Apathy rating scores and β -amyloidopathy in patients with Parkinson disease at risk for cognitive decline

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Neurology® 2020;94:e376-e383. doi:10.1212/WNL.00000000000008683

Abstract

Objective

To determine whether β -amyloidopathy correlates with apathy rating scores independently of mood changes and other neurodegenerative processes in Parkinson disease (PD).

Methods

In this cross-sectional study, patients with PD ($n = 64$, 48 male and 16 female, mean age 69.2 ± 6.7 years, Hoehn & Yahr stage 2.7 ± 0.5 , Montreal Cognitive Assessment score 25.3 ± 3.0) underwent [^{11}C]Pittsburgh compound B β -amyloid, [^{11}C]dihydrotetrabenazine vesicular monoamine transporter type 2 (VMAT2), and [^{11}C]methyl 4 piperidinypropionate acetylcholinesterase brain PET imaging and clinical assessments, including the Marin Apathy Evaluation Scale, Clinician Version. Patients were recruited on the basis of having at least 1 risk factor for PD dementia, but they were excluded if they had dementia.

Results

Mean apathy rating score was 25.4 ± 6.4 , reflecting predominantly subclinical apathy. Apathy rating scale scores correlated with amyloid binding, cognitive, depressive, and anxiety scores but not significantly with age, duration of disease, striatal VMAT2, or cholinergic binding. Multiple regression analysis model ($p < 0.0001$) showed significant regressor effects for global β -amyloid burden ($p = 0.0038$) with significant covariate effects for global cognitive z scores ($p = 0.028$) and for anxiety ($p = 0.038$) but not with depressive scores. Voxel-based analysis showed robust correlation between apathy rating scale scores and β -amyloid binding in bilateral nuclei accumbens, inferior frontal, and cingulate cortices (family-wise error rate-corrected $p < 0.005$).

Conclusion

Apathy is independently associated with β -amyloidopathy in patients with PD at risk of dementia. Regional brain findings are most robust for β -amyloidopathy in the nuclei accumbens, inferior frontal, and cingulate regions. Findings may provide an explanation for the often treatment-refractory nature of apathy in advancing PD despite optimized dopaminergic and antidepressant pharmacotherapy.

ClinicalTrials.gov identifier:

NCT01565473.

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Go to [Neurology.org/N](https://www.neurology.org/N) for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

AD = Alzheimer disease; **CI** = confidence interval; **DTBZ** = dihydrotetabenazine; **DVR** = distribution volume ratio; **FWE** = family-wise error rate; **PD** = Parkinson disease; **PiB** = Pittsburgh compound B; **PMP** = methyl 4 piperidinyl propionate; **VMAT2** = vesicular monoamine transporter type 2.

Apathy, or lack of motivation in completing goal-oriented activities, commonly occurs among patients with Parkinson disease (PD), with reported prevalence rates ranging from 23% to 70%.¹ Apathy negatively affects quality of life and, in turn, increases caregiver burden and adds to overall disability.^{1,2} Apathy is distinct from depression and anhedonia and is thought to be due in large part to mesolimbic dopaminergic denervation and reduced integrity of associated prefrontal cortex network connections in PD.^{2,3}

A recent meta-analysis showed that apathy is associated with older age, lower mean cognitive score, increased risk of comorbid depression, higher parkinsonian motor score, and more severe disability in PD.^{1,3,4} Although there is a clear dopaminergic contribution to the apathy syndrome of PD, there is also evidence that other pathophysiologies may play a role. Apathy is common not only in PD but also in other neurodegenerative disorders such as Alzheimer disease (AD) that generally lack nigrostriatal degeneration.^{5,6} This observation suggests that Alzheimer-type neuropathology such as amyloidopathy may also be a determinant of apathy.² This notion is supported by in vivo PET imaging studies showing that patients with AD and apathy have higher cortical β -amyloid levels compared to those without apathy.⁷ Similar findings of increased cortical amyloidopathy and apathy are reported in patients with mild cognitive impairment.⁸ Amyloidopathy may also occur in PD and has been associated with worsening of cognitive impairment and dementia.⁹ It is possible that more severe amyloidopathy in PD may be associated with apathy in PD, at least in the subset of patients at higher risk of dementia. The objective of this study was to test the hypothesis that amyloidopathy is associated with apathy independently of mood disturbances, cognition, and other neurodegenerative pathologies in PD. We also assessed whether such hypothesized association may localize to amyloid plaque deposition in specific brain regions.

