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Brain Amyloid Contribution to Cognitive Dysfunction in Early-Stage Parkinson's Disease: The PPMI Dataset

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Abstract.
Background: The pathological processes underlying cognitive impairment in Parkinson's disease (PD) are heterogeneous and the contribution of cerebral amyloid deposits is poorly defined, particularly in the early stages of the disease.
Objective: To investigate regional [^{18}F]florbetaben binding to amyloid-β (Aβ) and its contribution to cognitive dysfunction in early stage PD.
Methods: A multicenter cohort of 48 PD patients from the Parkinson's Progression Marker Initiative (PPMI) underwent [^{18}F]florbetaben positron emission tomography (PET) scanning. Clinical features, including demographic characteristics, motor severity, cerebrospinal fluid (CSF), and cognitive testing were systematically assessed according to the PPMI study protocol. For the purpose of this study, we analyzed various neuropsychological tests assessing all cognitive functions.
Results: There were 10/48 (21%) amyloid positive PD patients (PDAβ+). Increased [^{18}F]florbetaben uptake in widespread cortical and subcortical regions was associated with poorer performance on global cognition, as assessed by Montreal Cognitive Assessment (MoCA), and impaired performance on Symbol Digit Modality test (SDMT). Further, we found that PDAβ+ patients had higher CSF total-tau/A$\beta_{1\text{-}42}$ ($p = 0.001$) and phosphorylated-tau/A$\beta_{1\text{-}42}$ in ($p = 0.002$) compared to amyloid-negative PD.

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Conclusion: These findings suggest that multiple disease processes are associated with PD cognitive impairment and amyloid deposits may be observed already in early stages. However, prevalence of amyloid positivity is in the range of literature age-matched control population. Increased cortical and subcortical amyloid is associated with poor performance in attentive-executive domains while cognitive deficits at MoCA and SDMT may identify amyloid-related dysfunction in early PD.

Keywords: Amyloid, cerebrospinal fluid, cognition, cognitive dysfunction, dementia, neuropsychology, Parkinson's disease, positron emission tomography, synuclein

INTRODUCTION

Cognitive dysfunction is one of the most prevalent and disabling non-motor symptoms of Parkinson's disease (PD) [1]. Its point prevalence is about 30%, but over the disease course a significant proportion of patients progresses to dementia [2, 3], with negative consequences for quality of life and survival [4].

Deterioration in cognitive performance in PD is secondary to various conditions: cortical and limbic Lewy bodies [5], degeneration of basal forebrain cholinergic neurons [6], uneven dopamine loss in nigro-striatal neurons [7], as well as amyloid-β (Aβ) plaques and tau neurofibrillary tangles [8]. Measurement of cerebral amyloid uptake with positron emission tomography (PET), using specific tracers like [^{18}F]florbetaben [9], and cerebrospinal fluid (CSF) amyloid levels [10] have all been proposed as possible biomarkers of dementia in PD. Indeed, pathological processes may act synergistically, with detrimental effects on cognition, and significant impact on clinical progression and prognosis [8, 10–12]. In particular, it has been observed that up to half of patients with PD or dementia with Lewy bodies may show at death sufficient amyloid pathology to support a diagnosis of concomitant Alzheimer's disease (AD) [13], and that co-existence of elevated amyloid plaque and tau concentration decreases survival and increases dementia progression [14].

However, evidence about the role of amyloid on cognition in early stage PD is scarce and based mainly on CSF measurements, which is only an indirect index of cortical deposits [15–17]. Recently PET studies with [^{11}C]-Pittsburgh compound B (PIB) ligand [18, 19] have shown presence of amyloid deposition in PD patients, but prevalence in early PD stage has not been assessed.

The objective of the present study was to investigate the association between [^{18}F]florbetaben binding to Aβ, CSF amyloid levels, and cognitive dysfunctions in early PD from the Parkinson's Progression Markers Initiative (PPMI) database. We hypothesized that increased cerebral amyloid uptake modulates early cognitive manifestations, including attentive and executive abilities, already at very early disease stage.

METHODS

Participants

In this cohort study, we obtained approval to access the PPMI database, and investigated clinical, cognitive and neuroimaging data [20]. Objectives, methodology, and details of PPMI study assessments have been published and are available online (http://www.ppmi-info.org/study-design). The PPMI program was approved by the Institutional Review Board of each participating site and all participants gave their written informed consent to participate in the program.

