PRDOA 9 (2023) 100199

Contents lists available at ScienceDirect

Clinical Parkinsonism & Related Disorders

journal homepage: www.sciencedirect.com/journal/clinical-parkinsonism-and-related-disorders

Longitudinal hippocampal subfields, CSF biomarkers, and cognition in patients with Parkinson disease

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A B S T R A C T

Objective: Hippocampal atrophy is an indicator of emerging dementia in PD, though it is unclear whether cerebral spinal fluid (CSF) Abeta-42, t-tau, or alpha-syn predict hippocampal subfield atrophy in a *de novo* cohort of PD patients. To examine whether levels of CSF alpha-synuclein (alpha-syn), beta-amyloid 1–42 (Abeta-42), or total-tau (t-tau) are associated with hippocampal subfield volumes over time.

Methods: We identified a subset of Parkinson's Progression Markers Initiative (PPMI) *de novo* PD patients with longitudinal T1-weighted imaging (baseline plus at least two additional visits across 12, 24, and 48 months) and CSF biomarkers available at baseline. We performed cross-sectional, regression, and linear mixed model analyses to evaluate the baseline and longitudinal CSF biomarkers, hippocampal subfields, and cognition. A false discovery rate (FDR) was used to correct for multiple comparisons.

Results: 88 PD-CN and 21 PD-MCI had high quality longitudinal data. PD-MCI patients exhibited reduced bilateral CA1 volumes relative to PD-CN, though there were no significant differences in CSF biomarkers between these groups. Relationships between CSF biomarkers and hippocampal subfields changed over time, with a general pattern that lower CSF Abeta-42, higher t-tau and higher alpha-syn were associated with smaller hippocampal subfields, primarily in the right hemisphere.

Conclusion: We replicated prior reports that demonstrated reduced CA1 volumes in PD-MCI in a *de novo* PD cohort. CSF biomarkers were associated with individual subfields, with evidence that the increased CSF t-tau was associated with smaller subiculum volumes at baseline and over time, though there was no clear indication that the subfields associated with cognition (CA1 and HATA) were associated with CSF biomarkers.

1. Introduction

Cognitive dysfunction is a common and debilitating feature of Parkinson's disease (PD). Approximately 20% of PD patients meet the criteria for mild cognitive impairment (PD-MCI) at diagnosis, and 80% of those who survive two decades progress to PD dementia [1]. Cognitive impairment is also associated with greater functional decline and nursing home placement in PD [2]. PD patients exhibit a heterogeneous course of cognitive decline [3], with a variable progression related to the regional impact of alpha-synuclein aggregation (alpha-syn) and co-occurring neuropathological processes, such as co-occurring Alzheimer's disease (AD)-related changes (amyloid plaques and tau tangles) [4]. Notably, co-occurring AD-related changes are common and significant enough to meet pathological criteria for a pathological diagnosis of AD in up to 32–44% of PD Dementia (PDD) and 70% of Dementia with Lewy bodies at autopsy [5].

Hippocampal atrophy is associated with the development of dementia in PD, with recent evidence indicating that hippocampal subfields atrophy may be more sensitive indicators of emerging cognitive impairment than whole hippocampal volume [6,7]. Additionally, hippocampal atrophy may be associated with the development of co-occurring AD-related pathological changes in PD [8]. Studies examining the pattern of CSF biomarkers, hippocampal atrophy, and cognition in PD indicate that CSF amyloid-beta 1 to 42 (Abeta-42) is associated with cognitive impairment in PD but have demonstrated limited association with hippocampal volumes [9]. Relatedly, cognitive status, but not CSF Abeta-42 amyloid positivity, was associated with hippocampal volumes [7]. The same study indicated an association

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https://doi.org/10.1016/j.prdoa.2023.100199
Received 7 September 2022; Received in revised form 21 April 2023; Accepted 26 April 2023
Available online 5 May 2023
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between hippocampal subfields, cognition, and CSF total tau (t-tau). In sum, while Abeta-42 predicts cognition in PD, it has a limited association with hippocampal volume, whereas tau may be more closely associated with hippocampal atrophy in PD.

The current study aims to evaluate whether CSF Abeta-42, t-tau, or alpha-syn predict hippocampal subfield atrophy in a *de novo* cohort of PD patients collected as part of the Parkinson's Progression Markers Initiative (PPMI). Specifically, we first aim to replicate Becker et al. (2021) and hypothesize that hippocampal volumes will differ based on cognitive status (PD-MCI relative to PD cognitively normal [PD-CN]), but not CSF Abeta-42. Additionally, we conduct a novel examination of CSF Abeta-42, t-tau, and alpha-syn and hippocampal subfield volumes at baseline and over time. We hypothesize that CSF t-tau at baseline is associated with hippocampal subfield volumes and cognition in PD.

2. Methods

2.1. Participants

Data used in the preparation of this article were obtained from the PPMI database (https://www.ppmi-info.org/data). This study used data from a cohort of newly diagnosed, untreated patients with PD enrolled in the PPMI. This multicenter, prospective, longitudinal observational study aims to verify biomarkers of PD progression. Participants undergo a detailed assessment at baseline and every three months during the first year, and every six months during years 2 through 5. Enrollment of patients with PD occurred between June 2010 and April 2013. Data for the current study were accessed on May 22, 2020. PD patients that met criteria based on UK Brain Bank Criteria and exhibited dopamine deficits on 123-I-ioflupane dopamine transporter (DAT) imaging were included in the current study.

2.2. Standard protocol approvals, registrations, and patient consents

The PPMI study is registered at ClinicalTrials.gov (NCT01141023). Each PPMI site received approval from an ethics committee on human experimentation prior to study initiation. Written informed consent for the research was obtained from all individuals participating in the study.

