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Temporal ordering of cognitive impairment in Parkinson's disease patients based on disease progression models

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A B S T R A C T

Introduction: Identifying Parkinson's disease (PD) patients at risk of cognitive decline is crucial for enhancing clinical interventions. While several models predicting cognitive decline in PD exist, a new machine learning framework called disease progression models (DPMs) offers a data-driven approach to understand disease evolution.

Methods: We enrolled 423 PD patients and 196 healthy controls from the Parkinson's Progression Markers Initiative (PPMI). Our study encompassed a range of biomarkers, including motor, neurocognitive, and neuroimaging evaluations at baseline and annually. A methodology was employed to select optimal combinations of biomarkers for constructing DPMs with superior predictive capabilities for both diagnosing and estimating conversion times toward cognitive decline.

Results: At baseline, the approach showed excellent performance in identifying individuals at high risk of cognitive decline within the first five years. Furthermore, the proposed timeline from cognitive impairment to dementia was also used to explore clinical events such as the onset of cognitive impairment, the development of dementia or amyloid pathology. The presence of amyloid pathology did not alter the progression of cognitive impairment among PD patients.

Conclusions: Neuropsychological measures and certain biomarkers, including cerebrospinal fluid (CSF) amyloid beta 42 ($A\beta_{42}$) and dopamine transporter deficits, can be used to predict cognitive decline and estimate a timeline from cognitive impairment to dementia, with amyloid pathology preceding the onset of dementia in many cases. Our DPMs suggested that the profiles of CSF $A\beta_{42}$ and phosphorylated tau in PD patients may differ from those in aging patients and those with Alzheimer's disease.

Keywords:

Parkinson's disease

Cognitive decline

AD CSF Biomarkers

Disease progression models

1. INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by motor (tremor, rigidity, bradykinesia) and nonmotor symptoms (depression, anxiety, and cognitive impairment) (1). The incidence of dementia in PD patients is significantly greater than that in the general population; thus, identifying PD patients at risk for cognitive impairment is key to improving clinical trial enrollment, medical management, and patient autonomy.

Several predictive models for cognitive decline and the risk of conversion from cognitively unimpaired (PD-CU) to mild cognitive impairment (PD-MCI) or PD dementia (PDD) have been proposed using baseline or longitudinal data. Patients with lower scores on cognitive tests were more likely to experience cognitive decline (2). Additional biomarkers, such as dopamine transporter single-photon emission computed tomography (DAT SPECT) and cerebrospinal fluid (CSF) markers, are also predictive. Several studies have identified combinations of variables—such as age, mood variables, CSF and DAT imaging markers—that are strong predictors(3)(4). However, these models are limited in their ability to predict the future trajectories of biomarkers, estimate the time remaining until a clinical event (such as the onset of cognitive decline in a patient), or generate hypotheses about the disease's evolution within the population. To address these limitations, disease progression models (DPMs) have been introduced as a novel framework that represents disease evolution as a continuous process, leveraging a data-driven approach. This facilitates automatic diagnosis and provides a comprehensive description of disease progression. DPMs explicitly order biomarkers from normal to pathological stages via multivariate analysis.

In this study, a subtype of DPMs known as growth models by alternating conditional expectation (GRACE) was implemented to model cognitive decline in PD patients. By utilizing short-term clinical data, GRACE constructs long-term pathological trajectories through self-modeling regression (5). Data were collected from the Parkinson’s Progression Markers Initiative (PPMI) database. The proposed DPMs were selected according to quality metrics accounting for diagnostic accuracy and prediction of the onset time for cognitive impairment. Finally, a natural history of cognitive decline progression was used to estimate the time remaining until dementia onset, and the influence of amyloid pathology on cognitive decline was also evaluated.

2 Materials

2.1 Subjects

Data from the PPMI initiative (www.ppmi-info.org/data) included 423 drug-naive PD patients and 196 healthy controls (HCs). The inclusion criteria were a recent idiopathic PD diagnosis, being untreated for PD, having a dopamine transporter (DAT) deficit on imaging, and the absence of dementia at baseline. Clinical data were collected for up to 5 years. The participants underwent motor, neurocognitive, and neuroimaging evaluations at baseline and annually. The collected data included demographic, clinical, neurocognitive test, striatal binding ratios from DAT SPECT scans (mean caudate measure (MEANCAU)) and CSF biomarkers (Alpha-Synuclein (ASYN), Amyloid Beta 42 (Aβ42), Total Tau (tTau), Phosphorylated Tau (pTau)). PD patients were categorized into PD-CU, PD-MCI, or PDD groups on the basis of annual clinical diagnoses during follow-up, resulting in 323 PD-CU, 83 PD-MCI, and 17 PDD patients, with group assignments on the basis of the latest diagnosis.