Methods

Patients

This was a cross-sectional study conducted from 2007 to 2013 in an academic movement disorder clinic setting. Patients of either sex were invited to enroll and provide written informed consent if they met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.¹⁰ Study inclusion was also based on the presence of at least 1 of the following risk factors for PD dementia: older age, subjective cognitive complaints, mild cognitive impairment, and imbalance.^{11–13} Patients were excluded if they showed no signs of nigrostriatal denervation on vesicular monoamine transporter type 2 (VMAT2) PET

imaging or if they were on anticholinergic or cholinesterase inhibitor drugs. Other exclusion criteria included evidence of a stroke in a clinically relevant area (i.e., cerebral cortex, basal ganglia, thalamus) or mass lesion on MRI, contraindication for MRI, severe claustrophobia, previous participation in research procedures involving ionizing radiation, or positive pregnancy test or breastfeeding in women.

The Movement Disorder Society–revised Unified Parkinson Disease Rating Scale was assessed in the practically defined “off” state (i.e., the examination was performed in the morning after overnight withholding of dopaminergic medication).¹⁴

The Apathy Evaluation Scale clinician version was used to assess apathy severity.¹⁵ The Apathy Evaluation Scale has been validated in PD.¹⁶ The Beck Depression Inventory II was used to rate depressive symptoms,¹⁷ and the Spielberger¹⁸ State Trait Anxiety Inventory was used to rate trait anxiety.

Each participant underwent a detailed cognitive examination (while on dopaminergic medications) following the approach previously reported for cognitive impairment in PD.¹⁹ These tests included measures of verbal memory with the California Verbal Learning Test²⁰; executive/reasoning functions with the Wechsler Adult Intelligence Scale III Picture Arrangement test²¹ and Delis Kaplan Executive Function System Sorting Test²²; attention/psychomotor speed as absolute time on the Stroop naming test²³; and visuospatial function with the Benton Judgment of Line Orientation test.²⁴ A *z* score for every individual on every test was calculated on the basis of a dataset of a healthy elderly control group of similar age, sex, and educational level distribution. A *z* score for each cognitive domain was obtained by averaging all *z* scores on the tests or subtasks. A global cognitive *Z* score was computed as the average of all different domains. Details of the cognitive test scores in the patients and control persons can be found in table 1. After completion of detailed neuropsychological testing and assessment of functional abilities, 4 patients met criteria for mild dementia on the basis of abnormal cognitive test scores and impaired instrumental activities of daily living.^{25–27}

Cognitive and motor correlates of β -amyloidopathy of subsets of the patients from the present study have been reported previously.^{28–31}

Standard protocol approvals, registrations, and patient consents

This study (ClinicalTrials.gov identifier: NCT01565473) was approved by and study procedures were followed in accordance

Table 1 Demographic and cognitive characteristics of normal control vs participants with PD

	Normal controls (n = 46)	PD (n = 64)	<i>t</i> / χ^2 Value	<i>p</i> Value
Sex (M/F), n (%)	34/12 (73.9/26.1)	48/16 (75/25)	$\chi^2 = 0.03$	0.86
Age, y	69.2 ± 7.9	69.2 ± 6.7	<i>t</i> = 0.1	0.92
Education, y	15.5 ± 2.1	14.7 ± 2.9	<i>t</i> = 1.5	0.14
Montreal Cognitive Assessment score	26.4 ± 2.6 (n = 36)	25.3 ± 3.0	<i>t</i> = 20	0.048
Stroop naming score, s	50.0 ± 10.1	60.7 ± 16.5	<i>t</i> _{approx} = 4.3	<0.0001
Judgment of Line Orientation test score, total correct	24.2 ± 5.0	20.9 ± 5.7	<i>t</i> = 3.2	0.0017
Delis Kaplan Sorting test 1 score, total correct	18.0 ± 3.9	15.4 ± 5.8	<i>t</i> _{approx} = 2.8	0.006
Delis Kaplan Sorting test 2 score, total correct	19.2 ± 5.0	16.2 ± 5.1	<i>t</i> = 2.8	0.006
Wechsler Adult Intelligence Scales Picture Arrangement test score, total correct	13.7 ± 4.5	10.2 ± 5.1	<i>t</i> = 3.7	0.0004
California Verbal Learning test, immediate memory recall score, total correct	8.9 ± 1.7	7.9 ± 5.1	<i>t</i> = 2.7	0.008
California Verbal Learning test, short-term memory recall score, total correct	9.1 ± 2.7	7.7 ± 3.3	<i>t</i> = 2.3	0.027
California Verbal Learning test, delayed memory recall score, total correct	9.5 ± 3.0	8.5 ± 3.6	<i>t</i> = 1.5	0.13

