RESEARCH ARTICLE

Proteinopathy and Longitudinal Cognitive Decline in Parkinson Disease

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Abstract

Background and Objectives

People with Parkinson disease (PD) commonly experience cognitive decline, which may relate to increased α-synuclein, tau, and β-amyloid accumulation. This study examines whether the different proteins predict longitudinal cognitive decline in PD.

Methods

All participants (PD n = 152, controls n = 52) were part of a longitudinal study and completed a lumbar puncture for CSF protein analysis (α-synuclein, total tau [tau], and β-amyloid$_{42}$ [β-amyloid]), a β-amyloid PET scan, and/or provided a blood sample for *APOE* genotype (ε4+, ε4−), which is a risk factor for β-amyloid accumulation. Participants also had comprehensive, longitudinal clinical assessments of overall cognitive function and dementia status, as well as cognitive testing of attention, language, memory, and visuospatial and executive function. We used hierarchical linear growth models to examine whether the different protein metrics predict cognitive change and multivariate Cox proportional hazard models to predict time to dementia conversion. Akaike information criterion was used to compare models for best fit.

Results

Baseline measures of CSF β-amyloid predicted decline for memory (p = 0.04) and overall cognitive function (p = 0.01). *APOE* genotypes showed a significant group (ε4+, ε4−) effect such that ε4+ individuals declined faster than ε4− individuals in visuospatial function (p = 0.03). Baseline β-amyloid PET significantly predicted decline in all cognitive measures (all $p \leq$ 0.004). Neither baseline CSF α-synuclein nor tau predicted cognitive decline. All 3 β-amyloid–related metrics (CSF, PET, *APOE*) also predicted time to dementia. Models with β-amyloid PET as a predictor fit the data the best.

Discussion

Presence or risk of β-amyloid accumulation consistently predicted cognitive decline and time to dementia in PD. This suggests that β-amyloid has high potential as a prognostic indicator and biomarker for cognitive changes in PD.

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Glossary

AD = Alzheimer disease; **AIC** = Akaike information criterion; **CDR** = Clinical Dementia Rating; **CDR-SB** = CDR sum of boxes; **HLM** = hierarchical linear growth model; **MCBP** = mean cortical binding potential; **PD** = Parkinson disease; **PiB** = Pittsburgh compound B; **RR** = relative risk.

Parkinson disease (PD) is a neurodegenerative disease characterized by the accumulation of α-synuclein Lewy bodies throughout the brain, affecting cognitive function.[1,2] In addition, some research suggests that tau protein, a component of tangles within neurons related to the onset of dementia in Alzheimer disease (AD),[3] may play a role in cognitive decline in PD.[4] However, most people with PD do not have significant increases in tau accumulation in the brain.[5-7] Instead, research more consistently indicates that β-amyloid, a protein that contributes to plaque formation in AD,[3] relates to cognitive decline in PD.[8,9] Altogether, 1 or more of these 3 proteins may be useful prognostic biomarkers for understanding and predicting cognitive decline in PD.

Prior studies mainly investigated these 3 proteins separately. People with PD have lower levels of total α-synuclein in CSF levels than controls[5,10]; however, CSF total a-synuclein levels may not relate to disease progression.[2] CSF tau in PD may[4,11,12] or may not[5-7] play an important role in PD. Last, β-amyloid measures in CSF[1,13] or with PET[14,15] relate to cognitive function in PD. Not surprisingly, the presence of an *APOE* ε4 allele, a risk factor for β-amyloid accumulation, also predicts cognitive performance in PD.[16]

Only a few studies investigated 1 or more of these proteins or used different approaches to explore them.[17-19] Akhtar et al.[17] reported that higher β-amyloid accumulation, along with the presence of *APOE* ε4 allele, correlates with verbal memory performance. Using PET, Buongiorno et al.[18] showed that higher β-amyloid binding relates to cognitive decline, dementia, and reduced levels of β-amyloid in CSF. Shahid et al.[19] found that individuals with PD with low β-amyloid in CSF and the presence of an *APOE* ε4 allele have a higher rate of cognitive decline. To the best of our knowledge, no study applied all 3 methods (i.e., CSF, PET, and *APOE* genotype) to investigate the role of β-amyloid.

The relationship of any of the 3 proteins to longitudinal cognitive decline remains unclear,[16,20] as is how the different methods compare to one another for predicting cognitive change. Therefore, this study, using multiple measurement approaches, evaluates the relationships of α-synuclein, tau, and β-amyloid to longitudinal cognitive decline in people with PD.

Methods

Standard 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 were part of 2 larger longitudinal studies[21,22] examining PD progression (total PD n = 337; total controls n = 85). For inclusion in the parent studies, all participants needed to be at least 50 years old, to have a minimum of 12 years of education, and to agree to brain donation. Participants with PD had a clinical diagnosis of PD based on the modified United Kingdom PD Society Brain Bank clinical diagnostic criteria[23] with clear motor response to levodopa. In addition, participants in the parent studies could not have (1) other neurologic diagnoses, (2) head injury with loss of consciousness >5 minutes or neurologic sequelae, or (3) schizophrenia or bipolar disorder. In addition, controls needed to have normal cognition, defined as receiving a Clinical Dementia Rating (CDR)[24] global score of 0, and no first-degree family history of PD.