2.2 Statistical Analysis

To estimate the natural history of cognitive decline in PD patients via the GRACE approach, we employed a predictive modeling approach to identify high-performing subsets of markers from longitudinal data (see supplementary materials, S1) (6). In brief, DPMs were constructed via these proposed marker subsets, and their effectiveness in estimating the natural history was assessed. Finally, the DPM that most accurately captured the natural history while utilizing the fewest markers was chosen to facilitate its application in clinical practice.

GRACE estimates the time shift (δ_i) for each i-th patient to align their marker trajectories with the proposed cognitive decline timeline. It models the short-term trajectories, which correspond to the evolution of an individual's markers, via centered visit times $t_{ij}^{c} = t_{ij} - \left(t_{i_1} + t_{i_{end}}\right)/2$, where t_{ij} represents the j-th visit time, and i_1 and i_{end} denote the first and last visits of the i-th individual, respectively. Additionally, GRACE estimates the long-term trajectories of each marker, illustrating the temporal evolution of the population within the proposed timeline. For each constructed DPM, a natural history is proposed, along with an estimate of the onset time (t_{onset}) for cognitive decline.

For the estimated t_{onset}, the short-term trajectories of PD-CU individuals are expected to occur before t_{onset}, whereas those of PD-MCI/PDD subjects should extend beyond t_{onset}. To assess the proposed temporal ordering, we define several fitness scores. $SCORE_1$ represents the percentage of PD-CU subjects whose last visit, $t_{i_{end}}^{c} + \delta_i$, occurred before t_{onset}. For PD-MCI/PDD patients, $SCORE_2$ is the proportion of those who did not exhibit cognitive decline at baseline, where $\left(t_{i_1}^{c} + \delta_i\right) < t_{onset}$, and $SCORE_3$ is the proportion whose last visit occurred after t_{onset}. The optimal t_{onset} maximizes all three scores, with $SCORE_1$ and $SCORE_2$ increasing as t_{onset} increases and $SCORE_3$ decreasing. The best t_{onset} is the one that achieves the highest overall score while

minimizing the absolute differences between the scores. Additionally, we perform a linear regression analysis on the PD-MCI/PDD subjects, comparing their conversion times to the times estimated by the proposed DPM, $t_{onset} - \left(t_{i_1}^{c} + \delta_i\right)$, for all $i \in PD - MCI/PDD$.

Bootstrapping techniques were used to obtain confidence intervals for DPM parameters and analyze long-term marker trajectories in patient groups with and without amyloid pathology.

3. Results

3.1 Cross-sectional analysis

At baseline, significant differences were detected between PD-CU subjects and PD-MCI/PDD patients in specific cognitive tests (Letter-Number Sequencing (LNS), Symbol Digit Modalities Test (SDMT), Judgment of Line Orientation (JLO), Hopkins Verbal Learning Test (HVLT) Immediate (IMMEDIATE), HVLT Delayed Recall (HVLTRDLY), Semantic Fluency Test (SFT), Scales for Outcomes in Parkinson's Disease-Cognition (SCOPA)), clinical variables (University of Pennsylvania Smell Identification Test (UPSIT), REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)), and biomarkers (pTau/Aβ_{42}, MEANCAU)). No significant differences were found for the Montreal Cognitive Assessment (MOCA) score. The PD-MCI/PDD group was older (mean ages 66.0 and 69.4 years) than the PD-CU group (mean age 60.1 years). Comparisons between HCs and PD patients revealed significant cognitive differences, with poorer performance in the PD group despite age matching. The AD CSF biomarkers tTau and pTau were lower in the PD group than in the HC group, with no differences in Aβ_{42} or pTau/Aβ_{42} (see supplementary materials, S2).

