

An increased rate of longitudinal cognitive decline is observed in Parkinson's disease patients with low CSF A β 42 and an APOE ϵ 4 allele

Marian Shahid^a, Jeehyun Kim^a, Katherine Leaver^{a,b,1}, Taylor Hendershott^a, Delphine Zhu^a, Brenna Cholerton^c, Victor W. Henderson^{a,d}, Lu Tian^e, Kathleen L. Poston^{a,f,*}

^a Stanford University, Department of Neurology and Neurological Sciences, 300 Pasteur Dr. Room H3144, MC 5235, Stanford, CA 94305, United States of America

^b Mount Sinai Beth Israel, Department of Neurology, 10 Union Square East, New York, NY 10003, United States of America

^c Stanford University, Department of Pathology, 300 Pasteur Dr Rm L235, MC 5324, Stanford, CA 94305, United States of America

^d Stanford University, Department of Health Research and Policy (Epidemiology), 259 Campus Drive, MC 5405, Stanford, CA 94305, United States of America

^e Stanford University, Department of Biomedical Data Science, 150 Governor's Lane, Room T160C, MC 5464, Stanford, CA 94305, United States of America

^f Stanford University, Department of Neurosurgery, 300 Pasteur Dr. Room H3144, MC 5235, Stanford, CA 94305, United States of America

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ABSTRACT

Objective: Low concentrations of cerebrospinal fluid (CSF) amyloid-beta (A β -42) are associated with increased risk of cognitive decline in Parkinson's disease (PD). We sought to determine whether APOE genotype modifies the rate of cognitive decline in PD patients with low CSF A β -42 compared to patients with normal levels.

Methods: The Parkinson's Progression Markers Initiative is a longitudinal, ongoing study of *de novo* PD participants, which includes APOE genotyping, CSF A β -42 determinations, and neuropsychological assessments. We used linear mixed effects models in three PD groups (PD participants with low CSF A β at baseline, PD participants with normal CSF A β , and both groups combined). Having at least one copy of the APOE ϵ 4 allele, time, and the interaction of APOE ϵ 4 and time were predictor variables for cognitive change, adjusting for age, gender and education.

Results: 423 *de novo* PD participants were followed up to 5 years with annual cognitive assessments. 103 participants had low baseline CSF A β -42 (39 APOE ϵ 4+, 64 APOE ϵ 4-). Compared to participants with normal CSF A β -42, those with low CSF A β -42 declined faster on most cognitive tests. Within the low CSF A β -42 group, APOE ϵ 4+ participants had faster rates of decline on the Montreal Cognitive Assessment (primary outcome; 0.57 points annual decline, $p = .005$; 5-year standardized change of 1.2) and the Symbol Digit Modalities Test (1.4 points annual decline, $p = .002$; 5-year standardized change of 0.72).

Discussion: PD patients with low CSF A β -42 and APOE ϵ 4+ showed a higher rate of cognitive decline early in the disease. Tests of global cognition (Montreal Cognitive Assessment) and processing speed (Symbol Digit Modalities Test) were the most sensitive to early cognitive decline. Results suggest that CSF A β -42 and APOE ϵ 4 might interact to promote early cognitive changes in PD patients.

1. Introduction

Cognitive impairment and dementia are among the most devastating symptoms in Parkinson's disease (PD) (Levy et al., 2002; Hely et al., 2005; Hely et al., 2008). While it is now clear that all PD patients are at risk for eventual cognitive decline, the individual rate of decline is highly variable with some patients exhibiting dementia at 5 years and

others only mildly impaired at 20 years. At the time of diagnosis, most PD patients (60–85%) are cognitively normal (Terrelonge Jr et al., 2016; Aarsland et al., 2009; Foltynie et al., 2004), but over the first three years of disease, approximately one-third of cognitively normal patients will progress to mild cognitive impairment (Broeders et al., 2013). Those demonstrating mild cognitive impairments are then at higher risk of developing dementia (Broeders et al., 2013; Janvin et al.,

Abbreviations: CSF, Cerebrospinal fluid; HC, Healthy controls; HVLt-R, Hopkins Verbal Learning Test-Revised; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; PPMI, Parkinsons Progression Marker Initiative; SDMT, Symbol Digit Modalities Test

* Corresponding author at: Stanford University, Department of Neurology and Neurological Sciences, 300 Pasteur Dr. Room H3144, MC 5235, Stanford, CA 94305, United States of America.

E-mail address: klposton@stanford.edu (K.L. Poston).

¹ Present address.

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2006). Therefore, recognizing patients at the time of diagnosis who are at higher risk of early cognitive decline could also identify those at risk of earlier dementia, which is important to anticipate given its association with a greater loss of employment, caregiver stress and fatigue, increased cost to health systems, patient institutionalization, and decreased survival (Olanow and Schapira, 2013; Svenningsson et al., 2012; Marder, 2010; Armstrong et al., 2014; Burn et al., 2014; Barone et al., 2009; Martinez-Martin et al., 2011; de Lau et al., 2014; Kowal et al., 2013). Further, differentiating those patients at high risk for dementia as early as possible has therapeutic implications, since treatment is likely to be most effective prior to the onset of demonstrable cognitive decline.

By 15 years of disease, about half of PD patients will meet diagnostic criteria for dementia (Hely et al., 2005; Cholerton et al., 2013), but identifying those who will dement has been difficult. The most commonly reported predictors of dementia are older age at PD diagnosis, male gender, and longer duration of motor symptoms (Hely et al., 2005; Cholerton et al., 2013; Reid et al., 2011; Chahine et al., 2016; Wills et al., 2016; Cholerton et al., 2018). However, age, gender and duration alone do not explain the wide variance in risk for cognitive decline. Several longitudinal studies have identified other biomarkers predictive of cognitive decline in early PD. The most robust is cerebral amyloid, as assessed by CSF A β (Leaver and Poston, 2015) or amyloid PET imaging (Petrou et al., 2015). While some cross-sectional studies in PD did not find a relationship between low CSF A β or PET amyloid positivity (Petrou et al., 2015; Beyer et al., 2013; Yu et al., 2014), other studies showed that low CSF A β is correlated with poor memory (Stav et al., 2015; Goldman et al., 2018; Yarnall et al., 2014) and global cognitive impairment (Montine et al., 2010) in non-demented PD patients. To date, most longitudinal studies in PD agree that abnormal A β is linked to future cognitive decline (Leaver and Poston, 2015).