For inclusion in the present study, participants needed (1) protein biomarker data (CSF, β-amyloid PET, and/or *APOE* genotyping), (2) to be without dementia at the baseline visit (CDR global score <1), and (3) at least 1 subsequent clinical evaluation with cognitive testing after their baseline protein biomarker collection. In addition, controls needed a mean cortical binding potential (MCBP) ≤0.18 to reduce preclinical AD risk.[25] eFigure 1 (links.lww.com/WNL/B939) gives for more details on participant inclusion and exclusion for these analyses.

Data Collection and Processing

Clinical and Cognitive Assessments

All participants completed longitudinal study visits, which included completion of the CDR clinical assessment and comprehensive cognitive testing. Participants with PD completed cognitive testing in the "off" medication state, defined as overnight withdrawal (>8 hours) from PD medications, to reduce possible medication confounds[26]; therefore, tests were chosen to minimize motor demands. For cognitive evaluations, participants completed multiple tests for each cognitive domain: attention (Digit Span,[27] Digit Symbol[27]), memory (California Verbal Learning Test–II, short-form[28]; Logical Memory[29]), language (Boston Naming Test[30]), visuospatial function (Judgement of Line Orientation,[31] Spatial Relations Test[32]), and executive function (Trail Making Test,[31] Verbal Fluency- Switching,[33] Color-Word Interference[33]). The CDR sum of boxes (CDR-SB) score was also collected to measure overall cognitive function.

For participants who developed severe cognitive impairment and could not complete the entire cognitive battery (e.g., had

a CDR score ≥1, 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). For the longitudinal analyses, number of cognitive testing sessions (exposures) was used to control for potential practice effects. If participants completed testing on medication ("on"), took medication during the testing session, or were unable to complete the testing session for any reason, the cognitive test data from that session were omitted from the longitudinal analyses but included in the number of testing exposures. Thus, some study visit evaluations included only the CDR clinical assessment without formal cognitive testing (Table 1).

CSF Collection and Processing

Procedures for CSF collection and processing are described in detail by Buddhala et al.[5] In brief, participants underwent a lumbar puncture to collect CSF. Samples were collected between 1 and 2 PM at the study visit. A 22-gauge atraumatic Sprotte needle was used to collect ≈25 mL fluid. CSF samples were pulse vortexed and then centrifuged at 2,000*g* for 15 minutes at 4°C. After removal of all but the last 500 μL supernatant, 0.5- and 1-mL CSF aliquots were prepared and frozen at −80°C. CSF collection and freezing took ≈30 minutes.

To quantify levels of CSF α-synuclein, β-amyloid$_{42}$ (β-amyloid), and total tau (tau), sandwich ELISAs were used.[6] The Covance α-syn ELISA kit (Covance, Inc, Indianapolis, IN) measured α-synuclein. A CSF dilution of 1:4 provided the optimal CSF signal, such that all values fell within the range of the standard curve. The Innotest ELISA kit (Fujirebio US, Inc, Seguin, TX) quantified β-amyloid and tau. Hemoglobin levels in CSF were measured with the Human Hemoglobin ELISA Quantitation Set (Bethyl Laboratories, Inc, Montgomery, TX) to assess the potential contribution of red blood cell a-synuclein to CSF measures. Because no correlation was observed between hemoglobin and a-synuclein for the a-synuclein assay, no samples were excluded on the basis of hemoglobin levels. Each ELISA plate contained at least 8 CSF samples run on previous ELISA plates to assess interassay variance. The interassay coefficient of variation was <15% for all CSF assay data included in this analysis.

APOE Genotyping

Participants provided blood samples for *APOE* genotyping. Specifically, TaqMan assays (Applied Biosystems, Waltham, MA) for rs429358 (ABI#C_3084793_20) and rs7412 (ABI#C_904973_10) were used, as we previously published.[34] ABI Sequence Detection software was used to detect the 6 combinations of *APOE* ε2, ε3, and ε4.

PET Scan and Image Processing

Dynamic [^{11}C] Pittsburgh compound B (PiB) PET images were acquired with a Siemens (Munich, Germany) 962 HR+ ECAT scanner to measure fibrillar β-amyloid. Scans were processed as described previously.[35] Sixty-minute dynamic scans were reconstructed with 3-dimensional filtered-back projection with a ramp filter to a voxel size of 2.1 × 2.1 × 2.4 mm with an approximate full-width half-maximum of 5 mm. Images were aligned to T1-weighted structural MRI scans with vector-gradient registration.[36] Segmentation was conducted with FreeSurfer5.3[37] for region-based analyses. Reference-region–based Logan binding potentials were calculated from a model window of 30 to 60 minutes of PiB injection with the cerebellar gray matter used as the reference region. To account for partial volume effects, region-spread function partial volume correction was applied.[35] Mean cortical binding potentials used regions defined by Su et al.[35]

Datasets

We created 3 datasets for each method (CSF, *APOE*, and PET) in which each participant's baseline (i.e., first visit) included data collection for the respective protein metric. We also compiled a fourth dataset (all protein), which included participants with all 3 protein metrics, specifically with the PET and CSF data collected at the same visit. Thus, for the CSF, PET, and all-protein datasets, the baseline visit was defined as the visit at which the lumbar puncture, PET scan, or both were performed. For the *APOE* dataset, the baseline visit was defined as the participant's first study visit with complete cognitive data. For each dataset, symptom duration equaled time from first motor symptom to baseline visit. Age in each dataset equaled age at baseline visit. To account for practice effects in cognitive testing, we calculated the number of times a participant was exposed to cognitive testing; thus, the number of cognitive testing exposures remained constant across all protein biomarker datasets. Last, for the *APOE* dataset, participants carrying at least 1 ε4 allele were categorized as ε4+, and participants without an ε4 allele were categorized as ε4−.