From the PPMI dataset, as of March 2018, there were 87 participants who had [^{18}F]florbetaben PET. From this sample, we excluded 14 healthy controls, 16 prodromal PD, and nine unaffected subjects from the genetic cohort, leaving the final sample with 48 symptomatic PD patients investigated at five centers. For this analysis, we also included neuropsychological and clinical features and CSF results.

Neuropsychological and clinical features

Demographic and clinical variables included age, years of education, sex, disease duration, levodopa equivalent daily dose, dopamine agonist equivalent daily dose, disease severity measured using the Movement Disorder Society Unified Parkinson's Disease Rating Scale motor score (MDS-UPDRS III) assessed in ON and OFF state, and daily functioning using the Activities of Daily Living (ADL). Further, we classified PD patients as manifesting tremor dominant (TD), postural instability–gait disturbance (PIGD), and intermediate PD phenotype, using the method previously described [21].

Global cognition was assessed using Montreal Cognitive Assessment (MoCA) scores collected at

the time of neuroimaging examination. Specific cognitive functions were assessed by the Benton Judgment of Line Orientation 15-item version (JLO) for visuospatial domain [22]; the Symbol-Digit Modalities Test (SDMT) for attention, visual scanning, and motor speed [23, 24]; the Hopkins Verbal Learning Test-Revised (HVLT-R) with immediate and delayed recall for memory [25]; the Letter-Number Sequencing (LNS) for attention and working-memory [26] and the semantic fluency test for language abilities [27]. All the cognitive tests' scores were corrected according to the published norms (referenced previously). Depression was evaluated with the 15-item Geriatric Depression Scale. This sample did not include PD with dementia, as all patients were independent in daily living activities (as assessed by ADL score >80/100).

CSF sample measures

A subsample of the participants [$n = 44$ (10 PDAβ+ and 34 PDAβ–)] underwent lumbar puncture at the baseline visit (with a mean of 2.5 ± 0.8 years before amyloid PET) to obtain CSF samples. Due to the ability to reduce CSF biomarker measurements variability across laboratories and improve its reliability, the Roche Elecsys fully automated immunoassay developed by Roche Diagnostic [28], were used to analyse $A\beta_{1\text{-}42}$, total tau (t-tau) and phosphorylated tau (p-tau) concentrations, while α-synuclein concentrations were measured using a commercially available enzyme-linked immunosorbent assay kit (BioLegend). The related method is described comprehensively on the PPMI website (http://www.ppmi-info.org/study-design/research-documents-and-sops/). We also calculated the p-tau and T-tau to $A\beta_{1\text{-}42}$ ratios, and p-tau to T-tau ratio.

PET data acquisition and image processing

Images were acquired at PPMI centers according to a standard imaging protocol (http://www.ppmi-info.org/wp-content/uploads/2015/12/PPMI-AM10_protocol.pdf). [^{18}F]florbetaben PET images were imported to PMOD Biomedical Image Quantification Software (PMOD Technologies, Zurich, Switzerland) for processing and analysis following technical quality control performed at an imaging core lab (Institute for Neurodegenerative Disorders, New Haven, Connecticut). Dynamic PET frames were assessed for motion; and if necessary, motion correction was performed. These files were then averaged (time weighted mean) to create a single PET volume. The PET volume was normalized to standard Montreal Neurologic Institute (MNI) space so that all scans were in the same anatomical alignment. The normalized PET volume was then converted to standard uptake values (SUVs). Volumes of Interest (VOIs) from the MNI modified Automated Anatomical Labeling template, which include cortical and subcortical regions, were applied to the SUV PET volume and adjusted as needed for subject atrophy [29]. The VOI placement was saved for each subject. Semi-quantitative measurements (average SUV per voxel) were extracted from the regions to calculate the regional SUV Ratios (SUVRs) using the cerebellar cortex as our reference region.

A composite SUVR for each subject was established by calculating the mean SUVRs from regions of interest, typically associated with increased uptake [30]. Composite SUVR values >1.43 were considered positive, indicating presence of Aβ in the range expected for AD [31]. We defined PDAβ+ and PDAβ– according to this SUVR cut-off.