Among 423 people with PD who underwent assessment at baseline, 374 were identified with T1-weighted MRI sequences. As only a subset of the cohort underwent longitudinal imaging, we identified participants with baseline data and at least two additional time points across Years 1, 2, and 4 of the study (the missing year will be imputed). The resulting sample was 109 PD patients with baseline and at least two additional time points: 102 Year 1, 104 Year 2, and 81 Year 4.

PD-MCI was diagnosed according to Level 1 criteria recommended by the Movement Disorders Society [10], using the Montreal Cognitive Assessment (MoCA), a measure of global cognitive functioning. MoCA scores below 26 points were classified as PD-MCI and higher values as PD-CN. This approach was used to be consistent with prior reports [7].

2.3. Assessment and clinical variables

PPMI cohort participants undergo a range of assessments. Baseline variables relevant to the present analyses include demographics (age at baseline, age at symptoms onset, years of education, and sex) and clinical characteristics (Movement Disorders Society Unified Parkinson's Disease Rating Scale Part III total score and Hoehn and Yahr Scale, PD disease duration [since symptom onset and diagnosis], and levodopa equivalent daily dose) [11]. Additionally, capacity to perform daily activities (The Modified Schwab and England Percent Activities of Daily Living [ADL] Scale) was assessed. The neuropsychological test battery includes assessments across several domains, including global functioning (MoCA), episodic memory (Hopkins Verbal Learning Test-Revised [HVLT; total recall, delayed recall, retention, and discrimination recognition score]), visuospatial functioning (Benton Judgment-of-Line-Orientation total score [JLO]), language (semantic fluency – animal naming [ANIM]), and executive functioning (Letter-Number Sequencing [LNS] and Symbol Digit Modalities Test [SDMT]).

2.4. Image acquisition

T1-weighted (echo time [TE] = 2–6 ms, repetition time [TR] = 5–11 ms, slice thickness 1–1.2 mm, 1x1x1-1.2 mm voxels, field of view = 256 mm) images were collected using 1.5- and 3-Tesla scanners, with all longitudinal data collected on the 3T scanners. More data on scan parameters can be found at https://www.ppmi-info.org.

2.5. Image processing

Volumetric gray and white matter and hippocampal subfield segmentations were completed using Freesurfer image analysis suite 7.1.0. The longitudinal processing portion of recon-all provided image parameters for each available study visit. Hippocampal subfields were generated [12] for the following 12 subfields: cornu ammonis (CA) regions (CA1; CA2 + 3; CA4), Granule Cell and Molecular Layer of the Dentate Gyrus (GC ML DG), hippocampal–amygdaloid transition area (HATA), hippocampal tail, fimbria, hippocampal fissure, molecular layer, parasubiculum, presubiculum, and the subiculum [7].

2.6. CSF analysis

CSF samples were collected following standardized lumbar puncture procedures and analyzed following a standard protocol (see the PPMI biologics manual at https://www.ppmi-info.org and prior publications [13]). Briefly, the samples were processed at the University of Pennsylvania Biomarker Research Laboratory to measure CSF Abeta-42, total-tau (t-tau), and phosphorylated tau at threonine 181 position (p-tau). The samples were processed using the Elecsys electrochemiluminescence immunoassays on the cobas e 601 analysis platform (Roche Diagnostics), detailed elsewhere [14,15]. The total CSF alpha-synuclein (alpha-syn) was collected from the PPMI database and calculated by BioLegend (San Diego, CA), detailed elsewhere [16,17].

2.7. Analyses

Analyses were performed in R (v4.1.2 [18]). Descriptive statistics were calculated to summarize patient characteristics. Medians and interquartile ranges (IQR) were calculated for continuous variables and were compared across groups by the Kruskal-Wallis test. Frequencies and percentages were calculated for categorical variables and were compared with the χ^2 test. Demographic, cognitive, fluid, and volume numeric variables were standardized (z-scored) to interpret on a common standard deviation scale. Exceptions are that sex was coded with female as the baseline category, while LEDD was scaled to have standard deviation equal to one, but not centered to retain a meaningful zero.

2.8. Baseline replication and extension

We first conducted baseline analyses similar to a prior report [7] to replicate their findings in an independent, *de novo,* cohort of PD patients. To evaluate whether differences in neuropsychological test assessments and hippocampal volumes are associated with CSF biomarkers, we conducted a multiple linear regression for each assessment and each subfield as the dependent variables with the CSF biomarkers of Abeta-42, $\log_2$(t-tau), and alpha-syn as predictors adjusting for intracranial volume (ICV), age, sex, education, and MDS-UPDRS Part 3. Additionally, we evaluated the interaction between CSF biomarkers and diagnosis (cognitive status; PD-CN and PD-MCI). The full model was fit and then reduced with backward model selection using the Bayesian information criterion (BIC), but the main effects for ICV, age, and sex were retained for all models. Model fit assumptions on the residuals are equal variance

and normality, which were both assessed visually.

2.9. Longitudinal study

Outcomes included neuropsychological test assessments and hippocampal subfield volumes. Outcomes over time (0, 1, 2, and 4 years) were analyzed using longitudinal linear mixed modeling [19,20] to account for the repeated measure effects, to assess time and diagnosis (cognitive status) interactions with CSF Abeta-42, $\log_2$(t-tau), and alpha-syn, and to adjust for patient demographic characteristics (ICV, age at baseline, sex, education, MSD-UPDRS Part 3, and LEDD concomitant medication total). Patients were included if they had Year 0 and at least three total time measurements, leaving up to one measurement to impute via linear interpolation for Years 1 or 2 or last observation carried forward for Year 4, since most values change slowly and smoothly over time. The model uses an unstructured covariance over time. The full model was fit and then reduced with backward model selection [20] using conditional Akaike information criterion (cAIC [21,22]), but main effects for year, ICV, age, and sex were retained for all models. Model fit assumptions on the residuals are equal variance and normality, which are both assessed visually; however, results are robust to violations of the model distributional assumption [23]. The restricted maximum-likelihood (REML) adjusted least-squares mean difference estimates are reported [24].