Data Standardizing

For each dataset, age, education, symptom duration, number of cognitive testing exposures, and raw values for each cognitive test were standardized to the mean and SD of the baseline visit. Next, cognitive domain scores (attention, language, memory, visuospatial function, and executive function) and CDR-SB score were computed for each participant for each visit by averaging the standardized test scores for each domain. Thus, scores represent how individuals change over time relative to baseline performance.

Statistical Analyses

Longitudinal Cognitive Change

We used hierarchical linear growth models (HLMs) to examine longitudinal cognitive changes in our participants. These statistical models account for individual and group variance within the models and predict an individual's cognitive performance over time. For our analyses, a participant's intercept and time-slope were specified as random effects for each model, meaning that each participant's intercept and time-slope were specific to their data and thus varied across

Table 1 Demographics and Baseline Characteristics

Baseline characteristic	Controls (n = 52)	Participants with PD (n = 152)	*p* Value
Age, y	63.7 (9.7)	66.7 (8.2)	0.05
Sex, % female	71.2	38.8	<0.001
Education, y	14.8 (2.6)	15.9 (2.5)	0.01
Race/ethnicity, % White	86.5	90.1	0.44
Symptom duration, y	—	6.9 (4.0)	—
Cognitive testing exposures, n	3.2 (1.1)	4.1 (1.9)	<0.001
Time in study, y	6.0 (2.4)	4.1 (2.1)	<0.001
Executive function score	0.37 (0.43)	−0.15 (0.92)	<0.001
Visuospatial function score	0.29 (0.47)	−0.14 (1.07)	<0.001
Memory score	0.35 (0.65)	−0.13 (0.82)	<0.001
Attention score	0.22 (0.71)	−0.08 (0.83)	0.02
Language score	0.28 (0.61)	−0.09 (1.09)	0.003
CDR-SB score	−0.54 (0.00)	0.18 (1.10)	<0.001
CDR global score, 0/0.5	52/0	88/64	<0.001
CSF α-synuclein[a]	1,979.8 (669.6)	1,642.5 (613.1)	0.008
CSF $A\beta_{42}$[a]	941.4 (148.4)	789.5 (217.1)	<0.001
CSF total tau[a]	234.6 (90.4)	231.2 (112.8)	0.85
MCBP[b]	0.04 (0.04)	0.11 (0.18)	<0.001
***APOE* genotype, ε4+/ε4−, n (ε4+ allele frequency, %)**	10/42 (9.6)	40/112 (13.1)	0.4

Abbreviations: Aβ = β-amyloid; CDR = Clinical Dementia Rating; CDR-SB = CDR sum of boxes; MCBP = mean cortical binding potential.
All data calculated were with the *APOE* dataset unless otherwise indicated. All values represent mean (SD) unless otherwise noted.
[a] Data come from the CSF dataset.
[b] Data come from the PET dataset.

individuals. HLMs do not require participants to have the same number of data points (visits) or the same length of time between visits. This allows greater flexibility with participant inclusion and provides a more complete picture of between-group differences. All HLMs were run with the lmer function in the lme4 R package (R Foundation for Statistical Computing, Vienna, Austria).[38] The time between visits was calculated as the time from a participant's baseline visit within a dataset with the lubridate package in R. Covariates for all models included sex, symptom duration, education, number of cognitive testing session exposures, and age at baseline visit. After running of the growth models, slopes were extracted with ggeffects to assess the magnitude of change over time for each cognitive domain and CDR-SB score. We retested each significant model using the all-protein dataset to assess which growth model best predicts cognitive decline (i.e., all participants completed β-amyloid PET and lumbar punctures at the same visit). We ran growth models with only covariates to reduce the number of predictors to identify significant covariates for each cognitive measure. Baseline age, education, and sex were significant ($\alpha < 0.05$) for executive function, memory, and attention. Only age and education were significant for visuospatial function and CDR-SB score. We then compared the Akaike information criterion (AIC) for each significant model with its specific, significant covariates. An AIC difference of ≥2[39] was used as a threshold criterion for indicating the best-fitting model, and a χ^2 test compared models for statistically significant differences($\alpha < 0.05$).

