dataset to provide external validation of

these subtypes. Additionally, we acknowledge that the study lacks a scaled measure of anxiety; however, the groups do not differ in presence of anxiety at baseline,[10] suggesting anxiety may not differentiate subtypes. Our data also lack comprehensive psychiatric history, thus limiting our ability to differentiate between lifelong depression and development of new depression. Despite this, however, our results show that the presence of depressive symptoms at baseline is related to differences clinical progression of PD. Indeed, the ability to investigate the multiple behavioral domains (motor, cognitive, and psychiatric) remains one of the greatest strengths of this study. We not only analyzed global domain measures, but also specific domains within each category, providing a comprehensive understanding of disease progression in PD and the importance of cognitive and psychiatric features in prognosis. It should be noted that such understanding may not generalize perfectly onto the broader PD patient population from other geographic regions because the data come from a single center.

## Conclusions

We have demonstrated with our sample that PD clinical subtypes progress in distinct ways from one another and found no evidence that these subtypes represent sequential disease stages (i.e., "Motor Only" progresses to "Psychiatric & Motor"). This accentuates the importance of including cognitive and psychiatric features when considering clinical prognosis so that patients and their caregivers can prepare accordingly.

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## Author Contributions

Peter S. Myers contributed to the research project's conception, organization and execution, the statistical design, execution, and interpretation, and the writing and review of the final manuscript. Joshua J. Jackson contributed to statistical design and interpretation as well as review of the final manuscript. Amber K. Clover contributed to the research project's organization and execution, as well as final review of the manuscript. Christina N. Lessov-Schlaggar contributed to statistical design and interpretation as well as review of the final manuscript. Erin R. Foster contributed to the research project's organization and execution, as well as final review of the manuscript. Baijayanta Maiti contributed to the research project's execution, as well as final review of the manuscript. Joel S. Perlmutter contributed to the research project's conception and organization, as well as review of the final manuscript. Meghan C. Campbell contributed to the research project's conception, organization, and execution, the statistical design and interpretation, and the writing and review of the final manuscript.

## Conflict of Interest

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Figure S1**. Predicted change in each domain. All predictions are based on the HLM growth models. (A) Depicts change over time for each motor domain. A positive slope indicates worsening performance. (B) Depicts change over time for each cognitive domain for each group. For CDR-SB, a positive slope indicates worsening cognitive dysfunction. For all other cognitive domains, a negative slope indicates worsening performance. (C) Depicts change over time for each psychiatric domain. A positive slope indicates worsening severity. UPDRS3-Total, Unified Parkinson Disease Rating Scale, part 3 motor subscale; CDR-SB, Clinical Dementia Rating evaluation, sum of boxes; PIGD, postural instability and gait disturbance; GDS, Geriatric Depression Scale; FrSBe-A, Frontal Systems Behavior scale, apathy subscale; NPIQ, Neuropsychiatric Inventory questionnaire. *significant difference between Controls and "Motor Only"; ^significant difference between Controls and "Psychiatric & Motor"; #significant difference between Controls and "Cognitive & Motor"; &significant difference between "Motor Only" and "Psychiatric & Motor"; ¥significant difference between "Motor Only" & "Cognitive & Motor"; §significant difference between "Psychiatric & Motor" and "Cognitive & Motor." All $\alpha < 0.05$.

**Table S1**. Hierarchical linear growth models for motor domains. ¤indicates that values are from models where controls are the reference group. PIGD, postural instability and gait disturbance; UPDRS3-Total, Unified Parkinson Disease Rating Scale, part 3 motor subscale.

**Table S2**. Hierarchical linear growth models for cognitive domains. ¤indicates that values are from models where controls are the reference group. CDR-SB, Clinical Dementia Rating evaluation, sum of boxes.

**Table S3**. Hierarchical linear growth models for psychiatric domains. ¤indicates that values are from models where controls are the reference group. GDS, Geriatric Depression Scale; FrSBe-A, Frontal Systems Behavior Scale, Apathy subscale; NPIQ, Neuropsychiatric Inventory Questionnaire.