To understand if changes in cognitive performance on individual tests are associated with particular hippocampal subfield volumes, a supplemental analysis is included to model cognitive differences (Year 4 minus baseline) predicted based on baseline features: demographics, CSF biomarkers, and subfield volumes. Random forests (RF), a supervised ensemble machine learning algorithm that is based on regression trees [25] in which many trees (a "forest") are fit on bootstrapped resamples of the original observations and randomly selected subsets of features. RF provides a measure of variable importance (VIMP) for prediction accuracy, which is interpreted as the increase in prediction accuracy for regression trees within the forest with a given feature (variable) compared to regression trees without that feature; VIMP can be negative. Variable selection often improves prediction accuracy. RF and variable selection was performed in R software using the package "randomForestSRC" with 10,000 trees [26]. After variable selection, multiple regression models were fit with the selected variables to obtain the relationship directions between the features and cognitive differences; this sign was applied to the RF VIMP measure to summarize both the importance and relationship direction. Finally, within the three sets of feature types (demographic, CSF biomarkers, and subfield volumes), the features were sorted with the largest magnitude VIMP values on the left.

3. Results

3.1. Baseline replication and extension

Baseline characteristics for demographics (Table 1), cognitive tests (Table 2), and hippocampal volumes (Table 3) are presented. PD-MCI patients are roughly 6 years older than PD-CN, with similar year differences in age at symptom onset and diagnosis. There were no differences in CSF biomarkers between PD-MCI and PD-CN. PD-MCI patients exhibited significantly lower scores on the HVLT Imm (total recall), Del (delayed recall), and Rec (recognition) relative to PD-CN. PD-MCI patients exhibited significantly smaller left and right CA1 volumes, LH molecular layer, and LH whole hippocampus relative to PD-CN.

Multiple regression results are summarized in Fig. 1. Examination of cognitive outcomes indicate no associations with Abeta-42, t-tau, or alpha-syn. Examination of hippocampal subfields indicated that for the right hemisphere (RH) hippocampal fissure volume, there is a negative association with Abeta-42 ($p = 0.003$; CI: −0.412, −0.084). For the RH parasubiculum volume, there is a negative association with $\log_2$(t-tau) ($p = 0.016$; CI: −0.407, −0.043).

Table 1
Demographic and Clinical Characteristics.

Characteristic	Diagnosis		p-value
	PD-CN, N = 88	PD-MCI, N = 21	
Sex			0.4
Female	33 (38%)	6 (29%)	
Male	55 (62%)	15 (71%)	
Age (y)	61 (53, 69)	67 (61, 71)	**0.031**
Education	16.00 (13.00, 17.00)	15.00 (13.00, 16.00)	0.5
Age symptom onset (y)	59 (51, 65)	64 (59, 68)	**0.018**
Age diagnosis (y)	60 (52, 68)	67 (60, 71)	**0.027**
Illness duration (y)	0 [0; 1]	0 [0; 1]	0.542
MDS-UPDRS Part 3	20 (15, 27)	22 (12, 31)	0.8
Hoehn & Yahr			0.7
Unilateral movement only.	33 (39%)	7 (35%)	
Bilateral involvement without impairment of balance.	51 (61%)	13 (65%)	
LEDD Concomitant Medication Total	All 0 at baseline	All 0 at baseline	
t-tau	153 (125, 201)	149 (120, 160)	0.4
log2(t-tau)	7.26 (6.96, 7.65)	7.22 (6.91, 7.32)	0.4
Abeta-42	812 (649, 1,140)	896 (758, 944)	0.8
alpha-syn	1,374 (1,029, 1,877)	1,428 (1,059, 1,743)	0.9
Intracranial volume ($M/10^6$)	1.56 (1.45, 1.67)	1.61 (1.53, 1.70)	0.3

Note: Values are Median [Q1; Q3] or n (%). IQR bounds [Q1; Q3] are 25th and 75th percentiles.
P-values reported from the Wilcoxon rank sum test for continuous data, and from the Pearson's Chi-square test with continuity correction for categorical data with more than two levels and the Fisher's exact test for exactly two levels.

Table 2
Functional Ability and Cognitive Test Characteristics.

Characteristic	Diagnosis		p-value
	PD-CN, N = 88	PD-MCI, N = 21	
ADL			0.087
80	0 (0%)	1 (4.8%)	
85	1 (1.1%)	2 (9.5%)	
90	36 (41%)	7 (33%)	
95	9 (10%)	2 (9.5%)	
100	42 (48%)	9 (43%)	
ANIM	52 (45, 57)	53 (50, 59)	0.3
HVLT Del	50 (44, 55)	39 (32, 45)	**<0.001**
HVLT Imm	50 (39, 58)	40 (31, 48)	**0.005**
HVLT Rec	50 (37, 57)	42 (31, 45)	**0.018**
HVLT Ret	50 (43, 56)	45 (30, 55)	0.12
JLO	14.00 (12.00, 14.50)	13.00 (10.00, 14.00)	0.3
LNS	12.00 (10.75, 14.00)	12.00 (10.00, 13.00)	0.2
MoCA	28.50 (27.00, 29.00)	25.00 (24.00, 25.00)	**<0.001**
SDMT	47 (42, 51)	44 (36, 51)	0.6

Note: Values are Median [Q1; Q3] or n (%). IQR bounds [Q1; Q3] are 25th and 75th percentiles.
P-values reported from the Wilcoxon rank sum test for continuous data, and from the Pearson's Chi-square test with continuity correction for categorical data with more than two levels and the Fisher's exact test for exactly two levels.

3.2. Longitudinal study

Longitudinal mixed model results are in Fig. 2; pairwise post-hoc significant contrasts are interpreted for variables retained by model selection (while omnibus ANOVA test values are reported in the figure).