Conversion to Dementia

We used multivariate Cox proportional hazards regression models to determine whether different protein metrics predict the rate of dementia conversion in the PD group. All regressions were run with the SURVIVAL[40] and SURVMINER[41] packages in R. Censoring was based on the last date of contact. Events were defined as the date when a participant first received a CDR global score ≥1. Survival time was calculated as time since the baseline clinical assessment to the most recent CDR. Covariates included age, sex, symptom duration, and education, and all models were stratified by baseline CDR global score. Participants with PD were divided into high- and low-risk groups for converting to dementia according to

protein levels or genetic risk (*APOE*) (see eTables 1–3, links.lww.com/WNL/B940 for demographic information based on risk group). For CSF β-amyloid, high-risk (CSF Aβ+) participants had CSF β-amyloid <720 pg/mL, the lowest tertile, and low-risk (CSF Aβ−) participants had CSF β-amyloid >720 pg/mL. For *APOE*, the ε4+ group was considered high risk, and the ε4− group was considered low risk.[16] For MCBP, participants with MCBP >0.18[25] were considered high risk (PiB+), and individuals with MCBP <0.18 were considered low risk (PiB−).

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Baseline characteristics for PD and control groups can be found in Table 1. Controls and participants with PD differed in all baseline characteristics except CSF total tau and *APOE* allele ε4+ status.

Longitudinal Changes

First, growth models for each cognitive domain and overall cognitive function (CDR-SB group) showed group (PD vs control) differences in change over time (Figure 1). Compared to controls, participants with PD demonstrated significant decline in executive function ($p < 0.001$), visuospatial function ($p = 0.03$), attention ($p < 0.001$), and CDR-SB score ($p < 0.001$), showing a well-differentiated sample of controls from participants with PD. To better understand cognitive dysfunction changes in PD, controls were removed from further analyses. In addition, the language domain was removed from further analyses because this domain did not change over time. The memory domain was retained because of its prominent role in dementia.

Individual Protein Measures

Overall, CSF β-amyloid measures consistently predicted cognitive decline, whereas CSF α-synuclein and tau did not (all $p > 0.15$). Specifically, baseline CSF β-amyloid related to the rate of decline for memory ($p = 0.04$) and CDR-SB score ($p = 0.01$) (Table 2). For *APOE* genotypes, growth models showed that the ε4+ group declined faster than the ε4− group in visuospatial function ($p = 0.01$) (Table 3). Last, growth models with β-amyloid PET (i.e., MCBP) showed that baseline MCBP relates to all cognitive measures (all $p \leq 0.004$) (Table 3 and Figure 2) such that a higher MCBP predicted a faster rate of decline across all measures.

β-Amyloid Comparison

The individual models reveal that the 3 metrics of presence or risk for β-amyloid (CSF β-amyloid, *APOE* genotype, and MCBP) consistently predict cognitive decline. To determine the relative contribution of each metric to predicting cognitive decline, we built growth models with the significant covariates and interaction terms between time and CSF β-amyloid, *APOE* genotype, and MCBP individually for each cognitive domain (full model). Next, we ran 3 models, each model containing only 2 of the measurement interactions. Similarly, we ran models with a single interaction. All growth models for a cognitive domain were then compared to the full model (Table 4). This permits the identification of the best metric(s) for predicting cognitive decline in PD.

For executive function, the model including *APOE* and MCBP had the lowest AIC compared to the full model. However, the AIC difference was <2, so it did not reach the threshold criterion to be considered the best model. The MCBP model had the greatest AIC difference from the full model (>4) for visuospatial function, memory, attention, and CDR-SB score (Table 4), meeting the criterion for selection as the best model. In addition, this AIC difference reached statistical significance for both memory and CDR-SB score ($p < 0.05$) according to the χ^2 test.