Other studies suggest that PD patients with at least one copy of the *APOE* ϵ 4 allele are at higher risk of developing cognitive impairment and dementia (Mata et al., 2014). The *APOE* ϵ 4 allele is more common in PD patients with dementia and in patients with Dementia with Lewy Bodies (Arai et al., 1994). A recent large-scale multisite genetic study found that *APOE* ϵ 4 was over represented in PD patients with dementia compared to those without cognitive impairment (Mata et al., 2014), even in PD patients with a pure synucleinopathy at autopsy (Tsuang et al., 2013). In PD patients, the *APOE* ϵ 4 genotype is found to be specifically associated with poor episodic memory and semantic verbal fluency, but not visuospatial and executive impairments (Mata et al., 2014). However, other cross-sectional studies have failed to replicate this relationship between *APOE* ϵ 4 genotype and cognitive impairment in PD (Mengel et al., 2016). Therefore, it is possible *APOE* ϵ 4 only confers risk in a subset of PD patients. Finally, few studies have explored the relationship between *APOE* ϵ 4 genotype and early cognitive decline during the first several years after diagnosis. No studies have determined whether there is an interaction between *APOE* ϵ 4 genotype and abnormalities in CSF A β related to cognitive decline in patients with PD.

2. Material and methods

2.1. Participants

Participants enrolled in the Parkinsons Progression Marker Initiative (PPMI), an observational, international, longitudinal study that aims to identify biomarkers of PD progression (Parkinson Progression Marker, 2011; Marek et al., 2018). PPMI enrolled 423 drug-naïve, early stage PD patients into the *de novo* cohort and 196 age-matched healthy controls (HC) from 24 clinical sites in the United States, Europe and Australia. PPMI participants were within 2 years of PD diagnosis and not expected to require PD medications within 6 months. Patients were excluded if they had a clinical diagnosis of dementia, had MRI evidence of another clinically significant

neurological disease, or were unable to tolerate a lumbar puncture. Clinical characteristics, CSF, and cognitive assessments were recorded at baseline and at annual follow up. Written informed consent was obtained from all participants, and all PPMI sites received approval from their respective ethics committees on human experimentation prior to study initiation. We obtained data on key variables (below) from the PPMI database on July 17th, 2018 (www.ppmi-info.org/data) and included all available data from baseline through the Year 5 visit.

2.2. Cognitive assessment

Baseline cognitive testing, which was repeated at each annual follow up, included six cognitive tests. The Montreal Cognitive Assessment (MoCA) is a test of global cognition, and assesses aspects of attention and concentration, executive function, memory, language, visuospatial skills, conceptual thinking, calculations, and orientation (Gill et al., 2008). The MoCA has been validated as a sensitive measure of cognitive impairment and decline in PD (Hendershott et al., 2017; Dalrymple-Alford et al., 2010a) and was therefore chosen as the primary cognitive outcome measure. We included the additional cognitive tests as secondary cognitive outcome measures. The Hopkins Verbal Learning Test-Revised (HVLT-R) measures episodic verbal memory and is comprised of 3 learning trials (Immediate Recall), a delayed recall trial (Delayed Recall), and a recognition trial (Vanderploeg et al., 2000). A Recognition Discrimination Index is calculated as the delayed recall trial score minus the number of related false positives. The Symbol Digit Modalities Test (SDMT) assesses visual scanning, attention, and processing speed (Smith, 1982; Strauss et al., 2006). Letter Number Sequencing assesses auditory working memory (Wechsler, 1997). The Semantic verbal Fluency Test assesses spontaneous word production that is dependent upon semantic memory and executive cognitive processes (Tombaugh et al., 1999). Finally, the Judgement of Line Orientation is a motor-free measure of visuospatial perception and orientation (Benton, 1994). We evaluated scores from each of these cognitive measures at six time points (Baseline, Years 1, 2, 3, 4 and 5).

2.3. CSF analyses

CSF samples were collected at baseline by standardized lumbar puncture procedures and analyzed as described in the PPMI biologics manual (<http://ppmi-info.org>) and previously reported (Kang et al., 2013; Kang et al., 2016). Participants with missing CSF A β or *APOE* ϵ 4 genotype data at baseline were excluded from our analysis (Fig. 1). To address our primary aim to determine the interaction between low CSF A β and *APOE* ϵ 4 genotype in predicting cognitive decline in PD participants, we used the CSF A β -42 values of the HC group to determine our cutoff for low CSF A β . *A priori*, we defined low CSF A β as values < 310.3 pg/mL, which is the low quartile for the HC A β values (Q1 = 310.3, Q2(median) = 378.2, Q3 = 439.4). Of the 379 *de novo* PD participants with baseline CSF A β data, 276 PD participants had normal CSF A β and 103 PD participants had low CSF A β .

2.4. Genetic analyses

At baseline, blood samples were collected from all participants, and genomic DNA was extracted from whole blood. *APOE* genotypes were determined using allele-specific oligonucleotide probes labeled with fluorogenic reporter (TaqMan method), as previously described (Kang et al., 2016; Nalls et al., 2016). Within each CSF group (low CSF A β and normal CSF A β), we defined *APOE* ϵ 4+ by the presence of at least one *APOE* ϵ 4 allele and *APOE* ϵ 4- as no *APOE* ϵ 4 allele (Fig. 1). Of the 39 PD participants in the low CSF A β *APOE* ϵ 4+ group, three had two *APOE* ϵ 4 alleles. Of the 61 PD participants in the normal CSF A β *APOE* ϵ 4+ group, six had two *APOE* ϵ 4 alleles.