Statistical analysis

Due to the non-normal distribution of the sample, descriptive and non-parametric statistics (Mann-Whitney U test) were conducted to analyze the demographic, clinical and imaging data. Categorical variables were compared using the Fisher's exact test. Then, Spearman rank correlations were performed to study the association between cognition and amyloid depositions. Statistical analysis was performed using IBM SPSS Statistics version 20.0 and significance was set at a five percent level. The false discovery rate (FDR) approach was also employed to correct for multiple comparisons.

RESULTS

Study cohort characteristics

Among the 48 PD, 10 (21%) had [^{18}F]florbetaben PET SUVR >1.43 and were classified as PDAβ+, while the remaining 38 were PDAβ–. The clinical and demographic data of the patients are presented in Table 1. PDAβ+ patients had lower MoCA and SDMT score compared to PDAβ– ($p = 0.01$ and $p = 0.03$, respectively). Between-groups differences were present also in CSF p-tau/$A\beta_{1\text{-}42}$ ($p < 0.002$) and T-tau/$A\beta_{1\text{-}42}$ ratios ($p < 0.001$).

Table 1
Demographic, clinical and neuropsychological characteristics according to amyloid status

	PDAβ– ($n=38$)			PDAβ+ ($n=10$)			p
	Mean (SD)	Min	Max	Mean (SD)	Min	Max	
Age, y	63.97 (8.89)	49.00	84.00	70.40 (8.54)	55.00	81.00	0.062
Education, y	16.24 (2.71)	12.00	26.00	17 (2.11)	14.00	20.00	0.248
Sex (m/f)	26/12			8/2			0.701
Disease duration, m	3.76 (1.41)	1.00	8.00	3.98 (1.63)	1.59	7.51	0.750
LEDD	424.24 (236.23)	50.00	1100.00	282.25 (148.77)	105.00	562.50	0.090
DAED	83.53 (168.81)	0	825.00	30.50 (50.03)	0	120.00	0.556
MDS- UPDRS III (on)	23.79 (11.00)	5.00	56.00	25.10 (9.24)	17.00	48.00	0.866
MDS- UPDRSIII (off)	29.96 (10.29)	10.00	51.00	29.33 (4.46)	24.00	35.00	0.750
Motor phenotype							
TD/ PIGD/IND	24/11/3			6/4/0			0.574
TD subscore	5.18 (3.59)	0	13.00	5.90 (4.61)	0	12	0.680
PIGD subscore	1.58 (0.98)	0	5.00	2.00 (1.49)	0	4.00	0.415
CSF markers, pg/mL[a]							
$A\beta_{1-42}$	1002.29 (367.65)	516.90	1700.00	837.63 (348.07)	497.20	1373.00	0.202
p-tau181	13.72 (5.11)	8.00	29.63	18.06 (10.42)	10.07	45.90	0.098
T-tau	164.62 (58.25)	80.00	299.70	208.66 (105.56)	107.00	475.20	0.218
α-Syn	1505.55 (830.64)	638.9	4954.90	1609.41 (959.65)	660.70	4105.30	0.695
T-tau/$A\beta_{1-42}$ ratio	0.17 (0.05)	0.10	0.33	0.28 (0.21)	0.16	0.85	**0.001**
p-tau/$A\beta_{1-42}$ ratio	0.01 (0.004)	0.01	0.03	0.02 (0.02)	0.01	0.08	**0.002**
p-tau/T-tau ratio	0.08 (0.01)	0.07	0.10	0.09 (0.01)	0.07	0.10	0.363
Cognitive tests							
MoCA	27.11 (2.25)	21.00	30.00	24.80 (2.62)	22.00	29.00	**0.013**
LNS	11.76 (2.67)	8.00	18.00	10.80 (3.23)	6.00	16.00	0.459
SDMT	48.60 (8.96)	29.17	66.25	41.19 (9.33)	30.00	56.67	**0.030**
Benton JLO	12.50 (2.47)	7.12	16.38	10.72 (2.98)	6.20	13.44	0.233
HVLT-R immediate recall	51.55 (10.05)	33.00	71.00	49.80 (8.30)	38.00	60.00	0.721
HVLT-R delayed recall	50.13 (8.62)	36.00	64.00	46.40 (13.44)	25.00	61.00	0.502
Semantic fluency	52.87 (10.24)	35.00	80.00	50.90 (10.83)	38.00	69.00	0.479
GDS	4.89 (1.24)	1.00	7.00	4.90 (1.52)	2.00	7.00	0.898
ADL	87.24 (8.20)	70.00	100.00	89.5 (7.62)	80.00	100.00	0.457