Conversion to Dementia

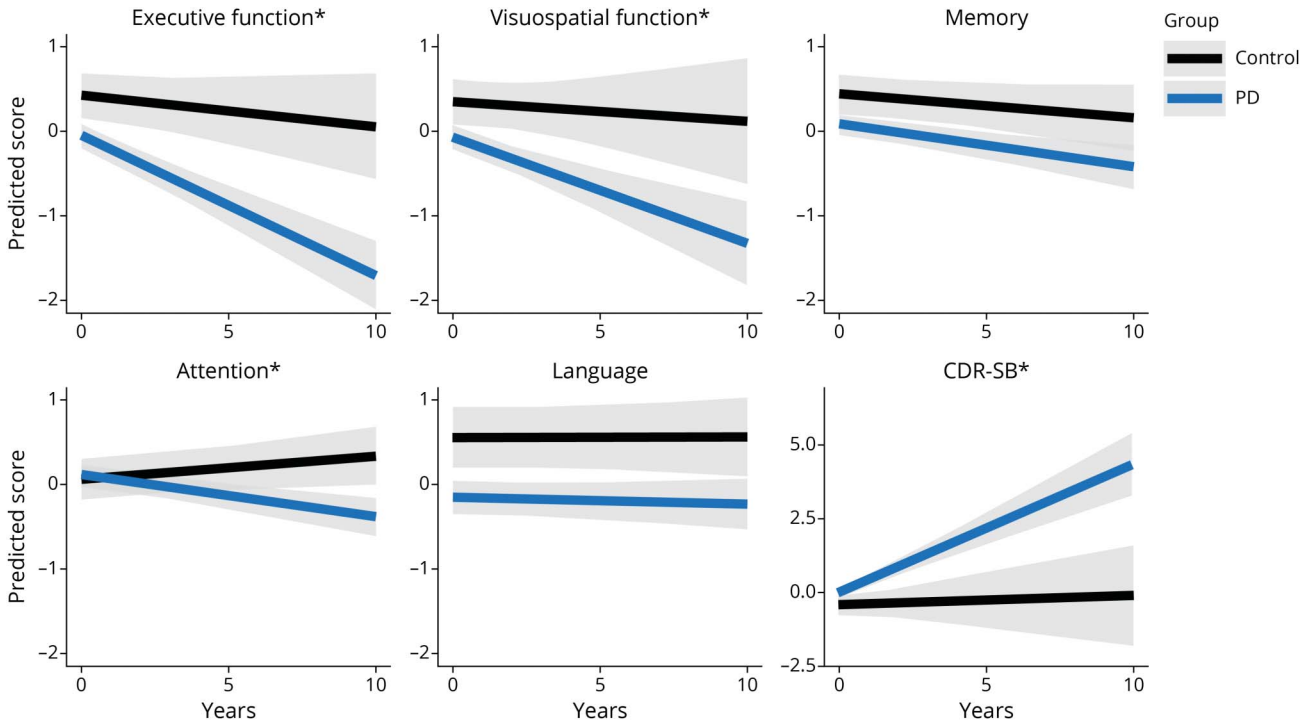
Last, we examined whether the different protein metrics predict conversion to dementia. A greater proportion of the CSF Aβ+ risk group converted to dementia compared to the CSF Aβ− risk group (CSF Aβ+: 21 of 45 [46.7%]; CSF Aβ−: 15 of 89 [16.9%]; $\chi^2 = 12.0$, $p < 0.001$); a greater proportion of *APOE* ε4+ individuals converted to dementia compared to *APOE* ε4− individuals (ε4+: 18 of 36 [50.0%]; ε4−: 27 of 112 [24.1%]; $\chi^2 = 7.5$, $p = 0.006$); and a greater proportion of PiB+ individuals converted to dementia compared to PiB− individuals (PiB+: 23 of 43 [53.5%]; PiB−: 26 of 112 [23.2%]; $\chi^2 = 11.8$, $p < 0.001$).

Multivariate Cox proportional hazard regression revealed a faster dementia conversion rate (relative risk [RR] 3.8, $p = 0.001$) for the CSF Aβ+ group (Table 5), but multivariate Cox proportional hazard regression showed no significant difference in risk between the ε4+ and ε4− groups (RR 0.54, $p = 0.09$) or the PiB+ and PiB− groups (RR 0.50, $p = 0.11$). We also ran the multivariate Cox proportional hazard regression with CSF β-amyloid and MCBP as continuous variables. This revealed higher risk of dementia for CSF β-amyloid (RR −3.6, $p < 0.001$, indicating that higher values of CSF β-amyloid reduced the risk of dementia conversion) and for MCBP (RR 2.16, $p = 0.03$, indicating that higher values of MCBP increased the risk of dementia conversion).

Discussion

This study examines the relationships between different proteins and longitudinal cognitive decline in PD, including α-synuclein, β-amyloid, and tau. Through multiple measurement modalities, the presence and risk of β-amyloid consistently predicted longitudinal cognitive decline. In addition, models with the direct measure of β-amyloid aggregation in the brain (MCBP) were the most parsimonious. Last, the results indicate that both CSF and PET measures of

Figure 1 PD vs Controls



Group (Parkinson disease [PD] n = 152, controls n = 52) changes in each cognitive domain and Clinical Dementia Rating Scale sum of boxes (CDR-SB) scores are depicted using the *APOE* genotype dataset to best depict change over time from the beginning of the study. *Significant difference in change over time between participants with PD and controls.

β-amyloid predict conversion to dementia, highlighting the potential role of β-amyloid as a prognostic biomarker of PD dementia.

Our results illustrate that β-amyloid provides the greatest utility and potential for understanding and predicting cognitive change in PD. While prior research investigated β-amyloid in CSF,[1,13] PET,[14,15] and *APOE* genotypes[16] separately, the present study examines each metric separately and compares across modalities, at least for β-amyloid. This comparison established that for visuospatial function, memory, attention, and overall cognitive function (CDR-SB score), the growth model with only β-amyloid PET (MCBP) as a predictor was the best fit for the data (i.e., had the lowest AIC), meaning that it maintained the most information from the data compared to the other models. In the case of memory and overall cognitive function, the model with only β-amyloid PET (MCBP) as a predictor reached our threshold criterion (i.e., AIC difference >2 points) and statistical significance. The best-fitting model had both *APOE* and β-amyloid PET (MCBP) as predictors for executive function. While this model did not surpass the full model, the importance of