3.2 AT profiles in PD

The AT profile framework stages AD on the basis of amyloid (A) and tau (T) biomarkers (7). Amyloid pathology (A+) was defined as $A\beta_{42} \leq 683.45$ *pg/ml* (8), and tau pathology (T+) was defined as *pTau* > 23 *pg/ml.* In our study, CSF biomarker data were available for 374 PD patients and 174 HCs. At baseline, 23.4% of PD-CUs, 26.5% of PD-MCIs, 66.7% of PDDs, and 22.4% of HCs were A+. There were no significant differences in amyloid pathology between PD-CU patients and PD-MCI patients or between HC-CU patients and HC-MCI patients, and there were no significant differences between PD patients and HCs. However, a significantly greater percentage of PDD patients were A+. After 5 years, the percentage of A+ individuals increased across all groups, with 35.7% of PD-CU patients, 39.7% of PD-MCI patients, 66.7% of PDD patients, and 32.2% of HCs. Tau pathology was less common, with isolated tau pathology in less than 10% of patients in all groups, except in PDD patients, where 20.7% had isolated tau pathology (A-T+) and 26.7% had combined amyloid and tau pathology (A+T+), indicating coexistence with Alzheimer's disease (AD). At baseline, the biomarkers pTau and tTau were highly correlated (R=0.96-0.98) across all the clinical groups. Moderate correlations (R=0.59-0.88) were observed between ASYN and Aβ42 or pTau. However, no correlation was found between the CSF biomarkers and neuropsychological measures (see supplementary materials, S3).

3.3 Predictive models

The best predictive model for progression from PD-CU to PD-MCI/PDD included the following features: HVLTRDLY, LNS, SDMT, SFT, Aβ_{42}, and MEANCAU. At baseline, this

model effectively distinguished between PD-CU patients and PD-MCI/PDD patients with a sensitivity of 73.7% (70.9%-76.6%), specificity of 73.5% (71.9%-75.1%), accuracy of 73.4% (72.0%-74.7%), and an area under the curve of 0.796 (0.779-0.821) (see supplementary material for details, S4).

3.4 DPM

The proposed feature vector was used to train the GRACE approach in the studied population. Figure 1 shows the number of subjects as a function of the time shift, δ_i, and the relationship between the conversion times to PD-MCI or PDD ($t_{convert}$) and their estimates by GRACE ($\hat{t}_{convert}$), with a regression line of $\hat{t}_{convert} = 2.12 \cdot t_{convert} - 7.36$ and a Pearson coefficient of $R = 0.55\ (0.53 - 0.56)$. Using patients' age for estimation yielded $\widehat{age}_{convert} = 0.74 \cdot age_{convert} - 12.75$ with $R = 0.76\ (0.74 - 0.77)$. The classification scores were optimized according to $t_i^c + \delta_i$, and clinical groups estimated that the onset of cognitive decline was approximately 5.2 years. For $\hat{t}_{onset} \approx 5.2$ years, $SCORE_1$ = 82.3% (81.6% − 82.9%), $SCORE_2$ = 62.4% (60.1% − 64.7%) and $SCORE_3$ = 66.5% (64.4%−68.6%).

[Fig. 1]

Using the progression timeline from PD-CU to PD-MCI and PDD established with δ_i values, long-term trajectories for various features can be inferred. Key events in dementia progression were estimated as follows: a) $\hat{t}_{A\beta_{42}=683\text{pg/ml}} = 6.8\ years$, b) $\hat{t}_{pTau=23\text{pg/ml}} > 15\ years$, c) $\hat{t}_{MOCA=25} = 5.7\ years$ and c) $\hat{t}_{MOCA=21} = 13.3\ years$. (see supplemental material, S5). These estimates indicate that cognitive decline (MOCA=25) occurs at approximately 5.7 years, similar to the estimated onset time of 5.2 years, with dementia (MOCA=21) occurring at 13.3 years. Amyloid pathology develops after the onset of cognitive decline and before dementia (6.8 years). There was a 7.6-year period between cognitive decline (MOCA=25) and dementia (MOCA=21). These times can be mapped to the PD progression timeline via the regression line of the converters.

Figure 2 shows the application of bootstrap techniques to analyze long-term trajectories of various features in PD individuals classified as A+ or A- at baseline. The results indicate that there is no accelerated cognitive decline in subjects with amyloid pathology (A+) at baseline compared with those without amyloid pathology (A-).

[Fig. 2]

4. Discussions

A data-driven approach was proposed to predict conversion to PD-MCI and dementia, as well as to estimate the timeline of cognitive decline progression. The approach uses both supervised and unsupervised learning techniques and selects a reduced, interpretable set of markers to ensure robustness, verifiability, and reliability. At baseline, the method effectively identified subjects at high risk of progressing from PD-CU to PD-MCI/PDD within five years. Additionally, the proposed cognitive decline timeline was validated through patient diagnoses and observed clinical events, including cognitive decline onset, dementia development, and amyloid pathology.