PD, Parkinson's disease; Aβ, amyloid-β; SD, standard deviation; LEDD, levodopa equivalent daily dose; MDS-UPDRS, Movement Disorder Society Unified Parkinson's Disease Rating Scale; TD, tremor dominant; PIGD, postural instability–gait disturbance; IND, intermediate; CSF, cerebrospinal fluid; T-tau, total-tau, p-tau, phosphorylated-tau; α-Syn, α-synuclein; MoCA, Montreal Cognitive Assessment; LNS, Letter Number Sequencing test; SDMT, Symbol Digit Modalities Test; JLO, Judgement of Line Orientation; HVLT-R, Hopkins Verbal Learning Test-Revised; GDS, Geriatric Depression Scale; ADL, Activity of Daily Living; Significant value is in bold type. a: CSF data was available for a subset of PDAβ– ($n=34$) and for all PDAβ+.

Regional [^{18}F]florbetaben uptake in PDAβ+ versus PDAβ–

Table 2 shows [^{18}F]florbetaben regional SUVRs in PDAβ+ versus PDAβ–. There was highly significant increased uptake in several regions, particularly in the cortex (i.e., frontal, orbitofrontal, rectus, temporal, mesial and lateral temporal, parietal, occipital areas, posterior and anterior cingulate cortex regions), subcortical nuclei (caudate, putamen, thalamus) and pons.

Correlation between amyloid [^{18}F]florbetaben binding and cognitive tests

Considering the whole PD cohort (PDAβ+ and PDAβ–), there was a moderate negative correlation between MoCA score and [^{18}F]florbetaben amyloid uptake in cortical (frontal, parietal, temporal, occipital and anterior cingulate) and subcortical (caudate, putamen and thalamus) regions. Similar association was also seen between SDMT score and [^{18}F]florbetaben SUVR in selected cortical regions (see Table 3). These correlations indicate that greater amyloid burden in cortical and subcortical areas is associated with poorer performance in global cognition and attention, visual scanning and processing speed tasks.

DISCUSSION

This is one of the few PET-amyloid studies investigating the contribution of amyloid deposition and its effect on cognitive performance in early stage non-demented PD patients [15, 18].

