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Tau PET imaging in the Lewy body diseases

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Abstract

Importance—The causes of cognitive impairment in dementia with Lewy bodies (DLB) and Parkinson disease (PD) are multifactorial. Tau pathology is commonly observed at autopsy in DLB and PD dementia, but its contribution during life to these diseases is unknown.

Objective—To contrast tau aggregation in DLB, cognitively impaired PD (PD-impaired), cognitively normal PD (PD-normal), and normal control (NC) subjects and to evaluate the relationship between tau aggregation, amyloid deposition, and cognitive function.

Design—This cross-sectional study was conducted from 2014 to 2016.

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Author Contributions

SNG contributed to conceptualization of the study, analysis and interpretation of data, drafting and revision of the report, and statistical analysis. KAJ contributed to conceptualization of the study, interpretation of data, and drafting and revision of the report. JHG and BCD contributed to interpretation of data and drafting and revision of the report. JL contributed to analysis and interpretation of data, drafting and revision of the report, and the statistical analysis. RAS contributed to acquisition of data and drafting and revision of the report. SM, CC, and AS contributed to acquisition, analysis of data, drafting and revision of the report, and provided technical support. NV contributed to acquisition of data and drafting and revision of the report.

Conflicts of interest

BCD has provided consulting services for Merck DSMB, Forum, Ionis, Piramal, and receives royalties from Oxford University Press. RAS has provided consulting services for Roche, Genentech, Biogen and Bracket, Abbvie, received support from a joint NIH-Lilly-sponsored clinical trial (A4 Study – U19AG10483), and research funding from the National Institutes of Health/National Institute on Aging (R01 AG046396, P01 AG036694, P50 AG00513421) and the Alzheimer's Association. KJ has provided consulting services for Lilly, Novartis, Janssen, Roche, Piramal, GE Healthcare, Siemens, ISIS Pharma, AZTherapy, Abbvie, Lundbeck, and Biogen, received support from a joint NIH-Lilly-sponsored clinical trial (A4 Study – U19AG10483), and received research support from National Institutes of Health/National Institute on Aging (R01 AG046396, P01 AG036694, P50 AG00513421, U19AG10483, U01AG024904-S1), Fidelity Biosciences, the Michael J. Fox Foundation, the Marr Foundation, and the Alzheimer's Association.

Setting—Subjects were recruited from a tertiary care center’s Memory and Movement Disorders Units.

Participants—24 patients with Lewy body disease (7 DLB, 8 PD-impaired, and 9 PD-normal) underwent multimodal brain imaging, cognitive testing, and neurological evaluation, and imaging measures were compared to those of an independently acquired group of 29 NC subjects with minimal brain amyloid burden, as measured with [^{11}C]PiB PET.

Exposures for observational studies—[^{18}F]AV-1451 (formerly known as [^{18}F]T807), [^{11}C]PiB PET, MRI, detailed cognitive testing, and neurological examination.

Main Outcomes and Measures—Subjects underwent tau PET imaging with [^{18}F]AV-1451, MRI, detailed cognitive testing, and neurological examination. All but 3 subjects also underwent amyloid imaging with [^{11}C]PiB PET. The hypotheses being tested were formulated before data collection.

Results—In DLB, cortical [^{18}F]AV-1451 uptake was highly variable and greater than in NC, particularly in the inferior temporal gyrus (ITG) and precuneus. Foci of increased [^{18}F]AV-1451 binding in the ITG and precuneus were also evident in PD-impaired subjects. Elevated cortical [^{18}F]AV-1451 binding was observed in 4/17 Lewy body disease cases with low cortical [^{11}C]PiB retention. For DLB and PD-impaired subjects, greater [^{18}F]AV-1451 uptake in the ITG and precuneus was associated with increased cognitive impairment, as measured with the MMSE and the CDR sum-of-boxes score.

Conclusions and Relevance—Patients with Lewy body disease manifest a spectrum of tau pathology. Cortical aggregates of tau are common in DLB and PD-impaired patients, even in patients without elevated amyloid. When present, tau deposition is associated with cognitive impairment. These findings support a role for tau co-pathology in the Lewy body diseases.