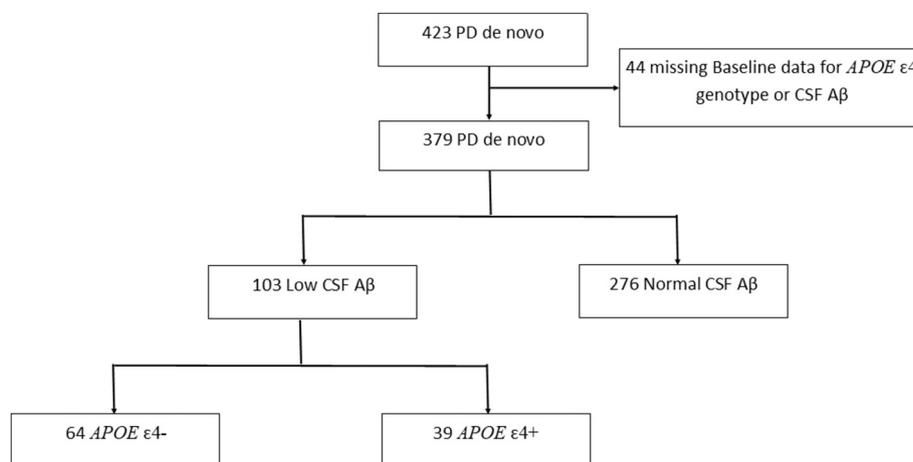


Fig. 1. Flowchart of Study Cohort. Flowchart illustrates the selection of PPMI study cohort according to CSF and genetic information. APOE = Apolipoprotein E; APOE ε4+ = presence of at least one APOE ε4 allele; APOE ε4- = absence of APOE ε4 allele; CSF Aβ = Cerebrospinal fluid Amyloid Beta.

2.5. Statistical analyses

To examine the differences in baseline clinical or demographic characteristics between PD patients with normal CSF Aβ and those with low CSF Aβ, we used the Kruskal-Wallis One-way Analysis of Variance for non-normally distributed continuous variables or chi-square for categorical variables. Normality was determined by the Kolmogorov-Smirnov test. In the primary analysis, we ran linear mixed effects regression analysis on the three PD groups. The first group included all 379 PD participants with baseline CSF Aβ and APOE ε4; the second group included the 103 PD with low baseline CSF Aβ; and the third group included the 276 PD participants with normal CSF Aβ. The linear mixed effects model includes APOE ε4, time, and APOE ε4 × time as the independent variables of primary interest, with age, gender and education as potential confounding variables. We selected age and gender because these variables (along with disease duration) are the most commonly reported predictors of PD cognitive decline and dementia (Cholerton et al., 2013; Reid et al., 2011; Wills et al., 2016; Cholerton et al., 2018). Baseline disease duration was similar in all PPMI participants (Marek et al., 2018; Simuni et al., 2018), thus not included as a separate covariate. We included education as the final variable because of the known impact of cognitive testing. The random intercept is included to account for within person correlations. For each group, we estimated the annual rate of change in cognitive scores for the primary cognitive outcome measure (MoCA) and the secondary cognitive outcome measures [HVLt-R (Immediate Recall, Delayed Recall, Recognition Discrimination Index), SDMT, Letter Number Sequencing, Semantic verbal Fluency Test, and Judgement of Line Orientation] by the regression coefficients of time and APOE ε4 × time. In the mixed effects regression analysis for all PD participants, i.e. the first group, we also included low/normal CSF Aβ and CSF Aβ × time as independent variables to examine the effect of CSF Aβ on baseline cognitive outcome measures and their annual change rate. Analyses were performed using R v3.0 (The R foundation of Statistical Computing) and SPSS (IBM SPSS Statistics for Windows, Version 24.0). In all statistical analyses, two-tailed *p* values were used; those values of *p* ≤ .05 were deemed as statistically significant.

3. Results

3.1. Participant characteristics

See Table 1 for complete group baseline characteristics. There were 215 participants in the normal CSF Aβ APOE ε4- group, 61 participants in the normal CSF Aβ APOE ε4+ group, 64 participants in the low CSF

Aβ APOE ε4- group, and 39 participants in the low CSF Aβ APOE ε4+ group ($\chi^2 = 9.595$, *p* = .002). The Kruskal-Wallis Test revealed significant differences between groups in age (*p* = .007) and MDS-UPDRS III (*p* = .048) but showed no other significant differences in baseline demographic characteristics (Table 1).

3.2. Effect of CSF Aβ on cognitive decline

Results from the linear mixed effects regression analysis on the full group of 379 PD participants can be found in Table 2. In this group, those who were male, older, and had fewer years of education showed lower baseline scores on all cognitive tests (all *p* < .05), except Judgement of Line Orientation where female participants had lower baseline score (*p* < .001), and Letter-Number Sequencing where there was no gender difference.

Participants with PD declined by 0.28 points annually on the SDMT (95%CI: 0.02–0.54), by 0.08 points annually on the Letter-Number Sequencing (95%CI: 0.01–0.14), and improved by 0.17 points annually on the HVLt-R Recognition Discrimination Index (95%CI: 0.08–0.26). No other cognitive tests declined or improved in the full PD group over the 5 years.

Participants with PD with low CSF Aβ at baseline had a faster rate of decline than those with normal CSF Aβ on all cognitive tests, except the Judgement of Line Orientation and HVLt-R Immediate Recall (see Table 2 for details). Participants with PD who were APOE ε4+ had a faster rate of decline than APOE ε4- by 0.17 points annually on the MoCA (95%CI: -0.02-0.33, standardized 5-year effect size 0.37). No other cognitive tests showed a significant effect of APOE ε4 on the annual change rate in the full PD group.

3.3. Effect of APOE ε4 on cognitive decline in PD with low CSF Aβ

Results from the linear mixed effects regression analysis on the 103 PD participants with low CSF Aβ at baseline can be found in Table 3. In this group, all cognitive tests were lower in those who were older (all *p* < .05), but only HVLt-R Delayed Recall was lower in those with fewer years of education (*p* = .019). MoCA (*p* = .014), HVLt-R Delayed Recall (*p* = .016), and HVLt-R Recognition Discrimination Index (*p* = .041) were lower in male PD participants with low CSF Aβ, while Judgement of Line Orientation (*p* = .003) was lower in female PD participants. The APOE ε4+ and APOE ε4- groups did not differ in any baseline cognitive tests.