Abbreviations: PD = Parkinson disease; *t*_{approx} = Satterthwaite approximated *t* value.

with the ethical standards of the Institutional Review Board of the University of Michigan. Written informed consent was obtained before any study procedures from all patients.

Imaging techniques

MRI was performed on a 3T Philips Achieva system (Philips, Best, the Netherlands), and PET imaging was performed in 3D imaging mode with an ECAT Exact HR+ tomograph (Siemens Molecular Imaging, Inc, Knoxville, TN), as previously reported.³²

[¹¹C]Pittsburgh compound B (PiB) β -amyloid, [¹¹C]dihydro-tetabenazine (DTBZ) VMAT2, and [¹¹C]methyl 4 piperidyl propionate (PMP) acetylcholinesterase were prepared as described previously.^{33,34} Bolus/infusion protocols were used for [¹¹C]DTBZ (15 mCi) in 60 minutes and for [¹¹C]PiB (18 mCi) in 70 minutes.³⁵ Dynamic PET scanning was performed for 70 minutes with a bolus dose of 15 mCi [¹¹C]PMP. [¹¹C]PMP PET scans were not available in 2 patients.

Image analysis

Imaging registration and volume-of-interest definition were performed as previously reported.³² MRI-based partial volume correction was performed.³⁶ Cortical acetylcholinesterase [¹¹C]PMP hydrolysis rates (*k*₃) were estimated with the striatal volume as the tissue reference.³⁷

[¹¹C]PiB and [¹¹C]DTBZ distribution volume ratios (DVRs) were estimated with the Logan plot graphical analysis method using cerebellar cortical and supratentorial cortical reference

tissues, respectively.³⁸ Striatal [¹¹C]DTBZ, striatal [¹¹C]PiB, and global cortical [¹¹C]PiB DVRs were calculated. We computed percentage scores of cortical and striatal PiB DVRs using the mean PiB DVR from healthy middle-aged controls and summed the cortical and striatal PiB DVR percentage scores to derive a global brain PiB DVR measure, as previously reported.³¹

Data analysis: Global β -amyloid burden analysis

Bivariate Pearson correlation coefficients were computed for the relationship between apathy rating scores and the clinical, cognitive, neurobehavioral, motor, and global β -amyloid burden and other PET imaging variables. Multivariable linear regression analysis was then used to evaluate the association between global brain β -amyloidopathy and apathy while accounting for confounder variables that were significantly associated with apathy rating scale score in the bivariate correlation analysis.

Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Regional brain voxel-based β -amyloid analysis

Voxel-based [¹¹C]PiB PET analyses were performed to explore regional cerebral β -amyloid binding correlates of apathy rating scale scores. With the use of statistical parametric mapping software (SPM12, Wellcome Department of Cognitive Neurology, London, UK), whole-brain voxel-based correlation was analyzed to assess the relationship between DVRs and apathy rating scores. The same confounder variables as in the volume of interest–based multiple regression

model were used for the voxel-based model. The results were considered statistical significant at the peak level threshold $p < 0.001$ and corrected for multiple comparisons on the voxel level (family-wise error-corrected $p < 0.005$), in conjunction with a cluster threshold of 20 voxels. The significant clusters were overlaid with MRICroGL (mccauslandcenter.sc.edu/mricrogl/) onto the PiB PET template derived as a mean of images of all patients.

Data availability

Anonymized data will be shared by request from any qualified investigator.