3.2.1. Cognition and functional abilities

Examination of cognitive outcomes and functional abilities indicated several associations with CSF biomarkers. The marginal mean trajectory

Table 3
Hippocampal Subfield Volume Characteristics.

Characteristic	Diagnosis		p-value
	PD-CN, N = 88	PD-MCI, N = 21	
LH-CA1	662 (601, 718)	607 (562, 644)	**0.011**
LH-CA3	212 (193, 241)	203 (188, 217)	0.14
LH-CA4	239 (220, 259)	226 (219, 256)	0.2
LH-fimbria	63 (54, 71)	63 (54, 73)	>0.9
LH-GC.ML.DG	279 (256, 301)	264 (250, 284)	0.13
LH-HATA	65 (59, 73)	63 (55, 68)	0.1
LH-hippocampal.fissure	181 (156, 206)	174 (155, 186)	0.092
LH-hippocampal-tail	600 (544, 673)	570 (528, 613)	0.081
LH-molecular_layer-HP	552 (524, 604)	524 (488, 565)	**0.039**
LH-parasubiculum	72 (62, 81)	72 (58, 82)	0.5
LH-presubiculum	336 (306, 364)	314 (294, 358)	0.4
LH-subiculum	427 (402, 473)	425 (391, 458)	0.5
LH-Whole-hippocampus	3,530 (3,302, 3,803)	3,249 (3,124, 3,637)	**0.034**
RH-CA1	685 (637, 772)	630 (615, 675)	**0.006**
RH-CA3	239 (218, 268)	225 (204, 249)	0.089
RH-CA4	245 (220, 265)	241 (230, 251)	0.4
RH-fimbria	56 (47, 67)	57 (48, 64)	>0.9
RH-GC.ML.DG	289 (257, 311)	277 (258, 290)	0.2
RH-HATA	67 (62, 74)	65 (54, 71)	0.13
RH-hippocampal.fissure	179 (162, 197)	170 (160, 180)	0.089
RH-hippocampal-tail	622 (571, 707)	600 (538, 629)	0.086
RH-molecular_layer-HP	569 (526, 616)	542 (514, 575)	0.088
RH-parasubiculum	68 (60, 78)	70 (60, 82)	0.6
RH-presubiculum	306 (269, 330)	293 (284, 338)	0.7
RH-subiculum	408 (385, 462)	396 (387, 438)	0.4
RH-Whole-hippocampus	3,582 (3,321, 3,865)	3,461 (3,292, 3,634)	0.13

Units for all characteristics are mm^3.
Note: Values are Median [Q1; Q3] or n (%). IQR bounds [Q1; Q3] are 25th and 75th percentiles.
P-values reported from the Wilcoxon rank sum test for continuous data, and from the Pearson's Chi-square test with continuity correction for categorical data with more than two levels, and the Fisher's exact test for exactly two levels.

of ADL decreases over time ($p < 0.001$, $\chi_3 = 18.318$). There was a significant interaction between Abeta-42 and cognitive status (diagnosis). For PD-CN, Abeta-42 was positively associated with ADL (lower Abeta-42 was associated with worse ADL), whereas in PD-MCI Abeta-42 was negatively associated with ADL. ADL generally exhibited an inverse association with $\log_2$(t-tau) with the least and greatest slopes for Years 1 and 2, respectively ($p = 0.014$, $\chi_3 = 10.357$). The marginal mean trajectory of ANIM increased over time ($p = 0.005$, $\chi_3 = 12.880$). The marginal mean trajectory of HVLT Rec increased over time ($p = 0.007$, $\chi_3 = 12.242$). The marginal mean trajectory of JLO does not change over time ($p = 0.670$, $\chi_3 = 1.552$), but increased Abeta-42 ($p = 0.015$, $\chi_1 = 5.921$) and decreased $\log_2$(t-tau) ($p = 0.015$, $\chi_1 = 5.939$) was associated with higher JLO performance. The marginal mean trajectory of LNS does not change over time ($p = 0.492$, $\chi_3 = 2.409$). LNS increased with $\log_2$(t-tau) in Years 0 and 1 but decreases in Years 2 and 4 ($p = 0.011$, $\chi_3 = 11.071$). The marginal mean trajectory of MoCA decreases from Year 0 to Years 1 and 2 and then increased in Year 4 ($p = 0.017$, $\chi_3 = 10.217$), while the relationship with Abeta-42 depends on Year with a negative relationship for Years 0 and 4, but positive for Years 1 and 2 ($p = 0.003$, $\chi_3 = 13.887$); the same was true for $\log_2$(t-tau) with positive/negative reversed ($p = 0.018$, $\chi_3 = 10.094$).

3.2.2. *Hippocampal subfields*

Examination of hippocampal subfields indicated larger effects for the RH than the left. Additionally, we observed differences in the associations between CSF biomarkers and hippocampal subfield volumes across time.

3.2.3. *CSF Abeta-42*

An interaction effect was observed between time and Abeta-42 for the RH whole hippocampus. Specifically, the marginal mean trajectory was roughly constant over time ($p = 0.237$, $\chi_3 = 4.236$), and the effect of Abeta-42 was positive in Years 0 and 4 ($p = 0.002$, $\chi_3 = 14.516$). For RH hippocampal fissure, the marginal mean trajectory was increasing over time ($p = 0.001$, $\chi_3 = 17.606$), and the effect of Abeta-42 was negative ($p = 0.013$, $\chi_1 = 6.131$). In the LH, the only effect is the LH HATA, where the marginal mean trajectory was roughly constant over time ($p = 0.454$, $\chi_3 = 2.620$), and Abeta-42 was positively associated with LH HATA ($p = 0.020$, $\chi_3 = 5.447$).

