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Elevated occipital β -amyloid deposition is associated with widespread cognitive impairment in logopenic progressive aphasia

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Abstract

Background—Most subjects with logopenic primary progressive aphasia (lvPPA) have beta-amyloid (A β) deposition on Pittsburgh Compound B PET (PiB-PET), usually affecting prefrontal and temporoparietal cortices, with less occipital involvement.

Objectives—To assess clinical and imaging features in lvPPA subjects with unusual topographic patterns of A β deposition with highest uptake in occipital lobe.

Methods—Thirty-three lvPPA subjects with A β deposition on PiB-PET were included in this case-control study. Line-plots of regional PiB uptake were created, including frontal, temporal, parietal and occipital regions, for each subject. Subjects in which the line sloped downwards in occipital lobe (lvPPA-low), representing low uptake, were separated from those where the line sloped upwards in occipital lobe (lvPPA-high), representing unusually high occipital uptake compared to other regions. Clinical variables, atrophy on MRI, hypometabolism on F18-fluorodeoxyglucose PET, and presence and distribution of microbleeds and white matter hyperintensities (WMH) were assessed.

Results—Seventeen subjects (52%) were classified as lvPPA-high. Mean occipital PiB uptake in lvPPA-high was higher than all other regions, and higher than all regions in lvPPA-low. The lvPPA-high subjects performed more poorly on cognitive testing, including executive and visuospatial testing, but the two groups did not differ in aphasia severity. Proportion of microbleeds and WMH was higher in lvPPA-high than lvPPA-low. Parietal hypometabolism was greater in lvPPA-high than lvPPA-low.

Conclusions—Unusually high occipital A β deposition is associated with widespread cognitive impairment and different imaging findings in lvPPA. These findings help explain clinical heterogeneity in lvPPA, and suggest that A β influences severity of overall cognitive impairment but not aphasia.

Introduction

The logopenic variant of primary progressive aphasia (lvPPA) is a neurodegenerative language disorder in which patients show phonological errors, problems repeating complex sentences and anomia, with preserved word comprehension¹. Patients with lvPPA typically show left-sided patterns of temporoparietal atrophy on magnetic resonance imaging (MRI) and hypometabolism on 18-F fluorodeoxyglucose positron emission tomography (FDG-PET)¹⁻⁴. The majority of lvPPA patients have Alzheimer's disease (AD) pathology^{5, 6}, with 92–100% showing β -amyloid (A β) deposition on Pittsburgh Compound B PET (PiB-PET) scans^{7, 8}. A β deposition on pathology has been shown to target the prefrontal cortex, temporoparietal lobes, posterior cingulate/precuneus and striatum in AD⁹, with similar topographic patterns of PiB-PET uptake observed in patients with dementia of the Alzheimer's type (DAT)^{10, 11}. The occipital lobe typically shows low PiB uptake values in DAT¹⁰. Less is known about the regional distribution of PiB uptake in lvPPA, with only 25 subjects reported from two centers, although it appears as though the group-level patterns of PiB uptake are similar to those reported in DAT^{4, 7, 8}.

We have however, observed a number of patients with lvPPA who have an unusual pattern of PiB-PET uptake with highest uptake observed in the occipital lobe. The aim of this study was therefore to examine regional patterns of PiB-PET uptake at the individual-level in a cohort of subjects with lvPPA to determine what proportion of patients show elevated occipital uptake and to determine whether there are any clinical or imaging differences between these patients and those with the typical pattern of PiB-PET uptake. We aimed to assess cognitive and language function, as well as patterns of atrophy and FDG-PET hypometabolism. In addition, we have recently shown that lvPPA is associated with the presence of small hemosiderin deposits in the brain, known as microbleeds, as well as white matter hyperintensities (WMH)¹². We therefore assessed the presence of microbleeds and WMH's in our cohort.