In PD participants with low CSF Aβ, the APOE ε4+ group had a faster rate of decline than the APOE ε4- group on the MoCA by 0.57 points annually (95% CI: 0.17–0.97, standardized 5-year effect size

Table 1

Baseline characteristics. Table depicts the median and interquartile range for the demographic and cognitive data at baseline, with *p* values computed using Kruskal-Wallis One-way Analysis of Variance, or * χ^2 test as appropriate.

Characteristic	Normal CSF A β APOE ϵ 4- (N = 215)	Normal CSF A β APOE ϵ 4+ (N = 61)	Low CSF A β APOE ϵ 4- (N = 64)	Low CSF A β APOE ϵ 4+ (N = 39)	<i>p</i> value
Age (years)					
Median	62.0	57.0	65.0	64.0	0.007[^]
[Interquartile range]	[55.0–68.0]	[51.0–66.0]	[57.3–70.0]	[58.0–70.0]	
Female*					
N (%)	80 (37%)	18 (30%)	18 (28%)	10 (26%)	0.298
Education (years)					
Median	16.0	16.0	16.0	16.0	0.982
[Interquartile range]	[14.0–18.0]	[14.0–18.0]	[14.0–17.8]	[14.0–18.0]	
MDS-UPDRS III					
Median	18.0	17.0	19.5	20.5	0.048
[Interquartile range]	[12.0–24.0]	[11.0–25.0]	[16.0–28.0]	[16.0–27.3]	
Hoehn & Yahr					
Median	2.0	1.0	2.0	2.0	0.335
[Interquartile range]	[1.0–2.0]	[1.0–2.0]	[1.0–2.0]	[1.0–2.0]	
MoCA total					
Median	28.0	28.0	27.0	28.0	0.669
[Interquartile range]	[26.0–29.0]	[26.0–29.0]	[26.0–28.8]	[26.0–29.0]	
HVLT-R immediate recall					
Median	25.0	25.0	25.0	23.0	0.053[†]
[Interquartile range]	[21.0–28.0]	[22.0–30.0]	[21.0–27.0]	[17.0–26.0]	
HVLT-R delayed recall					
Median	9.0	9.0	9.0	8.0	0.170
[Interquartile range]	[7.0–10.0]	[7.0–10.0]	[7.0–10.0]	[5.0–10.0]	
HVLT-R recognition discrimination index					
Median	7.0	8.0	7.0	7.0	0.186
[Interquartile range]	[5.0–10.0]	[6.0–10.0]	[4.3–9.0]	[4.0–9.0]	
SFT					
Median	48.0	52.0	47.0	46.0	0.070
[Interquartile range]	[42.0–56.0]	[43.0–58.0]	[40.0–53.0]	[36.0–52.5]	
JLO					
Median	13.0	13.0	14.0	13.0	0.649
[Interquartile range]	[12.0–15.0]	[12.0–14.0]	[12.0–14.0]	[10.0–14.0]	
LNS					
Median	11.0	11.0	11.0	10.0	0.187
[Interquartile range]	[9.0–12.0]	[9.0–13.0]	[9.0–12.0]	[8.0–12.0]	
SDMT					
Median	43.0	43.0	40.0	40.0	0.025[‡]
[Interquartile range]	[35.0–48.0]	[37.0–49.0]	[32.0–46.0]	[28.0–46.0]	

APOE = Apolipoprotein E; APOE ϵ 4+ = presence of at least one APOE ϵ 4 allele; APOE ϵ 4- = absence of APOE ϵ 4 allele; MDS-UPDRS = Movement Disorders Society United Parkinson's disease Rating Scale; MoCA = Montreal Cognitive Assessment; HVLT-R = Hopkins Verbal Learning Test Revised; SFT = Semantic verbal Fluency Test; JLO = Benton Judgement of Line Orientation; LNS = Letter-Number Sequencing; SDMT = Symbol Digit Modalities Test.

[^] *p* \leq .05 by post-hoc testing between Normal CSF A β APOE ϵ 4+ and Low CSF A β APOE ϵ 4- and between Normal CSF A β APOE ϵ 4+ and Low CSF A β APOE ϵ 4+.

[†] *p* \leq .05 by post-hoc testing between Normal CSF A β APOE ϵ 4+ and Low CSF A β APOE ϵ 4+.

[‡] *p* \leq .05 by post-hoc testing between Normal CSF A β APOE ϵ 4+ and Low CSF A β APOE ϵ 4-.

1.2). The APOE ϵ 4+ group also had a faster rate of decline on the SDMT by 1.40 points annually (95% CI: 0.50–2.29, standardized 5-year effect size 0.72) (Fig. 2).

The APOE ϵ 4+ group showed a trend toward faster rate of decline than the APOE ϵ 4- group on HVLT-R Delayed Recall (95% CI: -0.01–0.48, standardized 5-year effect size 0.23), but not on HVLT-R Immediate Recall or Recognition Discrimination Index (Fig. 3). There was no difference in rate of decline between APOE ϵ 4 groups on the Letter-Number Sequencing, Semantic verbal Fluency Test, or Judgement of Line Orientation (Supplemental Figure).

3.4. Effect of APOE ϵ 4 on cognitive decline in PD with normal CSF A β

Results from the linear mixed effects regression analysis on the 276 PD participants with normal CSF A β at baseline can be found in Supplemental Table 1. In this group, those who were male, older, and had fewer years of education showed lower baseline scores on all cognitive tests (all *p* < .05), except Judgement of Line Orientation where female participants had lower baseline score (*p* < .001), and Letter-Number Sequencing where there was no difference between genders.

PD participants declined by 0.38 points annually on the SDMT (95%CI: 0.12–0.64), by 0.07 points annually on the Letter-Number Sequencing (95%CI: 0.01–0.14), and improved by 0.16 points annually on the HVLT-R Recognition Discrimination Index (95%CI: 0.07–0.24). No other cognitive tests declined or improved in the PD participants with normal CSF A β over the 5 years (see Supplemental Table 1 for details). The APOE ϵ 4+ and APOE ϵ 4- groups did not differ in baseline scores and did not differ on the rate of decline on any cognitive tests. See Supplemental Table 2 for mean cognitive scores for all groups over time.