Results

This study involved 64 patients with PD (48 male, 16 female) with a mean age of 69.2 ± 6.7 years and mean duration of motor disease of 6.7 ± 4.8 years. Patients with PD met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria.¹⁰ All but 1 of the patients were on dopaminergic drugs; none were on anticholinergic or cholinergic drugs. Twenty-four patients were taking a combination of dopamine agonist and carbidopa levodopa medications; 29 were using carbidopa levodopa alone; and 10 were taking a dopamine agonist alone. Mean levodopa equivalent dose was 713 ± 571 mg.³⁹ Most patients had moderate severity of disease: 2 patients were in modified Hoehn and Yahr stage 1.5, 7 were in stage 2, 27 were in stage 2.5, 25 were in stage 3, and 3 were in stage 4.⁴⁰ The mean Movement Disorder Society–revised Unified Parkinson Disease Rating Scale part III motor score was 36.5 ± 14.4 . The mean Montreal Cognitive Assessment test score was 25.3 ± 3.0 .⁴¹

Table 2 provides a summary of the clinical, cognitive, neurobehavioral, and PET imaging findings. Mean apathy rating score was 25.4 ± 6.4 , reflecting predominantly subclinical apathy in the study population. Table 2 also lists the frequency of risk factors for PD dementia, including presence of subjective cognitive complaints, presence of mild cognitive impairment, older age, and presence of postural instability and gait difficulties motor features. All participants had at least 1 of these risk factors.

Clinical and imaging correlates of apathy rating scale scores

Bivariate correlation coefficients between apathy rating scores and the cognitive, neurobehavioral, motor, and PET imaging variables are shown in table 3. Higher ratings of apathy scores correlated with greater cognitive deficits, higher depression scores, anxiety ratings, and more severe global β -amyloid burden.

Multivariate confounder analysis of main voxel of interest-based cortical β -amyloid PET analysis

Multiple regression analysis using the apathy rating scale score as the outcome parameter was then used to evaluate the

Table 2 Summary of demographic, clinical, cognitive risk factors and cognitive, neurobehavioral, motor, and PET imaging findings (n = 64)

	Mean value (SD)
Age, y	69.2 $\pm$ 6.7
Age ≥ 70 y, n (%)	16 (25)
Education, y	14.7 $\pm$ 2.9
Duration of disease, y	6.7 $\pm$ 4.8
Subjective cognitive complaints (MDS UPDRS, part I, item 1.1), n (%)	29 (45.3)
Montreal Cognitive Assessment score	25.3 $\pm$ 3.0
Mild cognitive impairment (MDS Task Force guidelines level I assessment, ²⁵ Montreal Cognitive Assessment score < 26), n (%)	31 (48.4)
Global cognitive z score	-1.0 $\pm$ 1.1
Mild cognitive impairment (MDS level II assessment ²⁵), n (%)	37 (57.8)
Hallucinations/Psychosis (MDS UPDRS, part I, item 1.2), n (%)	6 (9.4)
LED, mg	713 $\pm$ 571
Apathy Evaluation Scale score	25.4 $\pm$ 6.4
Beck Depression Inventory score	8.5 $\pm$ 6.0
Spielberger Trait Anxiety Inventory score	34.2 $\pm$ 9.5
MDS UPDRS part III (motor) score	36.5 $\pm$ 14.4
Observed "off"-state freezing of gait, n (%)	11 (17.2)
Hoehn & Yahr stage	2.7 $\pm$ 0.5
Imbalance (Hoehn & Yahr stage ≥ 2.5), n (%)	66 (86.0)
History of falls, n (%)	30 (47.9)
Cortical [¹¹ C]PiB β -amyloid DVR	1.19 $\pm$ 0.18
Striatal [¹¹ C]PiB β -amyloid DVR	1.40 $\pm$ 0.24
Cortical [¹¹ C]PMP acetylcholinesterase hydrolysis rate (n = 61)	0.0231 $\pm$ 0.003
Striatal [¹¹ C]DTBZ VMAT2 DVR	1.93 $\pm$ 0.31

Abbreviations: DTBZ = dihydrotetrabenazine; DVR = distribution volume ratio; LED = levodopa equivalent dose; MDS = Movement Disorder Society; MDS UPDRS = Movement Disorder Society Revised Unified Parkinson's Disease Rating Scale; PiB = Pittsburgh compound B; PMP = methyl 4 piperidyl propionate; VMAT2 = vesicular monoamine transporter type 2.

