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Striatal and cortical β-amyloidopathy and cognition in Parkinson disease

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Abstract

Background—Although most prior cognitive studies of β-amyloidopathy in Parkinson disease (PD) focused on cortical plaque deposition, recent post-mortem studies point to an important role of striatal β-amyloid plaque deposition.

Objective—To investigate the relative contributions of striatal and cortical β-amyloidopathy to cognitive impairment in PD.

Methods—Patients with PD (n=62; age 68.9±6.4 years, Hoehn and Yahr stage 2.7±0.5, Montreal Cognitive Assessment score 25.2±3.0) underwent [^{11}C]Pittsburgh compound B β-amyloid, [^{11}C]dihydrotetrabenazine monoaminergic and [^{11}C]methyl-4-piperidinyl propionate acetylcholinesterase brain positron emission tomography imaging and neuropsychological assessment. [^{11}C]Pittsburgh compound B β-amyloid data from young to middle-aged healthy subjects were used to define elevated [^{11}C]Pittsburgh compound B binding in the patients.

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Results—Elevated cortical and striatal β-amyloid deposition were present in 38% and 16%, respectively, of this predominantly non-demented cohort of patients with PD. Increased striatal β-amyloid deposition occurred in half of all subjects with increased cortical β-amyloid deposition. In contrast, increased striatal β-amyloid deposition did not occur in the absence of increased cortical β-amyloid deposition. Analysis of covariance using global composite cognitive z-scores as the outcome parameter showed significant regressor effects for combined striatal and cortical β-amyloidopathy (F=4.18, P=0.02) after adjusting for covariate effects of cortical cholinergic activity (F=5.67, P=0.02), caudate nucleus monoaminergic binding, duration of disease and age (total model: F=3.55, P=0.0048). Post-hoc analysis showed significantly lower cognitive z-score for combined striatal and cortical β-amyloidopathy compared to cortical-only β-amyloidopathy and non-β-amyloidopathy subgroups.

Conclusions—The combined presence of striatal and cortical β-amyloidopathy is associated with greater cognitive impairment than cortical β-amyloidopathy alone in PD.

Keywords

Acetylcholinesterase; β-amyloid; cognitive impairment; cortex; dopamine; Parkinson disease; PET; striatum

Introduction

Proteinopathic degeneration of important subcortical projection systems, including nigrostriatal dopaminergic and corticopetal cholinergic projections, limbic and cortical pathology associated with α-synuclein deposits (Lewy bodies and Lewy neurites; α–synucleinopathy), and Alzheimer fibrillary β-amyloid plaque deposition (β-amyloidopathy) likely contribute to cognitive decline in Parkinson disease (PD) [1, 2]. Information on the relative frequencies of different proteinopathies in PD comes mainly from post-mortem studies. One recent large post-mortem series of PD dementia (PDD) subjects, for example, reports "pure" or exclusive Lewy body pathology in 38%, combined Lewy body pathology and β-amyloid plaques in 59%, and combined Lewy bodies, β-amyloid plaques and neurofibrillary tangles in 3% [3].

Most *in vivo* imaging and post-mortem neuropathological studies of comorbid β-amyloidopathy in relationship to cognitive functions in PD focused on cortical plaque deposition. We previously reported, for example, a significant relationship between *in vivo* measures of elevated cortical β-amyloid deposition and greater cognitive impairment in PD [4]. Recent neuropathological studies, however, point to an important role for striatal β-amyloidopathy in the development of cognitive impairment in PD [5-7], with evidence indicating that striatal β-amyloid deposition is significantly greater in demented than non-demented PD patients [8]. These post-mortem findings suggest that both cortical and also striatal β-amyloidopathy in PD have pathophysiological impact in PD. Using *in vivo* β-amyloid PET imaging, we investigated the relative respective contributions of cortical and striatal β-amyloidopathy to cognitive impairment in PD while controlling for the magnitude of cortical cholinergic and nigrostriatal dopaminergic neurodegenerations.