4. Discussion

Several longitudinal studies have shown that patients with PD and low CSF A β -42 have an increased risk of developing cognitive decline and dementia (Leaver and Poston, 2015). In this study, we extended these findings to show that patients with PD, who have low CSF A β in addition to at least one APOE ϵ 4 allele have the highest rate of global cognitive decline over the first five years after diagnosis. These patients also experienced faster declines in processing speed as compared to PD patients without the APOE ϵ 4 allele. By contrast, in PD patients with

Table 2

Effect of Predictor Variables on Cognitive Assessments in the full PD group. Table depicts the beta estimate, confidence intervals, and *p*-values of the predictor variables (Time, *APOE* ϵ 4, *APOE* ϵ 4 x time, CSF A β , CSF A β x time) and control variables (Age, Education, Gender) on cognitive assessments in the full PD group. R² for the fixed effects is shown, since this reflects the proportion of the variations explained by the observed covariates.

Cognitive assessment	R ²	Predictor variable	Beta estimate	95% CI		<i>p</i> value		
				Lower	Upper			
MoCA total	0.09	Education	0.08	0.00	0.15	0.039		
		Female	0.57	0.13	1.01	0.012		
		Age	-0.07	-0.09	-0.05	< 0.001		
		Time	-0.02	-0.10	0.07	0.729		
		<i>APOE</i> ϵ 4	0.05	-0.44	0.53	0.854		
		<i>APOE</i> ϵ4 x time	-0.17	-0.33	-0.02	0.032		
		CSF A β	0.00	0.48	0.48	0.990		
		CSF Aβ x time	-0.25	-0.41	-0.09	0.002		
		SDMT	0.24	Education	0.51	0.24	0.78	< 0.001
				Female	3.06	1.39	4.72	< 0.001
				Age	-0.44	-0.52	-0.36	< 0.001
Time	-0.28			-0.54	-0.02	0.036		
<i>APOE</i> ϵ 4	0.08			-1.76	1.91	0.937		
<i>APOE</i> ϵ 4 x time	-0.39			-0.86	0.09	0.110		
CSF A β	-1.62			-3.44	0.21	0.083		
CSF Aβ x time	-0.91			-1.37	-0.45	< 0.001		
HVLTR immediate recall	0.17			Education	0.29	0.15	0.43	< 0.001
				Female	2.07	1.20	2.93	< 0.001
				Age	-0.19	-0.23	-0.15	< 0.001
		Time	0.02	-0.12	0.16	0.783		
		<i>APOE</i> ϵ 4	-0.11	-1.07	0.86	0.824		
		<i>APOE</i> ϵ 4 x time	-0.02	-0.27	0.23	0.872		
		CSF A β	-0.24	-1.20	0.72	0.620		
		CSF Aβ x time	-0.20	-0.44	0.05	0.113		
		HVLTR delayed recall	0.17	Education	0.15	0.08	0.22	< 0.001
				Female	1.00	0.55	1.44	< 0.001
				Age	-0.09	-0.12	-0.07	< 0.001
Time	0.05			-0.02	0.12	0.171		
<i>APOE</i> ϵ 4	-0.09			-0.60	0.42	0.727		
<i>APOE</i> ϵ 4 x time	-0.03			-0.16	0.10	0.698		
CSF A β	-0.12			-0.62	0.38	0.646		
CSF Aβ x time	-0.20			-0.32	-0.07	0.003		
HVLTR recognition index	0.16			Education	0.15	0.06	0.23	0.001
				Female	1.26	0.72	1.81	< 0.001
				Age	-0.11	-0.13	-0.08	< 0.001
		Time	0.17	0.09	0.26	< 0.001		
		<i>APOE</i> ϵ 4	-0.12	-0.75	0.51	0.712		
		<i>APOE</i> ϵ 4 x time	0.00	0.16	0.16	0.998		
		CSF A β	-0.28	-0.91	0.35	0.380		
		CSF Aβ x time	-0.18	-0.33	-0.03	0.020		
		LNS	0.15					

Table 2 (continued)

Cognitive assessment	R ²	Predictor variable	Beta estimate	95% CI		<i>p</i> value		
				Lower	Upper			
SFT	0.20	Education	0.14	0.07	0.22	< 0.001		
		Female	-0.01	-0.47	0.45	0.966		
		Age	-0.10	-0.12	-0.08	< 0.001		
		Time	-0.08	-0.14	-0.01	0.025		
		<i>APOE</i> ϵ 4	-0.10	-0.62	0.41	0.695		
		<i>APOE</i> ϵ 4 x time	-0.09	-0.21	0.04	0.165		
		CSF A β	-0.16	-0.67	0.36	0.550		
		CSF Aβ x time	-0.13	-0.25	-0.01	0.032		
		JLO	0.12	Education	0.70	0.37	1.02	< 0.001
				Female	5.79	3.76	7.82	< 0.001
				Age	-0.36	-0.46	-0.26	< 0.001
Time	-0.09			-0.34	0.16	0.472		
<i>APOE</i> ϵ 4	0.93			-1.39	3.25	0.431		
<i>APOE</i> ϵ 4 x time	-0.29			-0.75	0.16	0.211		
CSF A β	-1.65			-3.95	0.65	0.161		
CSF Aβ x time	-0.45			-0.89	0.00	0.051		
LNS	0.12			Education	0.13	0.07	0.19	< 0.001
				Female	-1.18	-1.55	-0.81	< 0.001
				Age	-0.04	-0.06	-0.03	< 0.001
		Time	-0.02	-0.07	0.03	0.445		
		<i>APOE</i> ϵ 4	-0.35	-0.78	0.09	0.122		
		<i>APOE</i> ϵ 4 x time	-0.05	-0.14	0.05	0.337		
		CSF A β	-0.14	-0.58	0.29	0.521		
		CSF Aβ x time	-0.06	-0.15	0.04	0.225		

APOE = Apolipoprotein E; CSF A β = Cerebrospinal fluid Amyloid Beta; MoCA = Montreal Cognitive Assessment; HVLTR = Hopkins Verbal Learning Test Revised; SFT = Semantic verbal Fluency Test; JLO = Benton Judgement of Line Orientation; LNS = Letter-Number Sequencing; SDMT = Symbol Digit Modalities Test; CI = Confidence Interval.