Table 2
Regional [^{18}F]florbetaben SUVRs uptake by amyloid status

Region	PDAβ– ($n = 38$)			PDAβ+ ($n = 10$)			p
	Mean (SD)	Min	Max	Mean (SD)	Min	Max	
Frontal R	1.29 (0.08)	1.15	1.49	1.67 (0.30)	1.41	2.37	<0.001
Frontal L	1.31 (0.08)	1.16	1.49	1.67 (0.28)	1.41	2.29	<0.001
Orbitofrontal R	1.24 (0.09)	1.08	1.44	1.54 (0.29)	1.25	2.13	<0.001
Orbitofrontal L	1.24 (0.08)	1.10	1.43	1.51 (0.25)	1.29	2.01	<0.001
Rectus R	1.20 (0.11)	0.94	1.41	1.56 (0.34)	1.13	2.31	<0.001
Rectus L	1.24 (0.09)	1.05	1.47	1.55 (0.29)	1.15	2.19	<0.001
Temporal R	1.23 (0.07)	1.10	1.38	1.48 (0.17)	1.33	1.89	<0.001
Temporal L	1.22 (0.08)	1.00	1.46	1.45 (0.12)	1.29	1.71	<0.001
Mesial temporal R	1.22 (0.07)	1.08	1.38	1.41 (0.13)	1.31	1.72	<0.001
Mesial temporal L	1.22 (0.08)	1.07	1.48	1.39 (0.10)	1.28	1.62	<0.001
Lateral temporal R	1.24 (0.07)	1.10	1.38	1.50 (0.19)	1.33	1.94	<0.001
Lateral temporal L	1.23 (0.08)	1.11	1.45	1.48 (0.13)	1.30	1.75	<0.001
Anterior cingulate R	1.25 (0.11)	1.04	1.55	1.67 (0.38)	1.32	2.45	<0.001
Anterior cingulate L	1.30 (0.12)	1.05	1.52	1.74 (0.33)	1.40	2.47	<0.001
Posterior cingulate R	1.30 (0.13)	1.07	1.54	1.75 (0.29)	1.32	2.38	<0.001
Posterior cingulate L	1.37 (0.12)	1.10	1.56	1.83 (0.25)	1.56	2.37	<0.001
Parietal R	1.26 (0.09)	1.09	1.44	1.63 (0.26)	1.38	2.22	<0.001
Parietal L	1.26 (0.09)	1.08	1.43	1.62 (0.24)	1.38	2.09	<0.001
Occipital R	1.30 (0.08)	1.16	1.52	1.52 (0.09)	1.41	1.67	<0.001
Occipital L	1.32 (0.08)	1.18	1.52	1.57 (0.10)	1.44	1.73	<0.001
Caudate R	1.41 (0.11)	1.11	1.68	1.70 (0.27)	1.40	2.26	<0.001
Caudate L	1.35 (0.12)	1.12	1.61	1.63 (0.27)	1.36	2.17	<0.001
Putamen R	1.48 (0.11)	1.19	1.84	1.81 (0.26)	1.49	2.34	<0.001
Putamen L	1.44 (0.10)	1.22	1.67	1.70 (0.23)	1.37	2.15	0.001
Thalamus R	1.48 (0.13)	1.28	1.87	1.69 (0.11)	1.52	1.93	<0.001
Thalamus L	1.56 (0.13)	1.33	1.96	1.78 (0.15)	1.60	2.07	<0.001
Pons	1.73 (0.16)	1.30	2.02	1.99 (0.20)	1.80	2.41	0.001

SUVR, Standard Uptake Value ratio; PD, Parkinson's disease; Aβ, amyloid-β; SD, standard deviation; R, right; L, left.

We found presence of positive cerebral amyloid [^{18}F]florbetaben uptake, in 21% of our PD already at the beginning of the disease and in several neocortical and subcortical regions [9, 18]. However, overall prevalence was in the range of literature age-matched control population suggesting that PD by itself does not confer a specific risk of increased amyloid deposition [32, 33].

Further, we found that the amyloidosis was associated with increased p-tau/A$\beta_{1\text{-}42}$ and T-tau/A$\beta_{1\text{-}42}$ ratio and this is aligned with recent evidence of increased risk of PD+AD pathology in presence of both high T-tau/A$\beta_{1\text{-}42}$ level and high cerebral amyloid burden [34]. However, our results are based on disproportioned subsamples (10 PDAβ+ versus 38 PDAβ–), and they needed to be confirmed in a larger study.

From a cognitive perspective, we observed lower mean MoCA score in PDAβ+ patients compared to PDAβ– and a negative correlation between MoCA scores and amyloid deposits in cortical regions and basal ganglia.

MoCA is a global cognitive scale, assessing particularly executive-attentive functions, whose performance has been previously associated with nigrostriatal alterations [35, 36] and/or brain dopamine level [37]. However, a recent PD study investigating the contribution of CSF α-synuclein, Aβ, and tau to motor/non-motor symptoms in advanced non-demented PD, found that A$\beta_{1\text{-}42}$ was the only CSF biomarker associated with cognitive performance, in particular with MoCA remote recall and attention subscores [38]. Further, Schrag and colleagues (2017), in their attempt to explore which clinical variables and biomarkers best predict PD cognitive decline (assessed as MoCA change at 2 years follow-up) in the PPMI dataset, found a multifactorial predictive model which included both low CSF Aβ_{42} to t-tau ratio and nigrostriatal alterations at baseline [39]. In this regard, our data reinforce the role of cortical and subcortical amyloid burden as an additional biomarker contributing to cognitive impairment as assessed with MoCA performance.