Subjects and Methods

Subjects

This cross-sectional study involved 62 subjects with PD (46 males, 16 females), mean age 68.9±6.4 (range 55-84) and mean duration of motor disease of 6.5±4.7 (range 0.5-20) years. PD subjects met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria [9]. The diagnosis of PD was consistent with the presence of typical nigrostriatal dopaminergic denervation as revealed by [^{11}C]dihydrotetrabenazine (DTBZ) vesicular monoamine type 2 (VMAT2) PET imaging in all subjects. The majority of subjects were on dopaminergic drugs but none were on anti-cholinergic or cholinergic drugs. The mean Hoehn and Yahr (HY) stage was 2.7±0.5 (range 1.5-4.0) [10]. The mean Movement Disorder Society-revised Unified Parkinson Disease Rating Scale (UPDRS) in the practically defined "off" state (i.e., the examination was performed in the morning after overnight withholding of dopaminergic medication) was 36.3±14.3 (range 15-70) [11]. The subjects in this study were recruited based on at least one recognized risk factor for PDD, such as having cognitive complaints, older age, or greater motor symptom severity, but no existing clinical PDD diagnosis. The mean Montreal Cognitive Assessment (MOCA) test score was 25.2±3.0 (range 15-30) [12].

This study was approved by and study procedures were followed in accordance with the ethical standards of the Institutional Review Board of the University of Michigan. Written informed consent was obtained from all subjects.

Each subject underwent a detailed cognitive examination (while on dopaminergic medications) following the approach previously reported for cognitive impairment in PD [13]. These tests included measures of verbal memory: California Verbal Learning Test [14]; executive/reasoning functions: WAIS III Picture Arrangement test [15], and Delis-Kaplan Executive Function System Sort ing Test [16]; attention/psychomotor speed as absolute time on the Stroop 1 test [17]; and visuospatial function: Benton Judgment of Line Orientation test [18]. Composite z-scores were calculated for these different cognitive domains based on normative data from a database of non-PD control subjects with similar age, education and gender distribution as the PD subjects in our center [19]. A global composite z-score was calculated as the mean of the domain z-scores. After completion of detailed neuropsychological testing and assessment of functional abilities three subjects met criteria for mild dementia.

All subjects in this study completed three PET studies: [^{11}C]Pittsburgh compound B (PIB) β-amyloid, [^{11}C]DTBZ monoaminergic, and [^{11}C]methyl-4-piperidinyl propionate (PMP) acetylcholinesterase brain PET. Cognitive and motor (axial motor impairment, including freezing of gait) correlates of cortical (but not striatal) β-amyloidopathy of sub-sets of the subjects from the present study have been reported previously [4, 20, 21]. Furthermore, detailed analyses regarding relative cholinergic and dopaminergic determinants of cognitive impairment in PD from an expanded pooled data set from our center has also been previously reported [22].

Imaging techniques

MRI was performed on a 3 Tesla 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 [19].

[^{11}C]DTBZ, [^{11}C]PMP, and [**^{11}**C]PIB were prepared as described previously [23, 24]. Dynamic PET scanning was performed for 70 minutes using a bolus dose of 15 mCi [^{11}C]PMP dose. Bolus/infusion protocols were used for [^{11}C]DTBZ (15 mCi) in 60 minutes and for [^{11}C]PIB (18 mCi) in 70 minutes [25].

Image Analysis

Imaging registration and volume of interest definition were performed as previously reported [19]. Cortical AChE [^{11}C]PMP hydrolysis rates (k_3) were estimated using the striatal volume as the tissue reference [26].

[^{11}C]PIB and [^{11}C]DTBZ distribution volume ratio (DVR) were estimated using the Logan plot graphical analysis method using cerebellar cortical and supratentorial cortical reference tissues, respectively [27]**.** Caudate nucleus [^{11}C]DTBZ and global cortical and striatal [^{11}C]PIB DVRs were calculated.

Data Analysis

The major aim of the study was to investigate the relative contributions of cortical and striatal β-amyloidopathy to cognitive impairment in PD. We used [^{11}C]PIB β-amyloid data from young to middle-aged healthy subjects (n=11, 5M/6F), mean age 46.7±3.4 (range 40-50 yr) to define elevated [^{11}C]PIB binding in the patients because of age-related progressive β-amyloid deposition in a subset of cognitively normal elderly individuals [28]. The maximum normal range cortical and striatal [^{11}C]PIB DVR seen in our healthy middle-aged control subjects' ratios were 1.17 (mean 1.12±0.04) and 1.50 (mean 1.38±0.06), respectively. PD subjects with values exceeding the maximum thresholds were defined as exhibiting increased regional β-amyloid binding.