Statistically significant *p*-values (*p* < 0.05) are in bold.

normal CSF A β , having at least one *APOE* ϵ 4 allele was not associated with early cognitive change. These results suggest that in PD patients an *APOE* ϵ 4 genotype and A β might interact to promote cognitive changes early in the disease.

Consistent with prior studies in the PPMI cohort (Terrelonge Jr et al., 2016; Caspell-Garcia et al., 2017), we found that PD participants with lower CSF A β at baseline showed faster cognitive decline over 5 years on almost all cognitive tests. Prior studies have identified CSF A β as a predictor of cognitive impairment (Yarnall et al., 2014) and future decline (Siderowf et al., 2010; Alves et al., 2014) in early, *de novo* PD. Studies have also shown the *APOE* ϵ 4 genotype increases the risk of dementia in PD at end of life (Mata et al., 2014; Tsuang et al., 2013; Guerreiro et al., 2018). However, the association between cognitive impairment and *APOE* ϵ 4 is inconsistent when studies included earlier, more mildly impaired PD patients. For instance, the ICICLE-PD study did not find a higher rate of baseline cognitive impairment in the newly diagnosed PD patients with an *APOE* ϵ 4 allele (Yarnall et al., 2014), although this study showed *APOE* ϵ 4 + PD patients had decreased brain activation on fMRI during memory encoding. Our study agrees with the ICICLE-PD study, in that *APOE* ϵ 4 is not associated with having cognitive impairment at baseline in the full PD group or in those with low or normal CSF A β . However, we found global cognitive decline after baseline, as assessed on the MoCA, in the PPMI PD participants over 5 years. Further, when we separated PD participants by CSF A β , the *APOE* ϵ 4-associated decline on the MoCA was only present in those with low baseline CSF A β , and here the decline is large. This finding strongly

Table 3

Effect of Predictor Variables on Cognitive Assessments in PD patients with low CSF Aβ at baseline. Table depicts the beta estimate, confidence intervals, and p-values of the predictor variables (*APOE* ε4, Time, and *APOE* ε4 x time) and control variables (Age, Education, Gender) on cognitive assessments in the low CSF Aβ group. R² for the fixed effects is shown, since this reflects the proportion of the variations explained by the observed covariates.

Cognitive assessment	R ²	Predictor variable	Beta estimate	95% CI Lower	95% CI Upper	p value
MoCA total	0.12	Education	0.05	-0.10	0.12	0.526
		Female	1.28	0.26	2.31	0.014
		Age	-0.07	-0.12	-0.02	0.004
		<i>APOE</i> ε4	-0.01	-0.94	0.92	0.983
		Time	-0.16	-0.39	0.07	0.164
		<i>APOE</i> ε4 x time	-0.57	-0.97	-0.17	0.005
		SDMT	0.24	Education	0.35	-0.22
Female	3.39			-0.57	7.33	0.093
Age	-0.53			-0.72	-0.33	< 0.001
<i>APOE</i> ε4	0.72			-2.91	4.35	0.699
Time	-0.87			-1.38	-0.36	0.001
<i>APOE</i> ε4 x time	-1.40			-2.29	-0.50	0.002
HVLT-R immediate recall	0.19			Education	0.21	-0.08
		Female	1.77	-0.21	3.75	0.079
		Age	-0.24	-0.34	-0.14	< 0.001
		<i>APOE</i> ε4	-1.09	-2.90	0.72	0.237
		Time	-0.08	-0.34	0.18	0.552
		<i>APOE</i> ε4 x time	-0.34	-0.81	0.12	0.147
		HVLT-R delayed recall	0.21	Education	0.18	0.03
Female	1.29			0.24	2.34	0.016
Age	-0.12			-0.17	-0.07	< 0.001
<i>APOE</i> ε4	-0.78			-1.73	0.17	0.107
Time	-0.10			-0.23	0.04	0.173
<i>APOE</i> ε4 x time	-0.23			-0.48	0.01	0.058
HVLT-R recognition discrimination index	0.17			Education	0.12	-0.07
		Female	1.39	0.06	2.73	0.041
		Age	-0.14	-0.20	-0.07	< 0.001
		<i>APOE</i> ε4	-0.69	-1.90	0.53	0.267
		Time	0.05	-0.14	0.20	0.582
		<i>APOE</i> ε4 x time	-0.23	-0.51	0.06	0.117
		LNS	0.13	Education	0.07	-0.06
Female	0.40			-0.52	1.31	0.395
Age	-0.09			-0.14	-0.05	< 0.001
<i>APOE</i> ε4	-0.57			-1.41	0.27	0.184
Time	-0.23			-0.38	-0.08	0.002
<i>APOE</i> ε4 x time	-0.04			-0.30	0.21	0.740
SFT	0.16			Education	0.08	-0.57
		Female	2.44	-1.98	6.87	0.279
		Age	-0.48	-0.70	-0.26	< 0.001
		<i>APOE</i> ε4	-0.12	-4.27	4.02	0.953
		Time	-0.50	-0.94	-0.07	0.023
		<i>APOE</i> ε4 x time	-0.44	-1.20	0.33	0.261
		JLO	0.11	Education	0.04	-0.09
Female	-1.33			-2.20	-0.46	0.003
Age	-0.06			-0.10	-0.02	0.007
<i>APOE</i> ε4	-0.60			-1.47	0.28	0.180
Time	-0.06			-0.17	0.05	0.284
<i>APOE</i> ε4 x time	-0.11			-0.30	0.08	0.258

APOE = Apolipoprotein E; CSF Aβ = Cerebrospinal fluid Amyloid Beta; MoCA = Montreal Cognitive Assessment; HVLT-R = Hopkins Verbal Learning Test Revised; SFT = Semantic verbal Fluency Test; JLO = Benton Judgement of Line Orientation; LNS = Letter-Number Sequencing; SDMT = Symbol Digit Modalities Test; CI = Confidence Interval.

suggests that the combination of low CSF Aβ and *APOE* ε4 is an important predictor of impending global cognitive decline in PD. It also suggests that the effects of *APOE* ε4 genotype on early cognitive decline might be detectable in specific PD subgroups, but not in others (Mengel et al., 2016).