3.2.4. *CSF t-tau*

An interaction effect was observed between time and t-tau and the RH presubiculum. Overall, the marginal mean trajectory decreases at Year 4 ($p = 0.001$, $\chi_3 = 17.040$) and the association between $\log_2$(t-tau) and RH presubiculum was increasingly negative over time ($p = 0.010$, $\chi_3 = 11.433$). For RH molecular layer HP, the marginal mean trajectory was roughly constant over time ($p = 0.523$, $\chi_3 = 2.245$), and the associations between $\log_2$(t-tau) and the RH molecular layer HP are more negative in Years 1 and 2 ($p = 0.013$, $\chi_3 = 10.751$). For RH parasubiculum, the marginal mean trajectory was roughly contant over time ($p = 0.491$, $\chi_3 = 2.378$), there was a negative association between $\log_2$(t-tau) and the RH parasubiculum ($p = 0.010$, $\chi_1 = 6.701$).

3.2.5. *Alpha-syn*

An interaction effect was observed between time and alpha-syn for RH subiculum. While the marginal mean trajectory was roughly constant over time ($p = 0.457$, $\chi_3 = 2.606$), the association between alpha-syn and RH subiculum was roughly zero, except in Year 4 when it was positive ($p = 0.004$, $\chi_3 = 13.547$). An interaction effect was observed between and time and alpha-syn for RH presubiculum. The effect of alpha-syn was increasingly positively associated with RH presubiculum over time ($p = 0.008$, $\chi_3 = 11.785$). An interaction effect was observed between time and alpha-syn for RH hippocampal tail. The marginal mean trajectory was roughly constant over time ($p = 0.326$, $\chi_3 = 3.463$) and the association between alpha-syn and RH hippocampal tail was positive and greatest for Year 0 ($p = 0.020$, $\chi_3 = 9.860$). An interaction effect was observed between time and alpha-syn for the RH granule cell molecular layer of the dentate gyrus. The marginal mean trajectory was roughly constant over time ($p = 0.238$, $\chi_3 = 4.231$), and the effect of alpha-syn was positive for Years 0 and 4 but negative for Years 1 and 2 ($p = 0.017$, $\chi_3 = 10.148$, likely spurious). An interaction effect was observed between time and alpha-syn for RH CA4, the marginal mean trajectory was slightly increasing over time ($p = 0.086$, $\chi_3 = 6.604$), and the effect of alpha-syn was positive for Years 0 and 4 but negative for Years 1 and 2 ($p = 0.009$, $\chi_3 = 11.581$).

The associations between change in cognition over time and hippocampal subfield volumes are illustrated in Fig. 3. Among the demographic variables, ICV and Age were the most important. Among CSF biomarkers, alpha-syn was most important exhibiting an inverse relationship with change in ADL, with log2(t-tau) having the opposite relationship. Among subfield volumes, several areas are important. In particular, RH-HATA was negatively associated with change in MoCA and LNS while being positively associated with HVLT Ret; LH-HATA has a similar association with change in MoCA and was also negatively associated with change in SDMT.

4. Discussion

There is increasing interest in leveraging the use of biomarkers to determine the likelihood of cognitive impairment in PD (e.g. a prognostic biomarker), as well as characterizing the underlying pathological processes that contribute to cognitive impairment (e.g. alpha-syn versus AD related pathology). Hippocampal atrophy is an indicator of emerging dementia in PD, with recent evidence the hippocampal subfields may be more sensitive than overall hippocampal volumes to detect early cognitive changes in PD. It is unclear whether hippocampal degeneration is driven by AD related co-pathology or progression of alpha-syn in