Methods

Subjects

Between September 15th 2011 and December 1st 2012 a total of 42 subjects meeting clinical criteria for lvPPA were prospectively recruited into the Speech and Language Based Disorders study in the Department of Neurology, Mayo Clinic, Rochester, MN. All subjects underwent a neurological evaluation that included the Montreal Cognitive Assessment Battery (MoCA)¹³, the FTLT-modified version of the Clinical Dementia Rating Scale (CDR)¹⁴, the Frontal Behavioral Inventory (FBI)¹⁵, and a detailed speech and language examination that included the Western Aphasia Battery (WAB)¹⁶, a 22-item version of Part V of DeRenzi and Vignolo's Token Test¹⁷, and a 15-item version of the Boston Naming Test (BNT)¹⁸. Neuropsychological testing was also performed and included the Trail Making Test (TMT)¹⁹, the Auditory Verbal Learning Test (AVLT)²⁰, Rey-Osterrieth complex figure test (Rey-O)²¹ and the Visual Object and Spatial Perception (VOSP) battery²². Mayo Older Americans Normative (MOANS) scores adjusting for age and education were calculated for the TMT²³, AVLT²⁴ and Rey-O²⁵. All subjects also underwent volumetric MRI at 3T, FDG-PET and PiB-PET scanning within two days of the clinical assessment.

Clinical diagnosis of lvPPA was rendered based solely on data from speech and language assessments without any reference to neurological or neuroimaging results. The diagnosis of lvPPA was independently determined by two speech-language pathologists (JRD and EAS) by consensus. Criteria for the diagnosis of lvPPA were generally compatible with published consensus criteria²⁶, and included: 1) presence of aphasia, 2) impaired sentence repetition

and comprehension, 3) presence of anomia with evidence of spared single word comprehension, 4) evidence of phonemic paraphasias, 5) normal rate of verbal expression or slowed verbal expression due to pauses for word retrieval without evidence of motoric slowing, and 6) absence of agrammatic/telegraphic verbal output. All subjects showed patterns of left posterior perisylvian or parietal atrophy and hypometabolism characteristic of lvPPA. No subjects showed clinical or imaging features characteristic of the agrammatic or semantic variants of PPA²⁶.

In order to be included in the study, subjects had to have a positive PiB-PET scan (see below) demonstrating the presence of A β in the brain. Subjects were excluded if there were conditions that might confound brain imaging studies (e.g. subdural hematoma or tumors), or if image quality was degraded by artifacts. Nine subjects were excluded due to movement artifacts on MRI or negative PiB-PET scans, resulting in 33 subjects included in the study. One of these subjects has since died and underwent autopsy at Mayo Clinic, according to established procedures^{9, 27}. The lvPPA cohort was age and gender-matched to a cohort of 40 cognitively normal subjects that had undergone identical volumetric MRI, FDG-PET and PiB-PET scans. This study was approved by the Mayo Clinic IRB. All subjects provided written informed consent before participating in any research activity.

Image acquisition

PET images were acquired after injection of C-11 PiB (average=596MBq; range=292–729MBq, uptake period=40min) and F-18-FDG (average=540MBq; range=366–399MBq, uptake period=30min); both scans were performed as previously described on the same day with 1 hour between acquisitions²⁸. All lvPPA and cognitively normal subjects underwent a standardized MRI imaging protocol at 3T, that included 1) a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence, and 2) an axial T2-weighted fluid-attenuated inversion recovery (FLAIR). Twenty-two lvPPA subjects also underwent a T2*-weighted sequence. The majority of cases underwent a 2D GRE T2*-weighted sequence, although two underwent a 3D Swan T2*-weighted sequence¹².

PiB-PET based classification

All PiB-PET images were co-registered to the MPRAGE for each subject using 6 degrees-of-freedom affine registration. The automated anatomical labeling (AAL) atlas was transformed into the native space of each subject and used to calculate median PiB uptake for 6 regions-of-interest: temporal, parietal, posterior cingulate/precuneus, anterior cingulate, prefrontal, and orbitofrontal cortex (left and right were combined for all ROIs). Median PiB uptake in each region was divided by median uptake in cerebellar grey matter to create uptake ratios. A global cortical PiB retention summary was formed by calculating median uptake ratio values across all 6 regions. Subjects were classified as PiB-positive using a global cortical-to-cerebellar ratio cut-point of 1.5¹⁰.