Keywords

dementia with Lewy bodies; Parkinson; [^{18}F] AV1451; [^{11}C] PiB; biomarker

Introduction

Dementia with Lewy bodies (DLB), Parkinson disease (PD), and PD dementia (PDD) together comprise the Lewy body diseases (LBD), which are defined neuropathologically by Lewy body intracellular inclusions that are rich in α -synuclein (1). In individuals with DLB and PDD, co-existent Alzheimer’s disease (AD) pathology, in the form of extracellular amyloid plaques and intracellular paired helical filaments of tau, is commonly observed at autopsy (2–6). The relevance of these protein aggregates to the course of these diseases has been based primarily on clinico-pathological correlations. Now, with the advent of PET molecular imaging, it is possible to examine both the timing and extent to which amyloid and tau affect cognition during life in the course of disease (7,8).

Molecular imaging of neuropathological aggregates began with the introduction of Pittsburgh compound B ([^{11}C]PiB), and has enabled research studies to show that cortical A β deposition is common in PD and PDD, that high levels of A β are observed in most cases of DLB (9–12), and that greater deposition of A β is a risk factor for cognitive impairment in

PD, accelerating cognitive decline once established (13,14). These findings were consonant with prior neuropathological reports (reviewed in 7).

In AD, disease progression occurs in the context of high A β and is associated with spread of tau deposits from the medial temporal lobe to the basal temporal neocortex and then to other neocortical regions (15–17), in association with regional neuronal loss (18).

Neuropathologic studies have also linked tau deposition to the LBD, with the following observations. In both DLB and PDD, the presence of tau pathology in combination with A β and α -synuclein has been shown to potentiate dementia (5). Furthermore, as in AD (19,20), tau aggregates in PD have been found to correlate with the severity of cognitive impairment (3,4), and tau aggregates measured at autopsy, late in the course of disease, are commonly observed in both PDD and DLB. However, greater tau burden has been observed in DLB than PDD tissue (21), raising the possibility of a difference during life. The contribution of brain tau aggregates during life to the clinical manifestations and course of these diseases has been difficult to evaluate, as the ability to image tau in living humans has been lacking until recently.

In this study, we selected the radioligand [^{18}F]AV-1451, also known as [^{18}F]T807, to image tau in the LBD, based on its high affinity, selectivity and favorable kinetics for imaging tau (22,23). Recent work with postmortem tissue has confirmed that [^{18}F]AV-1451 binds strongly to tau in neurofibrillary tangles and neurites without binding A β and has shown, critically, that [^{18}F]AV-1451 does not bind α -synuclein aggregates or Lewy bodies (24,25). Based on these favorable characteristics, we conducted a study to evaluate the contribution of tau to clinical phenotype and to cognitive function in LBD. Based on neuropathological observations (3–5,21), we hypothesized that among diagnostic groups [^{18}F]AV-1451 uptake would be highest in DLB and that uptake would be related in our sample to the severity of cognitive impairment.

Methods

Study design

Seven DLB, 8 PD with a broad range of cognitive impairment (PD-impaired) ranging from mild (PD-MCI, n=4) to severe (PDD, n=4), and 9 cognitively normal PD (PD-normal) subjects were recruited from Massachusetts General Hospital's Movement and Memory Disorder Units. Subjects with DLB met clinical consensus criteria for probable DLB of the DLB consortium (26), with the presence of at least two of the following: parkinsonism, visual hallucinations, and fluctuations of cognition. All had a history suggestive for REM sleep behavioral disorder. PD subjects met the diagnostic criteria for idiopathic PD of the UKPDSBBRC (27). Cognitive function in PD-normal subjects was well-preserved, exceeding criteria for PD-MCI (28). PD-impaired subjects met current criteria for either PD-MCI or PDD (29), with subjective complaints and objective impairment on at least two cognitive tests. Interviews with caregivers were acquired in all cases. [^{18}F]AV-1451 PET and MRI were acquired in all subjects; [^{11}C]PiB PET was acquired in 5 DLB, 7 PD-impaired (either PD-MCI or PDD), and 9 PD-normal subjects. As AD co-pathology in some NC subjects could obscure findings in LBD, acquired data were contrasted with identical test data collected from a separately acquired cohort of 29 normal control (NC) subjects with

low cortical amyloid (<1.15 DVR, measured in the frontal-lateral temporal-retrosplenial (FLR) regions (30)), participating in a study of aging (R01 AG046396). NC subjects had a normal neurologic examination, global CDR=0, and MMSE >27 . All participants gave written informed consent according to the protocols approved by the Institutional Review Board of Partners Healthcare, Inc, and received a small stipend for participation.