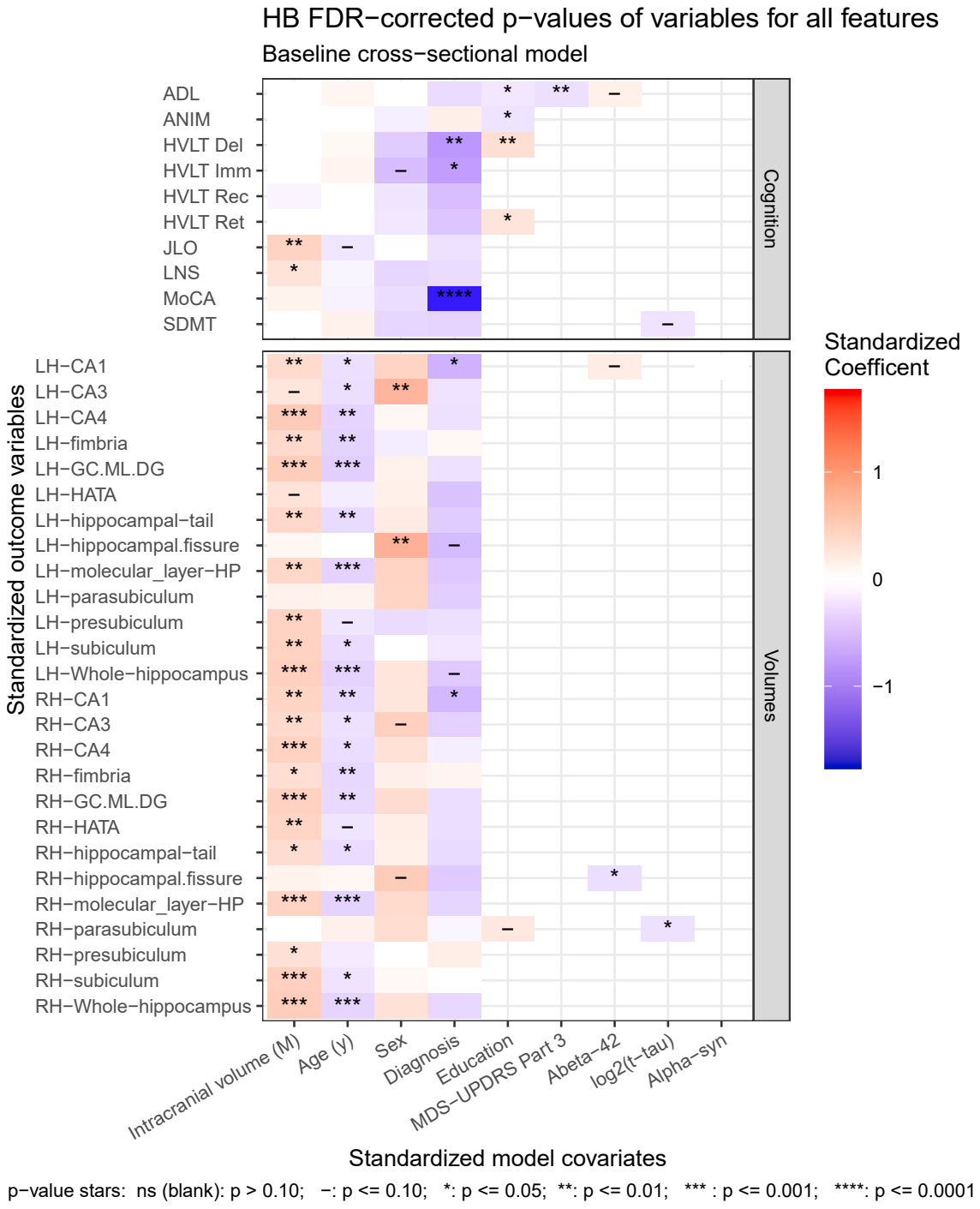

Fig. 1. Baseline results summary of cross-sectional multiple linear regression for functional abilities, cognition, and hippocampal volumes identifying significant terms after HB FDR p-value correction. Colored boxes indicate model terms retained by backward selection using BIC.

PD. We replicated prior reports that PD-MCI exhibited reduced bilateral CA1 volumes relative to PD-NC, highlighting that this region is one of the earliest hippocampal subfields to degenerate as individuals develop cognitive impairment. However, we failed to identify differences in CSF biomarkers based on cognitive status, with no clear indication that PD-MCI patients had altered CSF alpha-syn, t-tau, and Abeta-42 relative to PD-NC at baseline. Examination of associations between CSF biomarkers and hippocampal subfields, however, provided evidence that increased t-tau was associated with decreased subiculum volumes at baseline and over time. A major limitation is that there was substantial heterogeneity in the associations between CSF biomarkers, hippocampal subfields, and cognition in this *de novo* cohort.

Overall hippocampal volumes are reduced at each stage of cognitive impairment in PD (PD > PD-MCI > PD-Dementia), with associated decrements in memory performances [27]. Consistent with prior examinations of hippocampal subfields in a PD cohort at various disease durations/stages [7,27], we demonstrated that patients with PD-MCI have smaller bilateral CA1 volumes than patients with PD-CN, providing further evidence that reductions in this subfield volume may be one of the earliest indicators of emerging cognitive impairment. The AD literature has also found CA1 to be the earliest region that degenerates before spreading to other subfields [28]. It is thought that the hippocampal input regions (entorhinal cortex, CA1) are initially impacted, with anterograde progression through the perforant pathway