In the present study, 24% of PD-CU subjects converted to PD-MCI/PDD within five years. The control population had a conversion rate to MCI of less than 3% after five years. At baseline, 25.7% of PD patients and 22.4% of HCs were A+. It was reported that 21% of early-stage PD patients had positive cerebral amyloid uptake, and the overall prevalence was similar to that of age-matched controls (9). After five years, 29.2% of PD-A+ patients and 19.8% of PD-A- patients converted to PD-MCI/PDD patients, which was not a significant difference ($p=0.056$). Furthermore, 40% of PD patients who developed PD-MCI and 67% who developed dementia had amyloid pathology after 5 years. At baseline, pTau levels were lower in PD patients than in healthy controls, with less than 10% of those progressing to PD-MCI and 30% to PDD reaching tau pathology levels. We also observed that there was no greater cognitive decline among PD-A+ subjects than among PD-A- subjects when the bootstrap technique was applied to the proposed DPMs in the PPMI-PD patients (see Fig. 2). These findings indicate that the CSF Aβ42 and pTau profiles in PD differ from those in aging and AD patients.

Recent evidence suggests that individuals with prodromal features of PD, such as hyposmia, sleep behavior disorder, and reduced dopamine transporter binding, may exhibit worse cognitive performance than people without any or with only one of these features (10). Older age appears to be the most consistent demographic risk factor in PD-novo (2), whereas the contributions of male sex and fewer years of education are less consistent (11). These findings are consistent with the results reported here, where patients who progressed toward cognitive decline were older, exhibited olfactory disorders, and had lower cognitive scores at baseline (see supplementary material S2).

We developed multivariate predictive models for cognitive decline in newly diagnosed PD patients and demonstrated that a single baseline marker is inadequate. The study identified an optimal predictive set including several neuropsychological tests (HVLTRDLY, LNS, SDMT, and SFT), Aβ42 levels, and mean caudate uptake from DAT-SPECT imaging. Many proposed models also combine neuropsychological tests with biomarkers such as DAT SPECT, AD CSF biomarkers, UPSIT, and mood variables. Notably, Schrag et al. (3) identified five key predictors: age, the UPSIT, the RBDSQ, CSF Aβ42, and mean caudate uptake. Other studies also highlighted the predictive value of CSF Aβ42 levels, tau levels, and cognitive test scores (12). Overall, the proposed predictive model aligns with previous research, showing comparable classification performance.

A DPM was chosen for its effectiveness in diagnosing patients via three proposed scores and for estimating the timeline for cognitive decline in PD patients. The proposed DPM predicts dementia onset approximately seven years after initial cognitive decline (t_{onset}), with amyloid pathology emerging approximately 3.5 years from t_{onset}. The DPM supports the hypothesis that amyloid pathology precedes dementia by 5-10 years. Notably, 67% of PD patients who progressed to dementia exhibited amyloid positivity at baseline. The DPM also demonstrated that neuropsychological measures (HVLTRDLY, LNS, SDMT, and SFT) better capture the progression to cognitive decline than other types of biomarkers do.

Various DPM were constructed using different feature combinations, yielding consistent results (see supplemental material, S6). The onset times of cognitive decline, Pearson coefficients, quality scores, and marker values at the onset of long-term trajectories were nearly identical across the models, reinforcing the validity of the findings.

These findings suggest that, in clinical practice, monitoring of cognitive decline in PD patients should focus on neuropsychological measures, complemented by AD CSF biomarkers and the DAT-Scan. Importantly, GRACE shows robustness to missing data, allowing for an individualized estimation of both diagnosis and prognosis through regular follow-up of neuropsychological tests, accompanied by some additional samples of the other markers. Furthermore, no significant changes in amyloid pathology were observed during the follow-up period, and, according to the proposed DPMs, the AD CSF biomarker Aβ42 evolves more slowly than neuropsychological measures do, suggesting that these invasive tests can be performed less frequently than cognitive tests.

Further analysis is needed to align the estimated timelines with the natural history of cognitive decline in newly diagnosed PD patients. The moderate correlation between the conversion times and DPM estimates suggests that the model's accuracy needs improvement. Expanding the patient sample and extending follow-up could increase accuracy. Additionally, applying this methodology to other PD cohorts is necessary for a more comprehensive analysis of cognitive decline.

Authors roles

Carlos Platero: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing - original draft. **José Angel Pineda**: Scientific discussion, writing - review & editing.

Disclosure statement

All authors declare no conflict of interest.

Declaration of competing interest

The authors disclose no actual or potential conflicts of interest.