Clinical evaluation

Cognitive evaluation included the CDR scale, Mayo fluctuations screen (31), Mayo sleep questionnaire (32), visual form discrimination, and the tests of the National Alzheimer's Consortium Uniform Dataset (UDS; 33). Cognitive testing was conducted in the on-state to minimize the contribution of motor impairment. Evaluations of motor function included the Unified Parkinson Disease Rating Scale (UPDRS) part III (34) and Hoehn and Yahr (H&Y) staging (35). The interval between cognitive/motor testing and [^{18}F]AV-1451 PET was 67 ± 16 days for disease groups and 115 ± 26 days for NC.

Group demographics

Subjects had similar ages and education, but gender was nonsignificantly skewed towards males in the disease groups (Table 1). MMSE and CDR sum-of-boxes scores were similarly impaired for DLB and PD-impaired groups, and greater than PD-normal and NC groups (for each contrast, $p<0.01$). Motor function was similar across the disease groups (for both UPDRS and H&Y, $p>0.05$ for each contrast).

Imaging acquisition

MRI—An MP-RAGE sequence optimized for use with Freesurfer software (<http://surfer.nmr.mgh.harvard.edu>) was acquired on a Siemens 3T Tim Trio system to generate high-resolution anatomic data for morphometric analyses.

PET imaging—Synthesis, preparation and administration of [^{18}F]AV-1451 were conducted as previously described (36). [^{18}F]AV-1451 and [^{11}C]PiB data were acquired on a Siemens/CTI ECAT HR+ scanner (63 parallel planes; axial FOV: 15.2 cm; in-plane resolution: 4.1 mm full-width at half-maximum; slice width: 2.4 mm). For [^{18}F]AV-1451, administration of 10 mCi of radiotracer was followed by a 20-minute acquisition, beginning at 80 minutes post-injection. [^{11}C]PiB data were acquired using a 39-frame dynamic protocol ($8\times15\text{s}$, $4\times60\text{s}$, and $27\times120\text{s}$), reconstructed and corrected for scatter, attenuation and randoms with vendor-supplied software.

Image analyses

PET—[^{18}F]AV-1451 and [^{11}C]PiB data were co-registered to each subject's MP-RAGE MR. Each subject's [^{18}F]AV-1451 and [^{11}C]PiB PET data were spatially transformed into the PET native space using Statistical Parametric Mapping (SPM8). For anatomically-based analyses, we used Freesurfer to identify volumes and vertices (37,38) as performed previously (39,40). We expressed [^{18}F]AV-1451 data as the standardized uptake ratio (SUVR) with cerebellar grey reference, as reported (23,39), and [^{11}C]PiB as the distribution volume ratio (DVR) with cerebellar reference(37,38,41). We expected atrophy to have an

impact on PET measures and therefore chose to assess the ROI SUVRs with and without partial volume (PV) correction with the GTM method (42; results with PV corrected data are reported below; results with non-PV corrected data are reported in the Supplement).

Whole-brain group contrasts of PET data included Freesurfer-based assessments of cortical binding at vertices (43). Findings from the surface-based analyses were confirmed using inferior temporal gyrus (ITG) and precuneus regions of interest (ROI), according to the Desikan FS parcellation (39,44).

Each group's [^{18}F]AV-1451 SUVR and [^{11}C]PiB DVR ROI measures are shown in eTable 1 of the Supplement.

Data Analysis

For general linear models (GLMs), backward elimination of an initial full model of simultaneous predictor terms, including pertinent interactions and covariates, was employed using a cutoff of $p=0.01$. Post hoc tests adjusting for multiplicity of the tests were run as called for. Model residuals were checked for fit and conformance to assumptions. We used Spearman bivariate correlations to avoid violation of assumptions for the significance test of the Pearson's test and the excessive influence of some outliers. Analyses were run using SAS/JMP.

Results

Tau deposition

DLB patients had greater cortical retention of [^{18}F]AV-1451 than NC particularly prominent in the inferior and lateral temporal lobe and precuneus (exemplified in Figure 1A, with vertex maps in Figure 2, peak $p<0.0001$, uncorrected, FDR corrected $p<0.005$). A similar anatomy of high SUVR was observed in PD-impaired patients, but with lower magnitude and extent (Figures 1 and 2), which did not survive the FDR correction. In contrast, peak average DVR did not differ between PD-normal and NC (Figure 2).