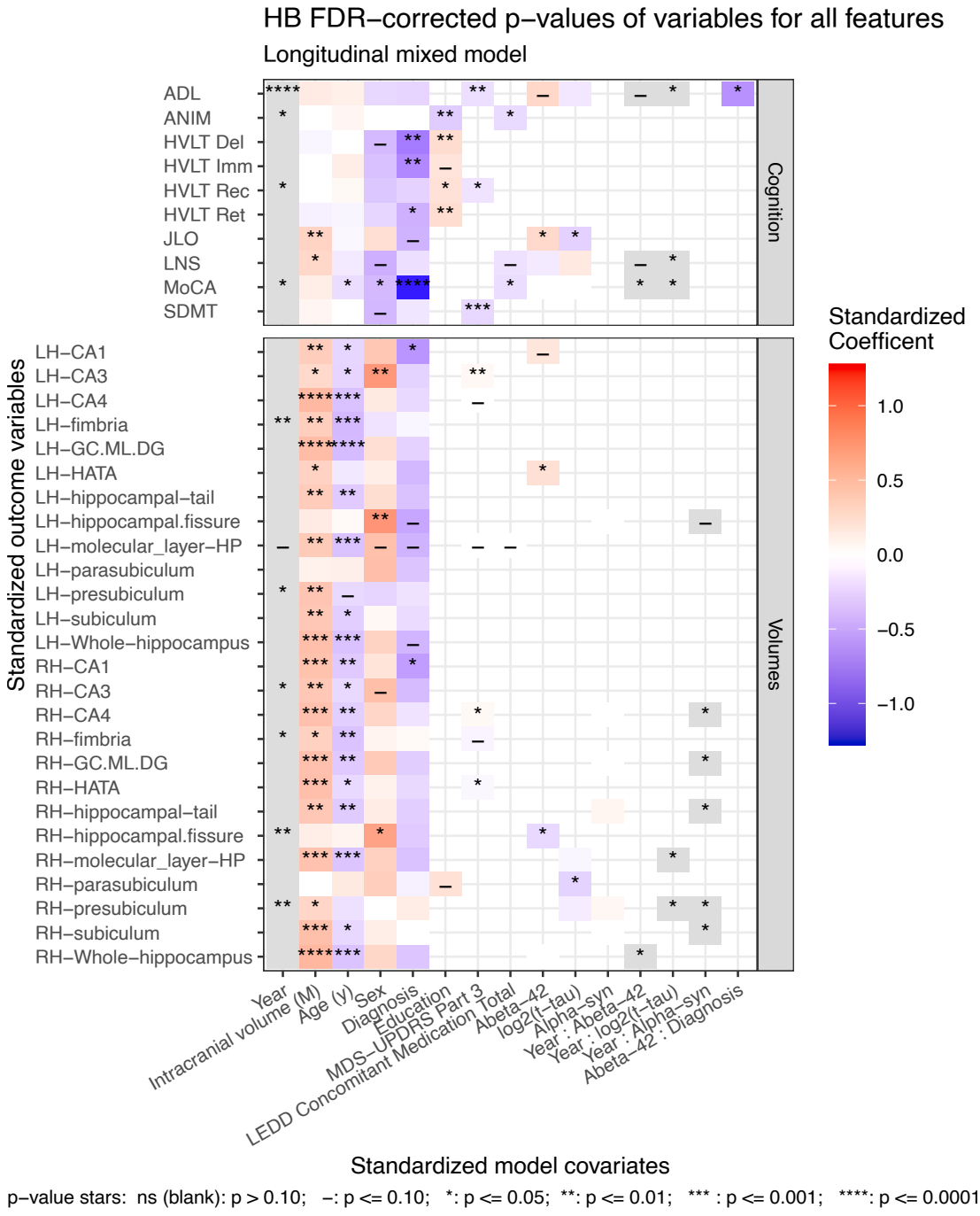

Fig. 2. Longitudinal results summary of cross-sectional multiple linear regression for functional abilities, cognition, and hippocampal volumes identifying significant terms after HB FDR p-value correction. Colored and gray boxes indicate model terms retained by backward selection using cAIC; gray boxes are multi-level factors where a single color is not available.

in AD. Our results are consistent with this model and suggestive that co-occurring AD pathology may be driving CA1 degeneration. However, we found no differences in CSF biomarkers between PD-NC and PD-MCI. It is possible that the PD-MCI cohort is heterogeneous in terms of the presence of co-pathology and alpha-syn progression, reducing our ability to detect group effects. Together, the hippocampal volume changes may be more sensitive to early changes relative to the CSF biomarkers, though our subsequent analyses indicated direct associations between CSF t-tau and hippocampal subfields.

Prior evaluation of CSF biomarkers and hippocampal volumes in PD focused on measures of Aβ [9]. While Aβ often precedes tau in AD [29], Aβ alone may be insufficient to produce cognitive changes in individuals at risk for AD [30]. Elevated tau, in contrast, is most closely associated with cognitive decline and hippocampal degeneration in AD [31]. AD co-pathology is common in PD, though it is unclear whether co-occurring AD pathology leads to a similar pattern of hippocampal degeneration [5,32]. When evaluating the direct associations between CSF biomarkers and hippocampal subfields at baseline and over time, the most consistent findings indicated increased t-tau is associated with decreased RH hippocampal parasubiculum volumes. Additionally, we observed that increased t-tau is associated with decreased RH presubiculum and the molecular layer volumes. As noted above, the atrophy of CA1 is the earliest observed in AD, with anterograde progression through the perforant pathway, which is consistent with our results

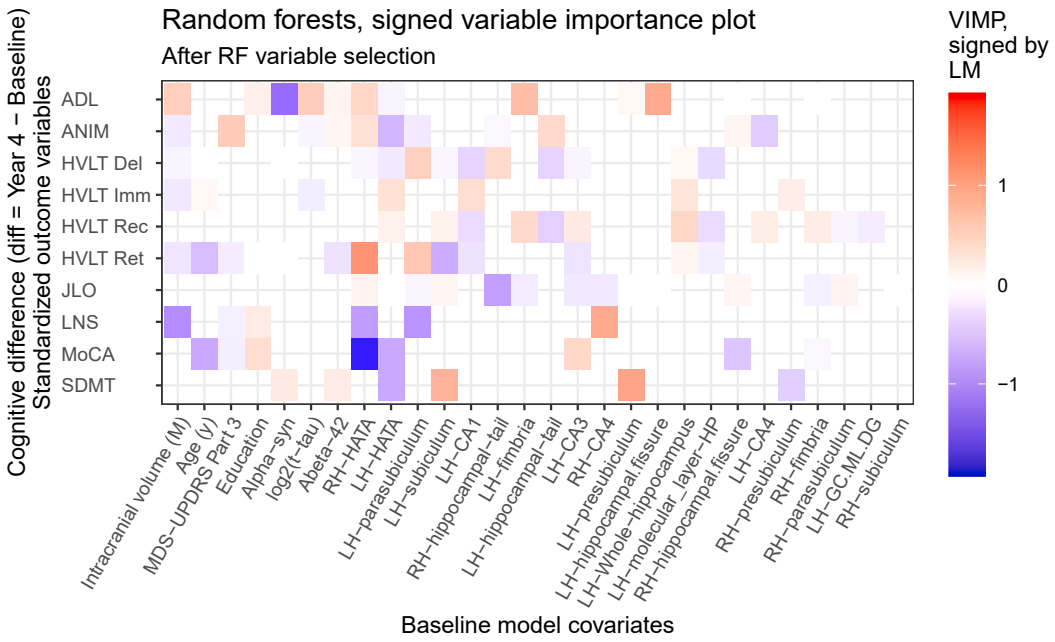

Fig. 3. Random forests signed variable importance plot predicting functional abilities and cognitive differences (Year 4 minus baseline) from the baseline features of demographics, CSF fluid variables, and subfield volumes.

indicating that the presubiculum and parasubiculum may be subsequently impacted following CA1. In addition to CA1, the presubiculum and subiculum have been found to be some of the earliest regions to degenerate in AD [33]. CSF t-tau is associated with lower subiculum volumes [7] and longitudinal decline in the presubiculum was found in individuals who progress to PD-dementia [34]. This suggests that t-tau may be associated with hippocampal degeneration, consistent with the AD literature. Additionally, the associations between t-tau and hippocampal subfield volumes increased over time in our cohort, suggesting as the disease progresses, there is likely an increase in the frequency of co-occurring t-tau and that this may be driving the increased associations over time.