specificity of the association between apathy rating scores (dependent variable) and global brain β -amyloidopathy burden while accounting for confounder variables (independent variables). The significant confounder variables that were used simultaneously for the model were global cognitive z score, Beck Depression Inventory score, and Spielberger Trait Anxiety score, as shown in table 3. Regression diagnostics, including tests of homogeneity of variance, multicollinearity testing, and normality of residuals,

Table 3 Bivariate correlation coefficients between apathy rating scores and cognitive, neurobehavioral, motor, and PET imaging variables (n = 64)

	Apathy rating, bivariate correlation coefficients (95% confidence interval)
Age	$R = 0.009$ (0.24–0.25; $p = 0.95$)
Duration of disease	$R = 0.07$ (0.31–0.18; $p = 0.58$)
Global cognitive z score	$R = 0.39$ (0.57–0.15; $p = 0.002$) ^a
Beck Depression Inventory score	$R = 0.46$ (0.24–0.63; $p = 0.0001$) ^a
Spielberger Trait Anxiety Inventory score	$R = 0.54$ (0.34–0.69; $p < 0.0001$) ^a
Hoehn & Yahr stage	$R_s = 0.21$ (0.0–0.46; $p = 0.10$)
MDS UPDRS part III (motor) score	$R = 0.24$ (0.0–0.46; $p = 0.049$)
LED	$R = 0.01$ (0.26–0.23; $p = 0.92$)
Global brain [¹¹ C]PiB β -amyloid burden measure	$R = 0.37$ (0.14–0.56; $p = 0.0026$) ^a
Cortical [¹¹ C]PMP acetylcholinesterase hydrolysis rate (n = 61)	$R = 0.12$ (0.36–0.13; $p = 0.34$)
Striatal [¹¹ C]DTBZ VMAT2 DVR	$R = 0.19$ (0.42–0.06; $p = 0.13$)

Abbreviations: DTBZ = dihydrotetrabenazine; DVR = distribution volume ratio; LED = levodopa equivalent dose; MDS UPDRS = Movement Disorders Society Revised Unified Parkinson's Disease Rating Scale; PiB = Pittsburgh compound B; PMP = methyl 4 piperidinyl propionate; R_s = Spearman rank correlation coefficient; VMAT2 = vesicular monoamine transporter type 2.
^a Significant after Holm-Bonferroni correction.

were performed and model assumptions were met. The analysis showed a significant model ($F_{4,59} = 13.0$, $p < 0.0001$) with significant regressor effects for global β -amyloid burden (standardized $\beta = 0.30$, 95% confidence interval [CI] 0.05–0.23, $t = 3.0$, $p = 0.0038$) with significant covariate effects for global cognitive z score ($\beta = 0.23$, 95% CI 2.6–0.2, $t = 2.3$, $p = 0.028$), and anxiety ratings ($\beta = 0.31$, 95% CI 0.01–0.41, $t = 2.1$, $p = 0.038$).

Regional brain voxel-based β -amyloid PET analysis

Voxel-based regression analysis was performed with apathy rating scale scores as the dependent parameter and β -amyloid binding as the independent parameter while adjusting for the same confounding variables used in the voxel of interest-based model (i.e., global cognitive z score, Beck Depression Inventory score, and Spielberger Trait Anxiety score). The voxel-based analysis showed regionally significant correlations between the apathy rating scale scores and amyloid binding in the bilateral frontal (especially the orbitofrontal cortices and gyri rectus), cingulate (anterior and posterior) cortices, and nuclei accumbens regions (family-wise error-corrected $p < 0.005$). Additional involved areas included bilateral insular cortices and lateral temporal and parietal regions (figure and table 4).