Confirmatory analyses using ITG and precuneus ROI (ITG shown in Figure 3) showed that the mean SUVRs in both ITG and precuneus differed by diagnostic group (for each ROI, main effect of group $p<0.005$; Kruskal-Wallis; PV corrected): between diagnostic groups, ITG and precuneus SUVRs were higher in DLB compared to NC ($p<0.004$; Wilcoxon rank sum) and PD-normal ($p<0.022$), but did not differ from PD-impaired ($p>0.3$). PD-impaired ITG and precuneus SUVRs were higher than NC ($p<0.022$), but only the ITG SUVR was greater in PD-impaired compared to PD-normal ($p<0.034$). The variance of ITG SUVR was greater in DLB than in any of the other groups ($p<0.05$, F test). Similar results with somewhat smaller effects were observed without partial volume correction (see the Supplement and eFigure 1).

Relation of [^{18}F]AV-1451 binding to age and duration of disease

Age was not associated with either ITG SUVR or precuneus SUVR in any diagnostic group ($p>0.05$). In the DLB group alone, shorter duration of disease was associated with greater SUVR in the ITG ($r=-0.86$, $p=0.01$) and precuneus ($r=-0.82$, $p=0.02$).

Relation of amyloid burden to tau deposition

17 out of 21 LBD subjects had PiB retention that was lower than DVR 1.15, a cut-point typically used in our laboratory to classify low amyloid burden. Across and within diagnostic groups, [^{11}C]PiB retention and [^{18}F]AV-1451 SUVR were uncorrelated, assessed either in ITG or precuneus (across groups, ITG $\text{Spearman } r = -0.05$, $p = 0.7$; precuneus $r = 0.22$, $p = 0.13$; within each LBD group, $p > 0.05$; eFigure 2). Consistent with this observation, 4/17 (24%) of the LBD cases with low [^{11}C]PiB had ITG [^{18}F]AV-1451 binding exceeding all NC subjects (Figure 3, eFigure 3). Thus, high amyloid status was not necessary for [^{18}F]AV-1451 binding in the impaired LBD groups; however, it is noteworthy that small foci of cortical amyloid were observed in 2 of these 4 impaired LBD subjects with low amyloid (eFigure 3).

Relation of ROI tau deposition to cognitive functional impairment

Given the shared anatomy of tau pathology in the DLB and PD-impaired groups, we aggregated these diagnostic groups to evaluate the impact of tau on cognitive function. In the aggregate DLB/PD-impaired group, performance on the CDR sum-of-boxes was significantly correlated with both ITG SUVR ($\text{Spearman } r = 0.68$, $p = 0.006$; Figure 4A) and precuneus SUVR ($r = 0.82$, $p = 0.0002$). Similarly, the MMSE score in the DLB/PD-impaired group was significantly correlated with both ITG SUVR ($\text{Spearman } r = -0.57$, $p = 0.026$; Figure 4B) and precuneus SUVR ($r = -0.69$, $p = 0.005$). Correlations were not significant in the PD-normal and NC groups, where the range of the cognitive functional measures was restricted.

When we analyzed the DLB and PD-impaired groups separately, using a GLM containing all diagnostic groups, we observed a significant interaction of ITG and of precuneus SUVR with diagnostic group in their relation to the CDR sum-of-boxes ($p < 0.0001$), with backward elimination of nonsignificant age and education. Specifically, higher SUVR was associated with greater impairment on the CDR sum-of-boxes in the DLB group in the ITG and precuneus ($p < 0.0001$), and in the PD-impaired group in the precuneus ($p = 0.001$). In contrast, relations were essentially flat for the PD-normal and NC groups. Consistent with these findings, in a second set of GLM analyses for MMSE, ITG and precuneus SUVR each interacted with diagnostic group ($p < 0.0001$, $p = 0.01$ respectively; age and education were nonsignificant). Specifically, a significant negative relation between SUVR and MMSE was observed in the DLB group ($p < 0.002$) in both the ITG and the precuneus, and in the PD-impaired group in the precuneus ($p < 0.001$), whereas the relation was flat for the other groups.

Relation of amyloid deposition to cognitive function

Across the sample as a whole, [^{11}C]PiB retention did not correlate with the CDR sum-of-boxes ($r = 0.07$, $p = 0.7$) or the MMSE ($r = -0.05$, $p = 0.7$), and within-group correlations were also nonsignificant ($p > 0.05$, for each group).