Beyond prediction, these biomarkers may reveal critical information

about the biology underlying differing rates of cognitive progression that is observed in PD patients. For instance, concomitant Alzheimer's disease pathology, defined by tau-positive neurofibrillary tangles and Aβ-positive plaques, could explain our findings. *APOE* ε4 is a major risk factor for Alzheimer's pathology, and one recent large autopsy series found that PD patients with Alzheimer's co-pathology had a greater rate

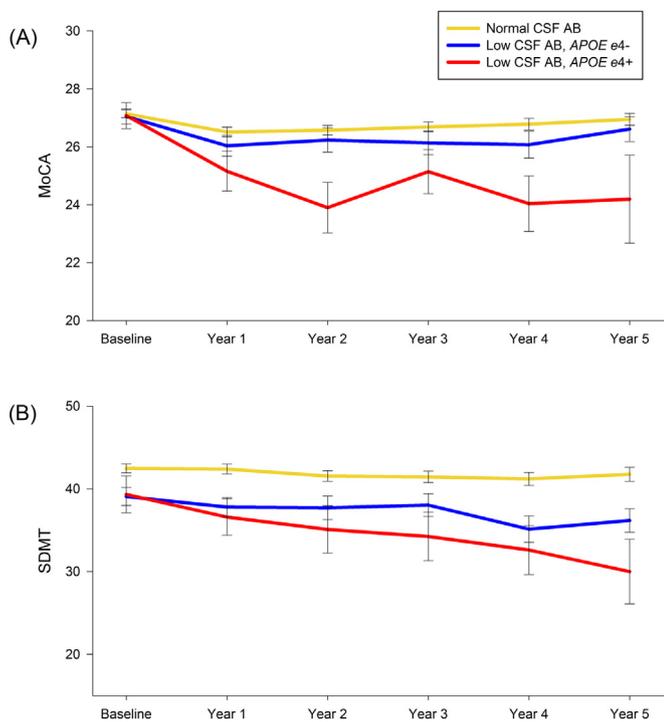


Fig. 2. (A) MoCA and (B) SDMT scores over time. Graph illustrates greater cognitive decline in low CSF Aβ APOE ε4+ compared to low CSF Aβ APOE ε4- and normal CSF Aβ groups.

MoCA = Montreal Cognitive Assessment; SDMT = Symbol Digit Modalities Test; CSF Aβ = Cerebrospinal fluid Amyloid Beta; APOE = Apolipoprotein E; APOE ε4+ = presence of at least one APOE ε4 allele; APOE ε4- = absence of APOE ε4 allele.

of cognitive decline on the Mini-Mental State Examination during the 10 years prior to death compared to PD patients with a pure synucleinopathy (Robinson et al., 2018). Therefore, in the PPMI cohort, Alzheimer's co-pathology could already be present in some patients at the time of motor onset, which may influence the rate of early cognitive decline. However, if this were the sole explanation, we might expect a more pronounced association with episodic memory, as is commonly seen in patients with early Alzheimer's disease pathology. Longitudinal cognitive analyses with diagnostic confirmation at autopsy are part of the PPMI protocol. Postmortem findings will eventually elucidate whether low CSF Aβ at PD diagnosis is indicative of co-morbid Alzheimer's pathology.

There are likely other factors that contribute to why PD patients with an APOE ε4 allele and low CSF Aβ show a faster rate of cognitive decline. While the APOE ε4 genotype is linked to dementia due to its direct effect on Alzheimer's co-pathology, it is possible that it increases risk through additional, independent mechanisms. For example, in PD patients with no or low levels of Alzheimer's co-pathology (*i.e.* low burden of tau neurofibrillary tangles), the APOE ε4 genotype still confers an increased risk of dementia (Tsuang et al., 2013) and increased severity of Lewy-body pathology (Dickson et al., 2018). The PPMI cohort consists of newly diagnosed PD patients. Thus, based on the Braak and Braak hypothesis, Lewy-body pathology is most likely limited to the brainstem, amygdala, or limbic regions (Braak et al., 2006) and not yet spread to the neocortex. Autopsy studies showed that the APOE ε4 genotype is associated with Alzheimer's co-pathologies in PD patients with neocortical Lewy-bodies but not patients with Lewy-bodies limited to the brainstem, limbic regions, or amygdala (Robinson et al., 2018). It is unclear how APOE influences biology in pure synucleinopathies, but APOE is a crucial element in the lipoprotein metabolism (Phie et al., 2017), lipid transportation (Corbo et al., 1999), and clearance of amyloid proteins in the brain (Bales et al., 2002). One study in

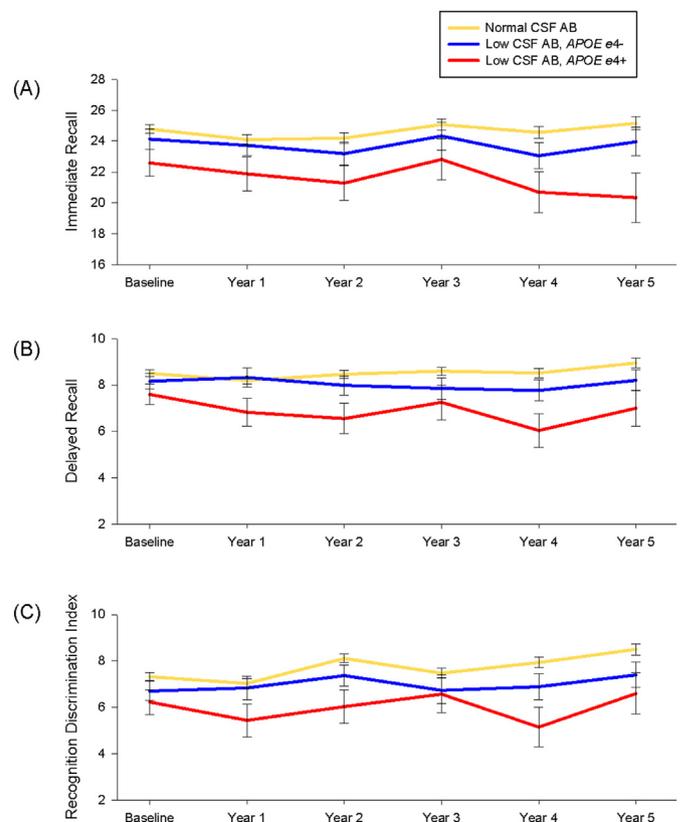


Fig. 3. HVLRT-R (A) Immediate Recall (B) Delayed Recall, and (C) Recognition Discrimination Index over time.