Increased CSF alpha-syn was associated with increased hippocampal volumes across time in the RH subiculum, presubiculum and hippocampal tail, with variable patterns observed in the RH granule cell molecular layer of the dentate gyrus and CA4. These results are challenging to interpret given the inconsistencies observed in the longitudinal trajectory of total alpha-syn biomarkers. CSF total alpha-syn has been found to increase [35], decrease [36] or not change over time [17]. Alpha-syn in its normal form is found within the presynaptic regions of neurons, either unfolded or contained in alpha-helical membrane-bound forms. Aggregation refers to the process by which alpha-syn becomes partially folded and aggregates to form oligomers, protofibrils, fibrils and mature Lewy bodies [37–39]. While other CSF biomarkers quantify the oligomeric or phosphorylated forms of alpha-syn, the current study uses total alpha-syn, which may initially be reduced when it is aggregated intracellularly [40], but over time as there is an increase in neuronal death, there may be a possible release of alpha-syn [41]. In this context, it is challenging to interpret associations as both low and high measures can be indicative of more severe pathological processes. More recently developed alpha-syn biomarkers, such as seed quantification approaches demonstrate superior performance and may be more appropriate to use to use for future analyses [42].

While there are several strengths of the current study, including longitudinal assessment of a well-characterized sample of *de novo* PD patients and advanced statistical analyses, there are several limitations. First, only a subset of PD patients exhibit co-occurring AD-related neuropathological change, particularly early in the disease course. Additionally, CSF cutoffs for Abeta-42 and t-tau in PD are not well established in PD. Due to these reasons, we chose to evaluate these measures as continues variables, an approach which has its strengths and weaknesses. Our examination of these CSF measures as continuous variables minimized the likelihood of missing such an effect. Once clear cutoffs are established in PD, it would be helpful to evaluate cross sectional differences based on these measures. Additionally, future studies in a cohort with clear co-occurring AD pathology are necessary to determine to what extent these associations are driven by AD versus alpha-syn pathological processes.

In summary, our results replicated prior findings that reduced bilateral CA1 volumes are associated with cognitive changes in a *de novo* PD cohort, providing further evidence that CA1 changes may be the earliest indicators of emerging cognitive impairment. However, there was limited evidence that the CA1 volumes corresponded to changes in CSF biomarkers between PD-NC and PD-MCI participants. Direct associations between CSF biomarkers and hippocampal subfields were observed at baseline and longitudinally, with the most consistent effects observed between t-tau and subiculum volumes. This highlights that in the earliest stage of PD, hippocampal subfield volumes may be more sensitive than CSF biomarkers to detect early changes associated with cognition. However, over time, increases in t-tau may be indicators of the progression of hippocampal subfield atrophy progressing from CA1 to the subiculum regions, following a similar pattern of atrophy to that observed in AD. Future studies are necessary to leverage better performing alpha-syn biomarkers as well as evaluate these effects in t-tau positive and negative cohorts to further understand the relative contributions of alpha-syn versus co-occurring AD pathology on hippocampal volumes and cognition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research funding partners 4D Pharma,

Abbvie, Acurex Therapeutics, Allergan, Amathus Therapeutics, ASAP, Avid Radiopharmaceuticals, Bial Biotech, Biogen, BioLegend, Bristol-Myers Squibb, Calico, Celgene, Dacapo Brain Science, Denali, The Edmond J. Safra Foundaiton, GE Healthcare, Genentech, GlaxoSmithKline, Golub Capital, Handl Therapeutics, Insitro, Janssen Neuroscience, Lilly, Lundbeck, Merck, Meso Scale Discovery, Neurocrine Biosciences, Pfizer, Piramal, Prevail, Roche, Sanofi Genzyme, Servier, Takeda, Teva, UCB, Verily, and Voyager Therapeutics. Funding sources had no involvement in the writing of this manuscript.

Funding

E. Erhardt is funded by NIH grant #P30GM122734.

A. Vakhtin is funded by NIH grant #P30GM122734.

A. Mayer is funded by NIH grant #P30GM122734.

J. Adair is funded by NIH Grants #UF1NS100698, #P20 AG068077.

J. Knoefel is funded by NIH Grants #UF1NS100698, #P20 AG068077.

G. Rosenberg is funded by NIH Grants #UF1NS100698, #P20 AG068077.

K. Poston is funded by grants from the NIH (U19 AG065156, R01 NS115114, R01 NS107513, P30 AG066515, P50 NS062684), Michael J Fox Foundation for Parkinson's Research (Grant 020756, 16921, 18411), Lewy Body Dementia Association, Alzheimer's Drug Discovery Foundation, and Sanofi US Services, Inc.

S. Pirio Richarson has active or recent grant support from the US government (National Institutes of Health and Department of Defense) and industry (Pharma 2B, AEON, ADDEX, SCION).

S.G. Ryman is funded by NIH grants #P30GM122734, #R03AG075408, #UF1NS100698, #P20 AG068077, #R61MH125126.

Conflict of Interest Statement

K. Poston has received consulting fees from Curasen.

S. Pirio Richarson has received honoraria for lectures from the International Parkinson's Disease and Movement Disorders Society and the American Academy of Neurology. Dr. Pirio Richardson serves on the Scientific Advisory Boards for private foundations including the Benign Essential Blepharospasm Research Foundation and the Dystonia Medical Research Foundation. She has received royalties from Springer.

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Glossary

Acronyms

PD: Parkinson's disease
PD-MCI: Parkinson's disease with Mild Cognitive Impairment
PD-CN: Parkinson's disease cognitively normal
AD: Alzheimer's disease
alpha-syn: alpha-synuclein
Abeta-42: β-amyloid 1–42
t-tau: total tau
PPMI: Parkinson's Progression Markers Initiative
MoCA: Montreal Cognitive Assessment
ADL: The Modified Schwab and England Percent Activities of Daily Living
HVLT: Hopkins Verbal Learning Test-Revised
JLO: Benton Judgment-of-Line-Orientation total score
ANIM: Animal Naming
LNS: Letter-Number Sequencing
SDMT: Symbol Digit Modalities Test
CA: cornu ammonis
DG: dentate gyrus
HATA: hippocampal-amygdaloid transition area