Analysis of covariance (ANCOVA) was used to evaluate the effects of the β-amyloidopathy grouping factor on cognitive z-scores while adjusting for cortical AChE hydrolysis rate, caudate nucleus monoaminergic terminal DVR, duration of disease and age covariates. Duncan Multiple Range post-hoc analysis was used to evaluate differences between the β-amyloidopathy subgroups. All analyses were performed using SAS version 9.2, SAS institute (Cary, North Carolina).

Results

Relative frequency of striatal and cortical β-amyloidopathy

Increased striatal and cortical β-amyloid deposition were present in approximately 16% and 38%, respectively, of this predominantly non-demented PD cohort. Increased striatal β-amyloid deposition occurred in half of all subjects with increased cortical β-amyloid

deposition. In contrast, increased striatal β-amyloid deposition did not occur in the absence of increased cortical β-amyloid deposition (Table 1).

The mean cortical β-amyloid PIB DVR in the different amyloidopathy subgroups were as following: Combined cortical and striatal β-amyloidopathy subgroup (n=10; 1.55±0.19), cortical-only β-amyloidopathy subgroup (n=13, 1.22±0.04) and non-β-amyloidopathy subgroup (n=39, 1.09±0.06). Corresponding mean striatal β-amyloid PIB DVR in the different subgroups were as following: Combined cortical and striatal β-amyloidopathy subgroup (1.88±0.20), cortical-only β-amyloidopathy subgroup (1.40±0.06) and non-β-amyloidopathy subgroup (1.29±0.07). Three subjects with mild dementia had cortical and striatal PIB DVR values in the average range of the combined cortical and striatal β-amyloidopathy subgroup.

Table 2 lists the mean clinical variables for each of the subgroups. None of these variables remained significant after correction for type I statistical error inflation. There was a non-significant trend for older age in the patients in the combined striatal and cortical β-amyloidopathy subgroup compared to the non-β-amyloidopathy and the cortical-only β-amyloidopathy subgroups. There was also a non-significant trend toward more severe motor parkinsonism in the combined striatal and cortical β-amyloidopathy subgroup.

Cognitive performance in the different β-amyloidopathy subgroups: combined striatal and cortical versus the cortical-only β-amyloidopathy versus the non-β-amyloidopathy subgroups

ANCOVA using global composite cognitive z-scores as the outcome parameter showed a significant regressor effect for the β-amyloidopathy grouping factor (F=4.18, P=0.02) while adjusting for covariate effects of cortical AChE activity (F=5.67, P=0.02), caudate nucleus monoaminergic terminal binding, duration of disease and age (total model: F=3.55, P=0.0048; Table 3). The model showed that the β-amyloidopathy grouping factor and cortical AChE activity were both independent significant predictors of cognitive impairment in the patients. Duncan Multiple Range post-hoc analysis showed significantly lower global composite cognitive z-scores for the combined striatal and cortical β-amyloidopathy (mean z-score: −1.57, adjusted: −1.52, SD: 0.88, confidence interval, CI: −2.09 to −0.95) compared to cortical-only β-amyloidopathy (mean z-score: −0.53, adjusted: −0.45, SD: 0.79, confidence interval, CI: −0.93 to 0.03) and non-β-amyloidopathy subgroups (mean z-score: −0.81, adjusted: −0.85, SD: 0.95, confidence interval, CI: −1.13 to −0.57); the latter two subgroups were not significantly different from each other (Figure 1).

Post hoc analysis: Cognitive domains

Post hoc analyses were performed to investigate the relationship between the β-amyloidopathy grouping factor and the four individual cognitive domain z-scores (verbal learning, attention, visuospatial and executive functions) while controlling for covariate effects of cortical cholinergic and caudate nucleus monoaminergic terminal densities, duration of disease and age. Significant regressor effects for β-amyloidopathy grouping factor were seen for the verbal learning (F=4.18, P=0.021) and attention (F=3.90, P=0.026) cognitive domain z-scores. Duncan Multiple Range post-hoc analysis showed significantly

lower verbal learning and attention cognitive domain z-scores for the combined striatal and cortical β-amyloidopathy compared to cortical-only β-amyloidopathy and non-β-amyloidopathy subgroups; the latter two were not significantly different from each other. No significant regressor effects for β-amyloidopathy grouping factor were seen for visuospatial or executive function cognitive domain z-scores.