Discussion

Our analyses suggest that cerebral amyloidopathy, notably in limbostriatal, limbofrontal, and cingulate regions, is a strong correlate of apathy ratings in PD. Because dopaminergic losses are already prominent in early PD, progressive apathy with worsening disease may be driven by nondopaminergic mechanisms in PD. These mechanisms may also contribute to cognitive decline. Our multivariate analysis shows that amyloidopathy is independently associated with apathy ratings even after accounting for confounders, including cognitive, depression, and anxiety rating scores. These observations support the hypothesis that apathy, cognitive, and mood disturbances are partially distinct disorders.⁴² Our findings showed an independent regressor effect for cognitive functions in the statistical model. Although apathy can occur independently of cognitive impairment, overlap is common.⁴³ The partial overlap between apathy and cognition may relate to our observation that apathy ratings are associated with posterior cingulum amyloidopathy. Similarly, a voxel-based MRI morphometry study found evidence of atrophy in the posterior cingulum in patients with PD with apathy.⁴⁴ We also observed independent regressor effects between the anxiety trait rating and apathy rating scale scores. The instruction for the trait anxiety scale was based on a more general assessment of how somebody feels, and this may likely reflect a component of more recent state-dependent anxiety ratings. Future research is needed to disentangle the complex interrelationships among apathy and cognitive and mood disturbances in PD in appropriately powered study samples.

We did not observe an association between striatal VMAT2 changes and apathy in our study. Our PD population was selected on the basis of an increased risk of dementia, i.e., older age, imbalance, and cognitive complaints. The relatively more advanced stage of PD in our study population may result in a dopaminergic denervation “floor” effect, thereby attenuating possible statistical associations. In contrast, other studies in drug-naïve patients with early-stage PD have shown cumulative evidence for anteroventral striatal and extrastriatal dopaminergic changes associated with apathy.² This correlates to findings in MPTP-lesioned monkeys in which postlesioning apathetic behavior was associated with extrastriatal dopaminergic changes in the ventral tegmental area insular cortical pathways.⁴⁵

Using PiB PET and voxel-based whole-brain analysis, we performed an exploratory analysis on the regional brain correlation between β -amyloid deposition and the severity of apathy in PD. The results showed that β -amyloid deposition had significant positive correlation with apathy scores in the predominant limbic striatal and limbofrontal regions. It has been suggested that dysfunction of reward-related circuits that connect the orbitofrontal cortex, ventromedial prefrontal cortex, anterior cingulum, and nucleus accumbens may contribute to the presence of apathy in PD.² A relationship between apathy and β -amyloid deposition in regions of bilateral

Figure Significant clusters of positive correlation between regional β -amyloid deposition and apathy rating scores (covaried for cognitive, depression, and trait anxiety rating) depicted in fire color

The most prominent findings localized to the bilateral frontal (especially orbitofrontal and gyrus rectus) and cingulate (anterior and posterior) cortices and nuclei accumbens regions (family-wise error-corrected $p < 0.005$). Additional involved areas included bilateral insular cortices and lateral temporal regions.

frontal, temporal, and right anterior cingulum has also been reported in patients with AD.⁷ This cortical deposition pattern is consistent with our findings, implicating a possible common neural pathway for apathy in both PD and AD, at least in advancing disease stages. In addition to cortical regions, we found an association of amyloidopathy with apathy in the bilateral nuclei accumbens. The results of this granular analysis are consistent with prior work associating anteroventral striatal changes with apathy. The ventral striatum is a key node in motivated behavior, and there are several possible explanations for the effects of β -amyloid deposition in this region. Using [^{11}C]DASB PET to image serotonin transporters, a recent study showed that apathetic patients with PD had greater serotonergic terminal reductions in the ventral striatum.⁴⁶ Our previous research showed evidence of an inverse relationship between amyloidopathy and loss of

serotonin nerve terminals in PD, especially in the striatum.⁴⁷ Therefore, some β -amyloid deposition effects on apathy might be mediated by local serotonergic deficits.

In addition to the frontostriatal circuits commonly associated with apathy, our study found significant β -amyloidopathy in other regions, including the temporal and insular cortices. Similar cortical changes extending beyond the frontostriatal circuits have been observed in structural whole-brain MRI morphometric studies.^{44,48}

Coincident AD pathology is regionally associated with increased Lewy body pathology in PD, indicating an interactive effect between these 2 proteinopathies.⁴⁹ A possible interactive vs common driver effect is also supported by a postmortem study showing that the *APOE* $\epsilon 4$ genotype is

Table 4 Significant clusters from whole-brain voxel-based β -amyloid PET analysis (covaried for global cognitive, depression, and trait anxiety scores)