We also observed significantly lower performance in SDMT in PDAβ+ patients, a measure of information processing speed, involving attention, working memory and visual processes and a significant correlation with increased amyloid deposits in cortical

Table 3
Spearman's rank correlation between cognitive tests versus amyloid depositions

		Regional [18F]florbetaben SUVRs									
		Mesial temporal	Anterior cingulate	Posterior cingulate	Occipital	Parietal	Lateral temporal	Orbito-frontal	Frontal	Temporal	Caudate	Putamen	Thalamus
MoCA	rs	–0.308	–0.387	–0.291	–0.38	–0.411	–0.315	–0.306	–0.386	–0.281	–0.369	–0.399	–0.385
	p	**0.033**	**0.007**	0.045	**0.008**	**0.004**	**0.029**	**0.035**	**0.007**	0.053	**0.010**	**0.005**	**0.007**
LNS	rs	–0.124	–0.053	–0.107	–0.076	–0.092	–0.141	–0.109	–0.055	–0.167	–0.126	–0.109	–0.139
	p	0.402	0.719	0.469	0.607	0.533	0.340	0.461	0.712	0.255	0.394	0.463	0.348
SDMT	rs	–0.220	–0.172	–0.346	–0.388	–0.393	–0.391	–0.168	–0.353	–0.372	–0.156	–0.245	–0.193
	p	0.132	0.243	**0.016**	**0.006**	**0.006**	**0.006**	0.254	**0.014**	**0.009**	0.289	0.093	0.189
Benton JLO	rs	–0.187	–0.178	–0.083	–0.192	–0.22	–0.13	–0.107	–0.188	–0.122	–0.246	–0.226	–0.199
	p	0.204	0.225	0.575	0.190	0.133	0.377	0.468	0.200	0.409	0.092	0.122	0.175
HVLT immediate recall	rs	–0.086	–0.059	–0.148	–0.155	–0.116	–0.124	0.041	–0.061	–0.143	–0.052	–0.025	–0.153
	p	0.562	0.689	0.317	0.294	0.433	0.400	0.782	0.682	0.333	0.724	0.865	0.299
HVLT delayed recall	rs	–0.115	–0.071	–0.111	–0.228	–0.173	–0.172	–0.076	–0.15	–0.179	–0.225	–0.042	–0.188
	p	0.436	0.630	0.453	0.119	0.240	0.243	0.608	0.310	0.222	0.123	0.777	0.200
Semantic fluency	rs	0.051	0.214	0.049	0.026	0.036	–0.001	0.103	0.081	–0.004	0.059	0.211	0.027
	p	0.732	0.144	0.742	0.858	0.808	0.993	0.485	0.585	0.976	0.690	0.150	0.855

MoCA, Montreal Cognitive Assessment; LNS, Letter Number Sequencing test; SDMT, Symbol Digit Modalities Test; JLO, Judgement of Line Orientation; HVLT-R, Hopkins Verbal Learning Test-Revised; SUVR, standardize uptake value ratio. Significant values corrected for multiple comparisons (false discovery rate) are in bold type.

regions (i.e., frontal, posterior cingulate, temporal, parietal and occipital) crucial for attentional processing.

These results are in line with functional neuroimaging studies showing activation of these cortical regions during performance of an adapted version of SDMT in healthy control [40], pointing to involvement of attentional network areas. Our findings are also consistent with another CSF and magnetic resonance imaging (MRI) study of the PPMI dataset. Those authors showed that domains outside episodic memory can be modulated by amyloidosis. In particular, they found reduced SDMT scores in cerebral amyloid positive drug-naïve PD patients with disproportioned frontal cortex atrophies rather than the more common AD pattern [15]. As at similar stage of disease, it is possible comparable cognitive findings in our PDAβ+ group, may be the results of analagous vulnerable structural brain pattern. Namely early and more severe gray matter frontal degeneration can be caused by additional amyloid presence in regions with early Lewy body pathology [41]. Further neuroimaging studies on similar samples are required to empirically evaluate this speculation.

Notably, the observation of attention-executive deficits in both unmedicated [15] and in our dopaminergic treated PDAβ+ patients reinforces the notion of synergistic effect of amyloid burden and synuclein on PD cognitive profile, already at early disease stage.

In this line, SDMT and MoCA scale should be considered suitable instruments to identify amyloid-modulated cognitive features, in established synucleinopathy. Moreover, as such cognitive tools can be easily administered they may be considered also for population screening.