Discussion

Although α -synuclein deposition in Lewy bodies is the core neuropathologic feature of the LBD, tau and A β co-pathologies are commonly observed in most patients with DLB and PDD at autopsy (2–6). Supporting their contribution to cognitive function in these diseases, neuropathological studies of DLB and PDD have tied both tau and A β to severity of dementia (3–5). To identify tau in living patients with LBD and evaluate its contribution to their course, we used [^{18}F]AV-1451 PET imaging.

The results of this study support a role for tau accumulation in DLB and in PD associated with cognitive impairment. In whole brain and ROI analyses, we found that [^{18}F]AV-1451 retention was higher in DLB and in PD-impaired patients than in low-amyloid NC, consistent with expected patterns reported in pathologic (45) and tau PET studies of AD (39,46–48). Even so, the amount of cortical [^{18}F]AV-1451 binding in DLB and PD-impaired patients was substantially lower than that reported in AD (39,46–48), which typically ranges from 1.5 to >2, consistent with neuropathological reports (3–6,26).

We also observed that the anatomic localization for abnormal [^{18}F]AV-1451 binding in both DLB and PD-impaired is similar to that reported in AD, including infero-lateral temporal and parietal/precuneus regions. This finding suggests that neuropathological processes that drive accumulation of tau deposits in DLB and PD-impaired patients are subject to the same regional vulnerabilities as those driving tau deposition in AD. Tau deposition was more variable in DLB and lower in magnitude and extent in PD-impaired patients. In contrast, the PD-normal patients did not have evidence for tau deposition. These observations are consistent with the variability of tau described in neuropathological studies of DLB and PD and support the concept that tau co-pathology is common in LBD but is not necessary for the presumptive driving neuropathology of α -synuclein aggregation.

In contrast to prior studies of advanced DLB, where A β burden is often high (9–12), most cases of DLB in this study had low amyloid burden. This difference may be due to the relatively modest cognitive impairment of DLB subjects in the present study and may have obscured a correlation of amyloid burden with cognitive function. Nevertheless, the low A β burden in our DLB patients was often associated with high levels of abnormal [^{18}F]AV-1451 binding in neocortex, a finding that is in marked contrast to PET findings in MCI and AD, in which the two pathologies are well correlated in neocortex and in which it is theorized that high A β is a critical factor in the expansion of tau pathology into neocortex (39,46,48). Thus, in LBD, tau can accumulate in the neocortex without demonstrably elevated fibrillar amyloid. Whether A β is necessary for tau accumulation in LBD remains to be determined, however, as small foci of cortical amyloid were present in some cases, as previously demonstrated in LBD (9), and soluble A β oligomers and non-fibrillar amyloid in diffuse plaques could also contribute (7). This distinction between AD and the LBD may reflect the synergistic relationship between α -synuclein aggregation and tau pathology (49,50).

Consistent with the hypothesis that tau deposition is deleterious to cognition in LBD, as previously demonstrated in AD (15,39,46–48), in an aggregate cohort of DLB and PD-impaired subjects, those with greater [^{18}F]AV-1451 binding in inferior temporal and

precuneus regions showed greater cognitive impairment. This result is consistent with a model in which neuropathological cascades that involve tau accumulation might act through local synaptic and cell loss (18), likely in concert with α -synuclein toxicity (51), to impair cognition in the LBD.

In this study, we sought to contrast LBD groups with an age-matched, healthy control group with no evidence of amyloid proteinopathy. Many cognitively normal subjects have high levels of cortical amyloid, however, and a small proportion of these has recently been shown to have elevated neocortical tau in the inferior temporal gyrus (39). Compared to these subjects, tau deposition in the DLB and PD-impaired groups would not be as evident. Even so, the levels of neocortical tau deposition observed in several of the DLB and PD-impaired subjects exceed levels of tau observed in those cognitively normal subjects with high amyloid and tau, and tau deposition in LBD was associated with cognitive impairment.

Strengths of this study include acquisition of multimodal PET molecular imaging and inclusion of well-characterized subjects across the spectrum of LBD. The use of a NC cohort with low amyloid burden increases sensitivity to detect AD neurofibrillary tangle co-pathology in the diagnostic groups. A limitation of this study is the small group sizes; future studies with a larger number of subjects will be required to confirm these observations. An additional limitation is the use of clinical diagnosis without neuropathological confirmation. Reported off-target binding of [^{18}F]AV-1451 to melanin and brain hemorrhagic lesions (24) is unlikely to affect the results of the study.