Cluster (voxels, p value) >50	Peak MNI coordinates, z value, t value	Peak BA voxel location
11,362, $p < 0.001$	[2, 26, -18], $z = 7.32$, $t = 9.63$	Right BA11
2,896, $p < 0.001$	[4, -36, 34], $z > 8$, $t = 11.07$	Right BA23
2,387, $p < 0.001$	[62, -22, -12], $z = 6.90$, $t = 8.81$	Right BA21
886, $p < 0.001$	[-54, -10, -10], $z = 6.90$, $t = 8.80$	Left BA22
242, $p < 0.001$	[-46, -70, 2], $z = 6.54$, $t = 8.12$	Left BA19
117, $p < 0.001$	[-48, -26, 38], $z = 6.50$, $t = 8.05$	Left-BA40
71, $p < 0.001$	[-20, 18, 56], $z = 6.37$, $t = 7.83$	Left BA6
66, $p < 0.001$	[54, -22, 36], $z = 6.98$, $t = 8.95$	Right BA40
211, $p < 0.001$	[12, 14, -6], $z = 6.30$, $t = 7.71$	Right accumbens
100, $p < 0.001$	[54, -14, 16], $z = 6.10$, $t = 7.37$	Right BA40
126, $p < 0.001$	[-40, -10, -2], $z = 6.08$, $t = 7.32$	Left Insula
78, $p < 0.001$	[-46, -40, -22], $z = 6.05$, $t = 7.28$	Left BA37
81, $p < 0.001$	[-6, 18, 38], $z = 6.04$, $t = 7.27$	Left BA32
114, $p < 0.001$	[32, -62, 48], $z = 5.95$, $t = 7.12$	Right BA39
56, $p < 0.001$	[34, 22, -4], $z = 5.67$, $t = 6.66$	Right Insula

Abbreviations: BA = Brodmann area; MNI = Montreal Neurological Institute. Most prominent findings are localized to the bilateral frontal (especially orbitofrontal and gyrus rectus) and cingulate (anterior and posterior) cortices and nuclei accumbens regions (family-wise error-corrected, $p < 0.005$). Additional involved areas included bilateral insular cortices, lateral temporal, and parietal regions. Family wise error-corrected p values are presented.

independently associated with a greater severity of Lewy body pathology independently of Alzheimer pathology in patients with Lewy body disorders.⁵⁰ It is possible that the increased PiB PET binding signal in our study may preferentially reflect sites of parallel occurrence of regional proteinopathies, including Lewy body pathology, rather than exclusively representing amyloid plaques per se.

A limitation of our study was that it did not include patients with more severe apathy. This is likely due to selection bias because patients with significant dementia were not eligible for the study. Another selection bias may be that patients with more severe apathy may be less motivated to volunteer for a multimodal imaging research study. Therefore, the average apathy rating scale scores in this study reflect a PD population with subclinical or borderline apathy ratings.

Our findings may explain the relatively greater severity of apathy in patients with dementia with Lewy bodies, who tend to have greater deposition of β -amyloid plaques compared to patients with PD or PD with dementia.⁹ Our study, however,

was limited by the exclusion of patients with dementia with Lewy bodies to confirm this hypothesized correlation. Nevertheless, these data reveal an association between amyloidopathy and apathy ratings that is independent of cognition, depression, and anxiety. This has implications for amyloid-based therapeutic strategies in alleviating not only cognitive but also apathetic aspects of PD. These results may also provide an explanation for the often treatment-refractory nature of apathy in advancing PD despite optimized dopaminergic or antidepressant pharmacotherapy.

Study funding

This work was supported by the Department of Veterans Affairs (I01 RX000317), the Michael J. Fox Foundation, and the NIH (grants P01 NS015655, P50 NS091856, and R01 NS070856).

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Publication history

Received by *Neurology* January 17, 2019. Accepted in final form July 19, 2019.

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Prabesh Kanel, PhD	University of Michigan, Ann Arbor	Co-investigator	Analysis and interpretation; critical revision of the manuscript for important intellectual content
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Appendix (continued)

Name	Location	Role	Contribution
Kirk A. Frey, MD, PhD	University of Michigan, Ann Arbor, MI	Principal investigator	Obtained funding; study supervision; critical revision of the manuscript for important intellectual content
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