In addition, PiB uptake ratios in these regions, as well as occipital lobe, for each PiB-positive lvPPA subject were converted into Z-scores reflecting how many standard deviations each subjects PiB uptake values were above the mean of the control group. Regional PiB Z-scores were plotted on a line chart for each subject, with regions ordered from anterior to posterior along the x axis (Figure 1). Subjects were then divided into two groups: 1) those in which the line sloped downwards in the occipital lobe, representing low occipital uptake (lvPPA-low), and 2) those in which the line sloped upwards or remained flat in the occipital lobe, representing unusually high occipital uptake (lvPPA-high) (Figure 1).

Voxel-level analyses

Voxel-level comparisons were performed for MRI, FDG-PET and PiB-PET using SPM5. All MPRAGE scans were spatially normalized to a customized template²⁹ and segmented using the unified segmentation model³⁰, followed by the hidden Markov random field clean-up step. All grey matter images were modulated and smoothed with an 8 mm full width-at-half maximum smoothing kernel. Both FDG and PiB-PET uptake images were co-registered to the subject's MPRAGE using 6 degrees-of-freedom registration. The AAL atlas, containing pons and cerebellum, was propagated to native MPRAGE space. All voxels in the FDG-PET image were divided by median uptake of the pons to form FDG uptake ratio images, and all voxels in the PiB-PET image were divided by median uptake of the cerebellum to form PiB uptake ratio images. The FDG and PiB-PET uptake ratio images were then normalized to the customized template using the normalization parameters from the MPRAGE normalization.

Voxel-level comparisons were performed using two-sided T-tests in SPM5. Differences between lvPPA groups and controls were assessed at $p < 0.05$, after correction for multiple comparisons using the family wise error (FWE) correction. Differences between the two lvPPA groups were assessed uncorrected for multiple comparisons at $p < 0.001$ with an extent threshold of 100 voxels. Age and gender were included in all analyses as covariates.

Microbleed and WMH analyses

Each T2*-weighted MRI sequence was reviewed by an experienced radiologist (CRJ or KK) and each microbleed was marked using in-house software. An in-house 22-region atlas in the space of the MPRAGE was created. The MPRAGE with its atlas images were registered into the space of the T2*-weighted image, and each microbleed was assigned an atlas location³¹. White matter hyperintensities were segmented from normal brain tissue on the FLAIR sequences using an automated intensity based algorithm using methods similar to the software tool Histoseg³², with additional manual clean-up. A white matter parcellation atlas was transformed into FLAIR space and used to calculate regional burden of WMH. The burden of WMH in each region was divided by the white matter volume in that region and multiplied by 100, resulting in a WMH proportion (WMHp) that reflects the percentage of white matter in each region that was affected by WMH. All imaging analyses were performed blinded to PiB-PET and clinical results.

Statistical analysis

Statistical analyses were performed utilizing JMP computer software (JMP Software, version 8.0.0; SAS Institute Inc., Cary, NC) with significance assessed at $p < 0.05$. Distribution plots demonstrated that the continuous outcome variables were not normally distributed. Non-parametric Wilcoxon Rank Sum tests were therefore used to compare demographic and MOANS variables across groups. In order to account for the potential confounders of age and education, rank transformations were applied to the remaining cognitive, language and imaging variables and regression models were used to compare groups, correcting for both age and education. Chi-Square tests were used to compare categorical data.

Results

PiB-PET findings

Of the cohort of 33 lvPPA subjects, 16 (48%) were classified as lvPPA-low and 17 (52%) as lvPPA-high. The regional PiB profile for each subject is shown in Figure 1. The mean occipital lobe PiB Z-scores were the lowest across all regions in lvPPA-low, but the highest

across all regions in lvPPA-high (Figure 1). Mean PiB-PET uptake ratios in occipital lobe ($p<0.0001$), as well as temporal ($p=0.0005$), posterior cingulate/precuneus ($p=0.006$), parietal lobe ($p=0.006$), and prefrontal cortex ($p=0.04$) were higher in lvPPA-high compared to lvPPA-low. No differences were observed in the orbitofrontal cortex ($p=0.15$) or anterior cingulate ($p=0.12$). The global PiB ratio was significantly higher in the lvPPA-high compared to lvPPA-low group ($p=0.007$) (Table 1).