We performed additional linear *post hoc* analysis using β-amyloid PIB DVR binding to complement our β-amyloidopathy subgroup findings. As cortical β-amyloid PIB DVR were higher in the combined cortical and striatal β-amyloidopathy subgroup compared to the other amyloidopathy sub-groups, we evaluated relative cognitive effects of global (i.e., cortical and striatal) versus cortical or striatal β-amyloid plaques using absolute β-amyloid PIB DVR binding values. For this purpose, we computed percentage scores of cortical and striatal PIB DVR based on the mean PIB DVR in the healthy middle-aged control subjects and summed the cortical and striatal PIB DVR percentage scores in order to derive a global PIB DVR measure. Stepwise regression was then used to predict global and cognitive domain scores using the global, cortical and striatal PIB DVR percentage scores together with the cholinergic and dopaminergic PET measures. Results confirmed our subgroup findings and showed that global composite cognitive z-scores were best predicted by cortical AChE ($F=9.42$, $P=0.0032$) and global PIB DVR ($F=4.24$, $P=0.04$; total model $F=7.09$, $P=0.0018$). Verbal learning cognitive domain z-scores were predicted by cortical PIB DVR ($F=9.55$, $P=0.003$) and cortical AChE activity ($F=7.42$, $P=0.008$; total model $F= 9.00$, $P=0.0004$). Attention cognitive domain z-scores were predicted by striatal PIB DVR ($F=4.86$, $P=0.03$) and caudate nucleus dopaminergic activity ($F=4.64$, $P=0.035$; total model $F=5.53$, $P=0.006$). There were no significant predictors for the visuospatial cognitive domain subscores (total model $F=2.34$, $P=0.13$). Executive functions cognitive domain scores were predicted by cortical AChE activity ($F=9.05$, $P=0.0038$; total model $F=6.74$, $P=0.0023$).

Discussion

There are probably at least two major sources of pathogenic proteinopathy in PD; variations within the spectrum of α–synucleinopathy and the effects of additional, probably independent, pathologic processes involving β-amyloid, and less commonly tau deposition. In this study, we assessed the regional effects of β-amyloidopathy in PD. Our data indicate that cortical β-amyloidopathy is present in approximately one third of subjects in this predominantly non-demented cohort. The one-third relative frequency of β-amyloidopathy in our subjects is consistent with the expected occurrence of cerebral β-amyloid deposition in otherwise cognitively normal elders [28], and may be a function of older age in PD [29], or longer duration of disease [29]. As expected, our *in vivo* estimate of the relative frequency of β-amyloidopathy in PD is lower than post-mortem estimates [3]. Post-mortem studies, typically, reflect changes found in end-stage disease and may not represent pathological changes at earlier disease stages with less severe cognitive impairments. The subjects in this study were at risk of development of dementia based on older age, presence of cognitive complaints, or more severe motor disease. Although these factors may put them at higher risk of β-amyloid deposition, the prevalence of β-amyloidopathy of about one in three is still relatively low compared to (approximately) half of post-mortem estimates [3].

Striatal β-amyloidopathy in our cohort, however, was less frequent, approximately one in six PD subjects. Increased striatal β-amyloid deposition occurred in half of all subjects with increased cortical β-amyloid deposition. In contrast, increased striatal β-amyloid deposition did not occur in the absence of increased cortical β-amyloid deposition. These findings imply a sequential or two-step process of β-amyloidopathy in PD where cortical changes antecede striatal plaque deposition. This is in keeping with post-mortem findings from patients with AD where a distinct sequence in which the regions are hierarchically involved has been observed [30]. This sequential nature of plaque deposition in PD needs to be confirmed in a prospective cohort study.

Accumulating post-mortem evidence indicates that comorbid cerebral β-amyloidopathy in PDD is associated with worse clinical outcome, shorter time to dementia conversion, and reduced survival rates compared to PDD patients with "pure" Lewy body pathology [3, 31]. These findings agree with *in vivo* CSF studies where abnormally low levels of β-amyloid are associated with more rapid cognitive decline in PD [32]. The comorbid presence of two neurodegenerations (α-synucleinopathy and β-amyloidopathy) in some patients with PDD suggests additive or even synergistic detrimental interactions of these proteinopathies [33].