HVLRT-R = Hopkins Verbal Learning Test Revised; CSF Aβ = Cerebrospinal fluid Amyloid Beta; APOE = Apolipoprotein E; APOE ε4+ = presence of at least one APOE ε4 allele; APOE ε4- = absence of APOE ε4 allele.

transgenic mice showed that α-synuclein-induced neurodegeneration involves activation of the ubiquitin/proteasome system with a massive increase in apolipoprotein E levels and accumulation of insoluble mouse Aβ (Gallardo et al., 2008). Other studies suggest Aβ, along with other protein aggregates, can be induced by α-synuclein pathology (Cookson and van der Brug, 2008; Ballard et al., 2006). Distinguishing the individual contributions of these proteins to clinical symptoms is critical, as trials targeting α-synuclein, Aβ, and tau are all currently underway.

Prior genotype-phenotype studies also show that the APOE ε4 genotype is specifically associated with poor episodic memory and semantic verbal fluency in PD patients (Mata et al., 2014). While we found a trend toward worsening episodic memory with delayed recall in the low CSF Aβ and APOE ε4+ group, these patients primarily showed a more pronounced decline on global cognitive measures and processing speed. Indeed, we found the MoCA to be the most robust measure, with PD participants who had low CSF Aβ and at least one APOE ε4 allele showing an annual decline of over half a point faster than those with no APOE ε4 allele. This adds to the growing literature supporting the MoCA as a sensitive test of global cognition in early PD patients (Hendershott et al., 2017; Dalrymple-Alford et al., 2010b; Hoops et al., 2009). In addition, we found the SDMT, a test of attention and processing speed, to decline faster in PD patients with low CSF Aβ and at least one APOE ε4. A recent large study ($n = 1741$, NET-PD) showed the SDMT declined by 0.21 annually in the total PD cohort over six years (Wills et al., 2016), which is similar to the rate of change seen in our total PD group (decline by 0.28/year). The group with low CSF Aβ declined by 0.87/year, whereas those with low CSF Aβ and at least one APOE ε4 allele declined by 1.40/year. These findings are unsurprising given that reduced processing speed is considered a general

proxy for hastened brain aging (Rabbitt et al., 2006) and both increased amyloid burden and the presence of an *APOE* $\epsilon 4$ allele have been previously associated with longitudinal decline in processing speed in cognitively normal older adults (Marioni et al., 2016; Clark et al., 2018). In PD, poorer performance on processing speed measures is associated with progression to dementia (Cholerton et al., 2018). Although reduced processing speed is ubiquitous in PD and generally attributed to dopaminergic deficits in fronto-striatal pathways, our results suggest that a faster rate of decline in processing speed may result from additional underlying factors related to *APOE* $\epsilon 4$ and A β .

The varying rate of cognitive decline in PD patients is a major impediment to clinical trial development. For therapeutics aimed at disease modification, the ideal patient population is one that is cognitively normal but at high likelihood to progress to cognitive impairment during the typical course of a clinical trial. Predictive models of imminent cognitive decline are thus necessary for such trial design. Currently, the most commonly reported predictors for PD-associated cognitive decline are older age and longer duration of motor symptoms (Hely et al., 2005; Cholerton et al., 2013; Reid et al., 2011; Chahine et al., 2016). However, older patients are commonly excluded from clinical trials given the increased risk of co-morbidities, such as diabetes, cancer, or stroke. Whereas male gender has also been associated with faster cognitive decline (Cholerton et al., 2018), gender alone is not a reasonable inclusion criterion for a clinical trial given the obvious lack of generalizability. By contrast, biomarkers such as CSF protein analysis and genetic data could be considered as screening tools.

This study has important strengths. The study is rooted in the *de novo* PPMI cohort. Disease duration is similar in all PPMI participants, thus reducing variability in one of the strongest predictors of cognitive impairment in PD patients. Other major predictors of PD cognitive decline, such as age and gender, are similar across the study groups. When we added other potential confounders to the models in an exploratory analysis (REM Sleep score, Epworth Sleepiness Scale, Geriatric Depression Scale, starting PD medications, and gender \times time) all of the significant predictors in Tables 2, 3 and Supplemental Table 1 were still significant with similar Beta Estimates. A further strength is that all of the CSF assays were performed by the same lab using standardized techniques. A major challenge to this study is that the optimal cutoff for 'low' CSF in PD patients is not known. There is large inter-assay variability and inconsistency of CSF A β measurements, even among different centers using the same assays. Therefore, we choose the PPMI healthy control group values to determine our cutoff for the low CSF A β group. Even with this fairly conservative estimate, our low CSF A β group, compared to our normal CSF A β group, shows similar cognitive progression as other studies investigating the risk of cognitive decline in PD patients with abnormal A β (Terrelonge Jr et al., 2016; Leaver and Poston, 2015).

5. Conclusions

Post-mortem studies show that *APOE* $\epsilon 4$ genotype increases risk for end of life dementia in PD patients, both in patients with and without co-morbid Alzheimer's pathology (Tsuang et al., 2013). Our study investigated the *APOE* $\epsilon 4$ genotype as predictive of early cognitive decline in newly diagnosed PD. We found that early PD *APOE* $\epsilon 4$ carriers, who also have abnormal CSF A β at diagnosis, are at the highest risk for global cognitive decline in the first five years of disease, whereas PD *APOE* $\epsilon 4$ carriers with normal CSF A β do not differ from non- $\epsilon 4$ carriers. Therefore, the combination of *APOE* $\epsilon 4$ genotype and abnormal CSF A β should be considered when developing predictive models of cognitive decline in early PD patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nbd.2019.02.023>.

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