Table 2 CSF Proteins as Predictors for Cognitive Change

	α-Synuclein		β-Amyloid		Tau	
Cognitive measure	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**
Executive function	0.02 (0.01 to 0.02)	0.59	0.04 (0.04 to 0.05)	0.11	0.02 (0.02 to 0.03)	0.41
Visuospatial function	−0.02 (−0.02 to −0.01)	0.67	0.07 (0.06 to 0.07)	0.06	−0.02 (−0.03 to −0.02)	0.54
Memory	0.01 (0.01 to 0.02)	0.57	0.04 (0.04 to 0.04)	0.04	−0.01 (−0.01 to 0)	0.73
Attention	0.02 (0.02 to 0.02)	0.27	0.03 (0.02 to 0.03)	0.09	0.01 (0.01 to 0.01)	0.52
CDR-SB	0.02 (0.01 to 0.04)	0.79	−0.21 (−0.22 to −0.2)	0.01	0.08 (0.07 to 0.09)	0.33

Abbreviation: CDR-SB = Clinical Dementia Rating sum of boxes.
Estimate values indicate how an increase in the measured value of the respective protein in CSF affects change in a cognitive domain. For CSF protein measurements, lower values relate to pathologic accumulation in the brain. Thus, for executive function, visuospatial function, memory, and attention, a positive estimate relates to better performance. For CDR-SB, a negative estimate relates to better performance.

Table 3 *APOE* ε4+ and MCBP as a Predictor of Cognitive Change

	APOE ε4+		MCBP	
Cognitive domain	**Estimate (95% CI)**	***p* Value**	**Estimate (95% CI)**	***p* Value**
Executive function	−0.08 (−0.08 to −0.09)	0.12	−0.06 (−0.07 to −0.06)	0.004
Visuospatial function	−0.19 (−0.18 to −0.2)	0.01	−0.14 (−0.14 to −0.13)	<0.001
Memory	−0.06 (−0.05 to −0.06)	0.12	−0.06 (−0.06 to −0.05)	<0.001
Attention	−0.04 (−0.03 to −0.04)	0.22	−0.04 (−0.04 to −0.04)	<0.001
CDR-SB	0.25 (0.27 to 0.23)	0.08	0.25 (0.24 to 0.26)	<0.001

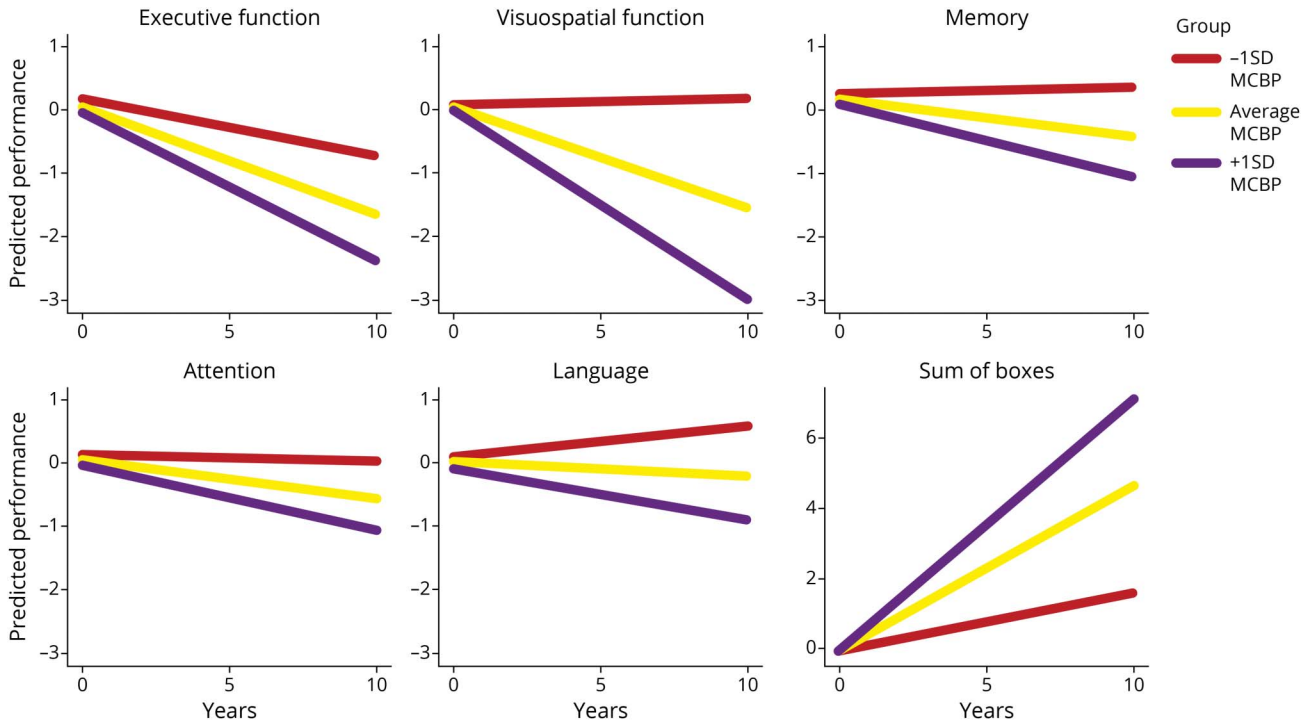
Abbreviations: CDR-SB = Clinical Dementia Rating sum of boxes; MCBP = mean cortical binding potential.
For executive function, visuospatial function, memory, and attention, a negative estimate relates to worse performance. For CDR-SB, a positive estimate relates to worse performance.