Conclusions

The results of this study suggest that deposits of tau are common in the LBD, especially in DLB; can arise in the absence of significant amyloid burden; and contribute to cognitive impairment. These observations highlight the contribution of non-canonical, extra-synuclein, tau co-pathology to cognition in the LBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Distribution of $[^{18}\text{F}]$ AV-1451 binding in Lewy body disease subjects.

A. Surface maps and PET images (coronal and axial views) of $[^{18}\text{F}]$ AV-1451 binding in two subjects with DLB (left, age 72, MMSE 17; right, age 61, MMSE 12). **B.** Surface maps and PET images of $[^{18}\text{F}]$ AV-1451 binding in two subjects with PD dementia (left, age 73, MMSE 20; right age 81, MMSE 19). In addition to gray matter binding of $[^{18}\text{F}]$ AV-1451, off-target binding to neuromelanin and a mucous retention cyst is also evident (24).

Figure 2.

Surface renderings of group contrasts of DLB with NC, PD-impaired with NC, and PD-normal with NC (GLMs). Color bar shows significant binding at the $p < 0.01$ – 0.0001 level.

Figure 3.

Tau deposition varies across the diagnostic groups and is not dependent on amyloid. Inferior temporal gyrus $[^{18}\text{F}]\text{AV-1451}$ SUVR values are displayed for each of the diagnostic groups, using the box-whiskers convention. Dots represent individual subject values. The horizontal line within each box is the group median $[^{18}\text{F}]\text{AV-1451}$ SUVR value. As indicated by the asterisks, $[^{18}\text{F}]\text{AV-1451}$ retention was higher in the DLB group than in the PD-normal ($p=0.022$, Wilcoxin test) and NC groups ($p=0.004$). Similarly, $[^{18}\text{F}]\text{AV-1451}$ retention in the PD-impaired group was also higher than in the PD-normal ($p=0.034$, Wilcoxin test) and NC groups ($p=0.022$). Black circles ($n=4$) designate subjects with high $[^{11}\text{C}]\text{PiB}$ (FLR > 1.15 SUVR); gray circles designate subjects with low $[^{11}\text{C}]\text{PiB}$; open circles ($n=3$) show cases who did not undergo $[^{11}\text{C}]\text{PiB}$ PET. Note that 4 of the 6 impaired

LBD subjects with elevated AV-1451 binding relative to NC were shown to have low amyloid burden.

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Figure 4.

Tau impacts global cognitive function in LBD subjects with cognitive impairment

A. In the LBD-impaired group, comprised of DLB (open circles) and PD-impaired (closed circles), higher [^{18}F]AV-1451 binding in the ITG was associated with greater impairment measured with the CDR sum-of-boxes score (Spearman $r=0.68$, $p=0.006$). In contrast, [^{18}F]AV-1451 binding did not relate to the CDR sum of box score in the PD-normal or NC groups ($p>0.05$). **B.** Within the LBD-impaired group ($r=-0.57$, $p=0.026$), but not the other groups ($p>0.05$), higher ITG SUVR was associated with lower MMSE score. 95% confidence intervals are shown.

Table 1

Group demographics

Group	N	M/F	Age (yrs)	Education (yrs)	UPDRS	CDR sum of boxes	MMSE	Amyloid status (fraction elevated)
NC	29	16/13	69 ± 2	16.0 ± 2.6	–	0.1 ± 0.2 ^{a,b}	29.5 ± 0.1 ^{a,b}	0/29
PD-normal	9	8/1	67 ± 3	16.9 ± 1.2	23.3 ± 12.8	0.2 ± 0.4 ^{a,b}	29.1 ± 0.4 ^{a,b}	1/9
PD-impaired	8	7/1	72 ± 2	17.3 ± 2.1	27.6 ± 10.1	3.6 ± 2.7 ^{c,d}	24.9 ± 1.5 ^{c,d}	2/7
DLB	7	6/1	68 ± 2	17.0 ± 1.1	26.3 ± 13.6	5.8 ± 5.8 ^{c,d}	22.4 ± 2.2 ^{c,d}	1/5

Error bars reflect standard deviation. For significance testing, the Kruskal-Wallis test was first used to assess a main effect of group. Where significant ($p < 0.05$), this was followed up with Wilcoxin post-hoc tests, with significance indicated as follows:

^a significantly different from DLB

^b significantly different from PD-impaired

^c significantly different from HCS

^d significantly different from PD-nl