Interestingly, we found that the presence of combined striatal and cortical β-amyloidopathy was a more robust determinant of cognitive impairment in PD compared to cortical-only β-amyloidopathy. A post-mortem study found greater frequency of striatal β-amyloid deposition in PDD compared to PD and found that β-amyloid deposition in the striatum strongly correlated with dementia in PD [8]. Another post-mortem study indicated that higher striatal β-amyloid plaque density predicted the presence of dementia in a mixed cohort of patients with AD and non-demented control subjects [34]. The majority of prior *in vivo* β-amyloid PET imaging studies describe associations between cortical β-amyloid plaque deposition and cognitive changes in Lewy body disorders, including PD, but do not report on the relationship between striatal β-amyloid deposition and cognitive functions [35-38]. Furthermore, most of these studies report on global measures of cognition rather than a detailed neuropsychological testing battery. Although Foster and colleagues reported also on correlations between cognitive measures and both cortical and striatal β-amyloid binding in patients with Lewy body disorders, including PD, they did not directly compare cortical to striatal β-amyloid measures [35]. The presence of β-amyloid plaques in the striatum, a key node in several cognitively important circuits, is likely to further aggravate cognitive deficits in PD.

We reported previously that even relatively low levels of cortical β-amyloidopathy in PD correlate with cognitive dysfunction [4]. These findings suggest that amyloidopathy, even at mildly elevated levels, may exert pathologic effects in PD subjects. A fraction of cognitively normal elderly individuals, however, exhibit higher β-amyloid burdens than documented in our PD subjects, and Alzheimer disease patients appear to become symptomatic at considerably higher levels of amyloid burden [39]. In PD, however, β-amyloidopathy occurs in the context of a-synucleinopathy and other degenerations, which likely reduce the ability of the brain to adapt to increased β-amyloid burden.

We found that 'global' (defined as summed effects of cortical and striatal) β-amyloid plaque burden best predicted global composite cognitive z-scores compared to either cortical or striatal measures alone. We also found regional effects on specific cognitive domains. Cortical β-amyloid PIB DVR best predicted verbal learning deficits, while striatal β-amyloid PIB DVR best predicted attention cognitive domain z-scores. These findings underscore the heterogeneity of cognitive impairment in PD related to β-amyloid plaque deposition in PD. We found also that the effects of cerebral β-amyloidopathy were independent from effects of cortical cholinergic and caudate nucleus dopaminergic denervations that are key contributors to the neurochemical processes underlying the cognitive decline in PD [22]. These data provide further support for a multifactorial basis of cognitive deficits in PD extending beyond the effects of α-synuclein deposition. These findings also emphasize the multisystem subcortical-cortical substrates of the cognitive decline in PD.

A limitation of our study was that because of the cross-sectional design no inference about the risk of conversion to dementia could be made. Our study subjects were clinically recruited based on known risk factors for dementia in PD with only three subjects meeting criteria for mild dementia after detailed neuropsychological evaluation. Future studies in PD subjects across the full spectrum of cognitive impairment are needed to investigate the relative impact of striatal β-amyloid plaques as the frequency of β-amyloidopathy appears higher in demented PD subjects [40].

Our findings suggest also that anti-amyloid therapies deserve further study as potential therapeutic interventions to mitigate cognitive decline in PD. The selection of eligible subjects for anti-amyloid treatment trials may be challenging as only a subset of PD subjects may develop β-amyloidopathy. The identification of at-risk candidates may be particularly impactful in PD, however, since the relatively low level of amyloidopathy may provide a unique window of opportunity to intervene earlier in the β-amyloid cascade and might attenuate synergistic interactions with α–synuclein pathology.

We conclude that the combined presence of striatal and cortical amyloidopathy is associated with greater cognitive impairment than cortical amyloidopathy alone in PD.