β-amyloid PET (MCBP) in the model remains evident. These data suggest that performing a baseline PET scan at minimum has significant clinical relevance for cognitive prognosis in patients with PD.

Our results expand on the predictive utility of β-amyloid for cognitive decline and dementia in PD. Our data clearly show that the presence or risk of β-amyloid (whether in CSF, PET imaging, or *APOE* genotypes) predicts cognitive decline. In addition, we show that β-amyloid, as measured in CSF or through PET imaging, predicts risk and time to dementia. Although the risk groups we created from the PET measures did not predict time to dementia, this likely reflects both the proportions of dementia conversions within the different risk groups and lower variability in time to dementia within each group, limiting the overall power of the Cox regression. Regardless, these results suggest clinical utility: knowing the β-amyloid burden would allow clinicians to better understand the prognosis of a patient with PD and to offer stronger guidance to the patient and family on disease progression.

It is important to note that, while prior research investigated relationships between different β-amyloid measures and cognitive change, these studies either had small sample

Figure 2 MCBP Predicts Cognitive Decline



Changes in cognitive performance as predicted by mean cortical binding potential (MCBP) are shown. For each graph, predicted change for the average MCBP is depicted, as well as change for ±1 SD from the average MCBP.

Table 4 AIC Model Comparisons

Model, AIC	Executive function, *df*	Visuospatial function, *df*	Memory, *df*	Attention, *df*	CDR-SB, *df*
All β-amyloid	820.6 (15)	978.3 (14)	700.1 (15)	564.3 (15)	1,302.6 (14)
No MCBP	818.8 (13)	981.4 (12)	697.5 (13)	566.9 (13)	1,304.2 (12)
No *APOE*	824.1 (13)	975.0 (12)	697.9 (13)	563.4 (13)	1,299.4 (12)
No CSF β-amyloid	818.7 (13)[a]	974.5 (12)	698.3 (13)	561.2 (13)	1,299.9 (12)
CSF β-amyloid only	822.3 (11)	979.2 (10)	694.8 (11)	566.3 (11)	1,300.6 (10)
MCBP only	821.4 (11)	973.0 (10)[a]	687.7 (11)[a]	560.0 (11)[a]	1,291.5 (10)[a]
***APOE* only**	819.9 (11)	979.2 (10)	698.1 (11)	564.8 (11)	1,303.7 (10)
Covariates only	824.5 (9)	979.5 (8)	695.0 (9)	563.7 (9)	1,301.7 (8)
No interaction	821.0 (12)	978.8 (11)	697.9 (12)	564.1 (12)	1,313.1 (11)

Abbreviations: AIC = Akaike information criterion; CDR-SB = Clinical Dementia Rating sum of boxes; MCBP = mean cortical binding potential.
[a]Within a cognitive domain, the model with the lowest AIC provides the best fit.

sizes[11,14] or short follow-up periods[14,42] or used global measures of cognition without consideration of specific domains.[16,19] In comparison, our research has an average follow-up of 4.1 years (range 1–12 years), >150 participants with PD, and comprehensive neuropsychological evaluations. It also includes *APOE* genotype, β-amyloid PET, and CSF measures of α-synuclein, β-amyloid, and tau. Importantly, this study combined 3 methods (CSF, PET, and genotype) and multiple proteins, compared to prior research which only used 2 of these methods.[17-19]

Further, our results agree with prior research on the limited prognostic role of CSF α-synuclein in PD,[10,43] indicating its low predictive ability of cognitive change, despite the findings that insoluble α-synuclein fibrils (i.e., Lewy bodies) represent key markers in the pathophysiology of PD.[44,45] Recent studies have shown that β-amyloid accumulation relates to higher levels of pathologic α-synuclein accumulation[5,46] and that increased α-synuclein accumulation has an association with the presence of *APOE* ε4 allele.[16] Together, these studies suggest a link between β-amyloid and α-synuclein accumulation. While our results could suggest that cognitive dysfunction in PD is not related to α-synuclein, it is more likely that total α-synuclein levels in CSF are not related to levels of aggregated α-synuclein in the brain or in specific regions of the brain that are critical for cognitive function. A direct measure of pathologic, aggregated α-synuclein accumulation (i.e., PET) may yield different results from the CSF measure of total α-synuclein. Indeed, the main challenge of using total CSF α-synuclein levels as a predictor for cognitive change in PD is that we do not know the strength of the correlation between total α-synuclein in CSF and the pathologic accumulation of α-synuclein in the brain and whether CSF concentrations reflect areas of brain closer to CSF bordering surfaces. Furthermore, pathologic β-amyloid accumulation is associated with higher pathologic α-synuclein accumulation at autopsy,[46] raising the possibility that the prognostic role of β-amyloid measures may relate to an association with a higher α-synuclein burden. In other words, β-amyloid may only reflect greater α-synuclein burden and does not independently contribute to dementia in PD. PET tracers for α-synuclein will be critical to disentangle the temporal sequence of proteinopathy in PD to delineate the role of α-synuclein and to determine the unique, synergistic, or nonessential marker role of β-amyloid.