Importantly, we found a similar proportion of PD with elevated amyloid uptake as in the general control population assessed by PET imaging [33], suggesting that PD by itself does not confer a specific risk of increased amyloid deposition. In particular, presence of amyloid positivity without cognitive impairment in individuals between 65 to 70 years of age is approximately one-third, and increased to 41.3% in those aged 80 to 90 years [33, 42]. Indeed, in individuals with mild cognitive impairment with specific MRI changes suggestive of AD neurodegenerative process, there is a 3-fold higher risk to develop dementia between ages 65 and 85 compared to negative healthy controls, while additional presence of amyloid increases this up to 9-fold [32]. Finally, a recent PET study demonstrated similar patterns of cortical Aβ and tau in people with PD and healthy

older adults [19], further emphasizing the role of synuclein in PD cognitive deterioration.

In addition, these results with [^{18}F]florbetaben PET imaging, are in line with other studies in PD showing similar rate of amyloid positivity (15–21%) (i.e., PIB or CSF A$\beta_{1\text{-}42}$) [15, 19, 43], suggesting high correspondence in the detection of amyloid positivity also using different approaches. However, evidence is heterogeneous most likely due to differences in methodology applied (i.e., PIB imaging and image processing protocols, different type of ligands used), and epidemiological factors (i.e., age distribution, severity of disease, degree of cognitive impairment) [18].

Another important observation was the finding of significant differences between PDAβ+ and PDAβ– only in A$\beta_{1\text{-}42}$ tau ratio (p-tau and T-tau), but not for CSF A$\beta_{1\text{-}42}$ alone. The superiority of tau/A$\beta_{1\text{-}42}$ over A$\beta_{1\text{-}42}$ alone possibly reflects the synergistic effect of tau and amyloid neurodegenerative process, which were combined into a single diagnostic biomarker [44, 45]. This is aligned with recent evidence from a neuropathology study demonstrating that CSF T-tau/A$\beta_{1\text{-}42}$ ratio had 100% specificity and 90% sensitivity in identifying presence of concomitant amyloid and synuclein pathology [34]. Hence, this evidence strongly confirms that our PDAβ+ sample has elevated cerebral amyloid and synuclein pathology. We also found the mean CSF values obtained with the fully automated immunoassay were in agreement with the previously published cut-offs for AD [45].

Finally, in our study, presence of significant amyloid deposits did not affect MDS-UPDRS motor score nor motor manifestations (PIGD versus TD) supporting recent findings showing that, among CSF neurodegenerative markers, only lower concentration of α-synuclein distinguishes patients with PIGD from TD motor phenotype [38]. However, other studies reported conflicting results possibly due to different methodology including type of ligand or PIGD criteria adopted [46].

There are some caveats to consider in our results. First, the total number of PDAβ+ was smaller than PDABβ–, which may have resulted in statistically underpowered results. Second, PPMI PET data were analyzed only by SUVR rather than with more sophisticated quantification methods [47]. Third, PET-amyloid and CSF measures were not concomitantly collected (up to 2.5 years of difference), although previous evidence in AD reported that CSF is a relatively stable biomarker and does not change significantly over time [48]. Further, we could not confirm presence of a recently reported positive association between APOE ε4 allele and [^{18}F]florbetapir binding because APOE status in our PPMI cohort was only available for 24 patients [49]. Finally, in our study it was not possible to evaluate the extent of Lewy body pathology contributing to cognitive decline, and thus it is impossible to establish the pathological mechanisms of early cognitive decline in PD.

Overall, our findings are consistent with a PD progression model, wherein amyloid burden represents a vulnerability factor to neuronal degeneration and cognitive impairment, possibly by impacting on brain structural and functional connectivity [50]. Results of our study further emphasize the concept that amyloid and synuclein coexistence contributes to a more severe form of disease than presence of each individual proteinopathy alone, possibly resulting in higher risk of dementia in PD compared with age-matched healthy controls. If these data will be confirmed by further longitudinal studies, identifying amyloid positive PD, who will probably convert to dementia, it could help to implement more efficacious cognitive stimulation treatments in selected at risk subjects [51, 52]. Indeed, targeting early amyloid depositions may represent a valuable strategy to slow cognitive decline in PD who are at higher risk for concomitant AD dementia.

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