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Abbreviations

AChE	Acetylcholinesterase
DVR	Distribution volume ratio
PD	Parkinson disease
PDD	Parkinson disease with dementia
PIB	Pittsburgh compound B
PET	positron emission tomography
PMP	methyl-4-piperidinyl propionate
VMAT2	vesicular monoamine transporter type 2

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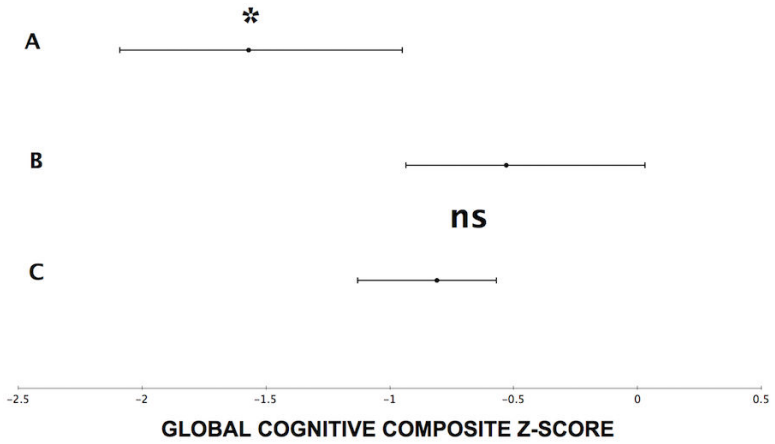

Figure 1.

Line plots showing the mean value and confidence interval ranges for the global cognitive composite z-score values for the three amyloidopathy subgroups: A= combined striatal and cortical amyloidopathy subgroup, B= cortical-only amyloidopathy subgroup, and C= non-amyloidopathy subgroup. *Duncan Multiple Range post hoc analysis showed significantly lower global composite cognitive z-scores for the combined striatal and cortical amyloidopathy sub-group (A) compared to cortical-only amyloidopathy (B) and non-amyloidopathy subgroups (C); the latter two were not significantly different from each other (ns).

Table 1

The proportion of patients with negative versus positive cortical and striatal β-amyloid deposition (n=62).

	Negative cortical β-amyloid deposition	**Positive cortical β-amyloid deposition**	
Negative striatal β-amyloid deposition	n=39 (62.9%)	n=13 (21.0%)	n=52 (83.9%)
Positive striatal β-amyloid deposition	n=0 (0%)	n=10 (16.1%)	n=10 (16.1%)
	n=39 (62.9%)	n=23 (37.1%)	Total: n=62 (100%)

Table 2

Mean (±SD) values of demographic and clinical variables in the different β-amyloidopathy subgroups. ANOVA F-values with level of significance are listed in the last column. None of the variables were significant after correction for multiple testing.

	Non-β-amyloidopathy subgroup (n=39)	Cortical-only β-amyloidopathy subgroup (n=13)	Combined cortical and striatal β-amyloidopathy subgroup (n=10)	ANOVA F-value, P level
Age	67.3+6.3	70.2±5.4*	73.3±6.3	F=4.13, P=0.02
Duration of disease	6.4+4.4	5.0±4.1	8.7±6.1	F=1.84, P=0.17
Hoehn & Yahr stage	2.6±0.4	2.8±0.5	2.9±0.5	F=2.72, P=0.07
MDS UPDRS motor scores	33.6±13.5	38.6±15.3	43.7±14.2	F=2.30, P=0.11

Table 3

Analysis of covariance using global composite cognitive z-scores as outcome parameter showed significant regressor effects for amyloidopathy grouping factor while adjusting for covariate effects of cortical AChE activity, caudate nucleus monoaminergic terminal binding, duration of disease and age. Duncan Multiple Range post hoc analysis showed significantly lower global composite cognitive z-scores for the combined striatal and cortical amyloidopathy sub-group (mean z-score: -1.57+0.88) compared to cortical-only amyloidopathy (mean z-score: -0.53+0.79) and non-amyloidopathy subgroups (mean z-score: −0.81±0.95); the latter two were not significantly different from each other.

	Amyloidopathy grouping factor effect	**Cortical AChE activity covariate effects**	**Caudate nucleus DTBZ binding covariate effect**	**Duration of disease covariate effect**	**Age covariate effect**	**Overall model**
Global cognitive z-score	F=4.18, P=0.02	F=5.67, P=0.02	F=1.17, P=0.38	F=0.70, P=0.38	F=0.55, P=0.46	F=3.55, P=0.0048