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ChatGPT, version 3.5, a language model developed by OpenAI (https://www.openai.com) was used for language refinement of this manuscript.

Supplementary material

Below is the link to the electronic supplementary material.

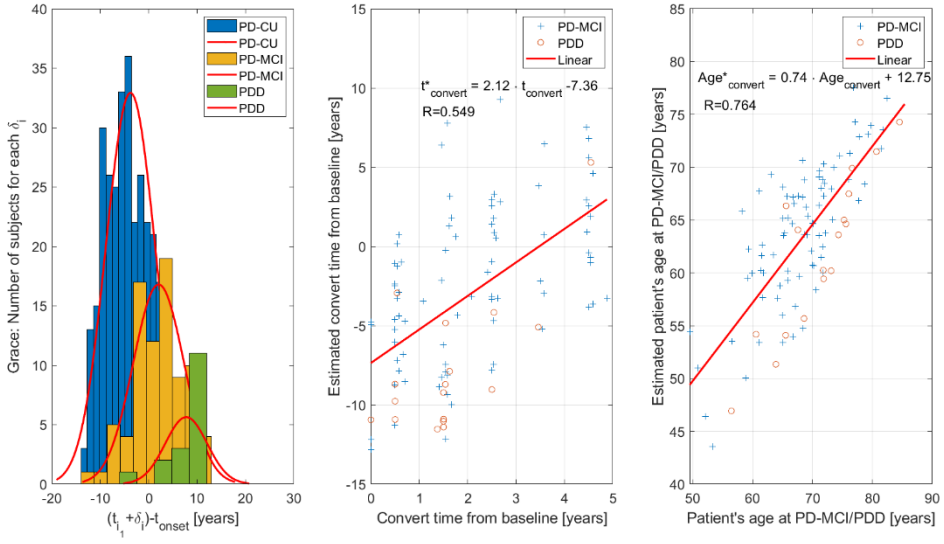

Figure 1: Classification of subjects according to the time shift δ_i. The first column displays a histogram of the number of subjects as a function of the temporal ordering proposed by GRACE, represented as $\left(t^c_{i_1} + \delta_i\right) - t_{onset}$. The second and third columns show the conversion times of PD-MCI/PDD subjects relative to their GRACE estimations, considering cognitive reserve and patient age. PD-CU=PD cognitively unimpaired, PD-MCI=PD mild cognitive impairment, PDD=PD dementia, GRACE=growth models by alternating conditional expectation.

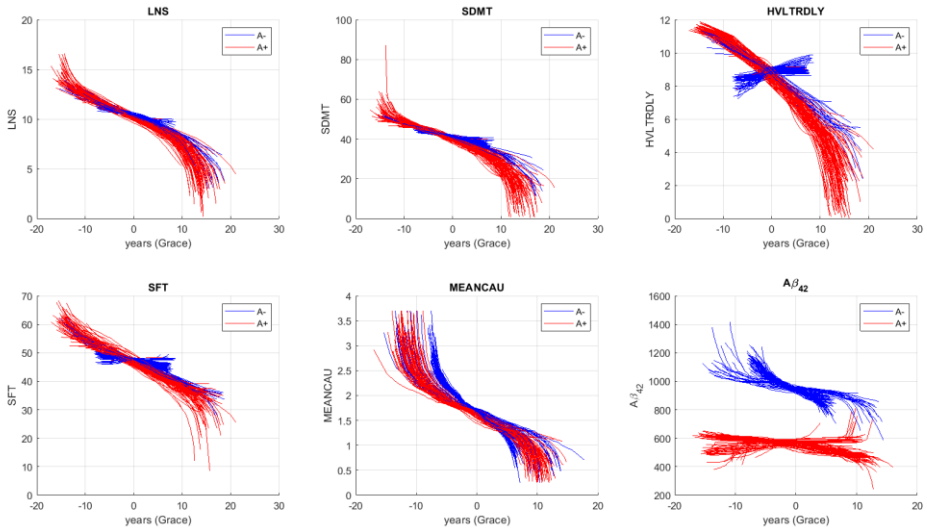

Figure 2: Long-term trajectories of the selected vector between A+ and A- subjects, using the bootstrap technique to infer the confidence intervals of these trajectories. LNS=Letter-number sequencing, SDMT=Symbol Digit Modalities Test, HVLTRDLY=Hopkins Verbal Learning Test Delayed Recall, SFT=Semantic Fluency Test, MEANCAU=mean caudate measure, Aβ42=Amyloid Beta 42, A+=amyloid pathology, A-=absence amyloid pathology.

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