In contrast, tau accumulation in the brain may not contribute to dysfunction in most people with PD,[5,6,16] even at autopsy.[7] Although the importance of tau in AD is clear, tau PET may be useful in only a small subgroup of people with PD and dementia who also have coexisting AD.[7]

Alternatively, cognitive decline and dementia in PD may represent neurotransmitter and synaptic dysfunction[47,48] associated with protein aggregation. For example, β-amyloid peptides disrupt neural transmission and synaptic function,[49] and Lewy body accumulation in brainstem nuclei disrupts various neurotransmitter systems.[47,50] Thus, protein levels may be an indirect assessment of the underlying neuropathogenesis of cognitive impairment in PD. Future research incorporating both protein and neurotransmitter measures will help delineate the relative contributions of these overlapping pathologies.

The robust sample size of individuals whose average symptom duration at baseline is ≈7 years and whose follow-up time is ≈4 additional years, provides a strong idea of how PD progresses over time. Our results consistently indicate that the presence or risk of β-amyloid accumulation, regardless of the measurement modality, is a strong predictor of cognitive decline in PD. This does not, however, mean that α-synuclein and tau are not also related to cognition. However, we do not have a PET radiotracer for α-synuclein, and PET measures of

Table 5 Multivariate Cox Proportional Hazard Models for Dementia Conversion

Covariates	Variables	Coefficients	Wald *Z* value	*p* Value	Multivariate relative risk (95% CI)
CSF β-amyloid[a]					
Covariates	Sex	−0.71	−2.88	0.004	0.49 (0.3, 0.8)
	Age	0.04	1.84	0.066	1.04 (1, 1.09)
	Education	0.03	0.35	0.728	1.03 (0.88, 1.19)
	Symptom duration	0.04	0.81	0.419	1.04 (0.95, 1.14)
Risk group	CSF Aβ− vs CSF Aβ+	1.33	3.11	0.002	3.79 (1.64, 8.79)
MCBP[b]					
Covariates	Sex	−0.26	−1.58	0.114	0.77 (0.56, 1.07)
	Age	0.05	2.55	0.011	1.05 (1.01, 1.1)
	Education	0.06	0.83	0.407	1.06 (0.92, 1.21)
	Symptom duration	−0.01	−0.19	0.852	0.99 (0.92, 1.07)
Risk group	PiB+ vs PiB−	0.5	1.56	0.118	1.64 (0.88, 3.07)
***ApoE* genotype[c]**					
Covariates	Sex	−0.21	−1.21	0.227	0.81 (0.58, 1.14)
	Age	0.07	3.61	<0.001	1.08 (1.03, 1.12)
	Education	0.04	0.55	0.583	1.04 (0.91, 1.17)
	Symptom duration	−0.01	−0.24	0.812	0.99 (0.92, 1.07)
Risk group	ε4− vs ε4+	−0.54	−1.7	0.089	0.58 (0.31, 1.09)

Abbreviations: Aβ = β-amyloid; MCBP = mean cortical binding potential; PiB = Pittsburgh compound B.
All multivariate Cox proportional models were stratified by baseline CDR global score (i.e., CDR global score = 0 or 0.5). CSF Aβ+, participants had <720 pg/mL soluble β-amyloid; CSF Aβ−, participants had >720 pg/mL soluble β-amyloid; PiB+, participants had MCBP >0.18; PiB−, participants had MCBP <0.18; ε4−, participants did not have an ε4 allele; and ε4+, participants had at least 1 ε4 allele.
[a] Data come from the CSF dataset.
[b] Data come from the PET dataset.
[c] Data come from the *APOE* dataset.

tau may apply to only a minority of those with PD and coexisting AD. In addition, while we demonstrate that baseline measures of β-amyloid predict cognitive change, the impact of changes in β-amyloid or the other 2 proteins on cognition remains unknown. Future research needs to incorporate multiple measures of β-amyloid over time (e.g., longitudinal PET scans) to better illuminate the role of β-amyloid in PD and cognitive decline. To test the underlying pathophysiology of cognitive deficits in PD, participants were tested "off" dopaminergic medications, in contrast to standard clinical conditions during which patients take medications, and should be interpreted accordingly. However, it is worth noting that a similar pattern of results was obtained with the CDR (assessed "on" medication), demonstrating that the presence or risk of β-amyloid also predicts cognitive decline and dementia on the basis of their functional abilities while medicated. Last, we acknowledge the low racial/ethnic diversity of our cohort and thus understand that our results may not generalize to the greater PD population. In addition, not all patients with PD are willing and able to complete a lumbar puncture or PET scan, and more severe motor symptoms (i.e., marked tremor) self-select participants out of our cohort. In these cases, *APOE* genotype may offer sufficient prognostic value until blood-based protein biomarkers become available for PD.

In this study, we investigated the relationship between α-synuclein, β-amyloid, and tau and longitudinal cognitive changes in people with PD. We found that CSF and PET measures of β-amyloid, as well as *APOE* genotype, predict cognitive decline. While these different modalities have been studied individually in PD, we compared the different modalities to better understand the relative predictive power of each modality. Although PET imaging for α-synuclein and tau warrants further research and development, our results emphasize the potential of β-amyloid as a prognostic biomarker for predicting cognitive changes in PD.

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Appendix *(continued)*

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