In the voxel-level analyses, lvPPA-low showed widespread PiB-PET uptake involving frontal, temporal and parietal lobes compared to controls (Figure 2). Patterns of PiB-PET uptake in lvPPA-high were also widespread but showed striking uptake in the occipital lobes. The lvPPA-high group showed greater PiB uptake in bilateral occipital lobes, as well as inferior temporal lobes and motor cortex compared to lvPPA-low (Figure 2). No regions in lvPPA-low showed greater PiB uptake compared to lvPPA-high.

Clinical findings

No demographic differences were observed between lvPPA-low and lvPPA-high, except lvPPA-high did have slightly lower education than lvPPA-low (Table 1). No differences were observed in the proportion of apolipoprotein e4 or e2 carriers, or the proportion of subjects with hypertension. The lvPPA-high group had worse performance on MoCA, MoCA calculations, TMT B, Rey-O and VOSP cube compared to the lvPPA-low group, but showed no difference in performance on VOSP letters, AVLT delayed recall, modified CDR, FBI or any of the language measures.

Voxel-level MRI and FDG-PET findings

The lvPPA-high group showed reduced FDG-PET metabolism in left lateral temporal lobe, inferior lateral parietal lobe, precuneus, and posterior frontal lobe compared to controls (Figure 3). The lvPPA-low group also showed involvement of left lateral temporal, parietal and frontal lobes, but showed additional involvement of right lateral temporal lobe. Reduced metabolism was not observed in the precuneus in lvPPA-low. The lvPPA-high group showed reduced metabolism in left parietal lobe and motor cortex compared to lvPPA-low, and lvPPA-low showed reduced metabolism in bilateral medial temporal lobes compared to lvPPA-high ($p<0.001$, uncorrected) (Figure 4).

The lvPPA-high group showed volume loss in left lateral temporal, lateral parietal, precuneus and occipital lobe compared to controls, whereas volume loss in lvPPA-low was restricted to the lateral temporal lobe, with involvement of the right hemisphere (Figure 3). The lvPPA-low group showed reduced volume in temporal lobes compared to lvPPA-high ($p<0.001$, uncorrected) (Figure 4).

Microbleed and WMH findings

The proportion of subjects with lobar microbleeds was higher in lvPPA-high (67%) compared to lvPPA-low (10%, $p=0.007$) (Table 1). Four lvPPA-high subjects showed multiple lobar microbleeds (with 2, 4, 13 and 29 microbleeds respectively). Lobar microbleeds in lvPPA-high were most commonly observed in frontal (51%), followed by parietal (23.5%), temporal (21.6%) and lastly occipital lobes (3.9%). The lvPPA-high group showed a greater total burden of WMHp than lvPPA-low ($p=0.04$) (Table 1). A greater burden of WMHp was observed in left subcortical and periventricular occipital lobe ($p=0.02$ and $p=0.05$) and frontal lobe ($p=0.03$ and $p=0.03$), and right subcortical temporal lobe ($p=0.04$), in lvPPA-high compared to lvPPA-low (Figure 5).

Autopsy findings

The subject that underwent autopsy fulfilled pathological criteria for a diagnosis of AD³³ (Braak stage V⁹) and had cortical Lewy bodies, as well as CAA predominantly in motor and visual cortex. This subject was classified as lvPPA-high and did not have any microbleeds on MRI.

Discussion

We demonstrate in this study that approximately 50% of subjects with lvPPA show an atypical distribution of PiB uptake on PET imaging, with unusually high levels of uptake in the occipital lobe. These subjects show a different clinical profile to those with the typical pattern of PiB uptake, with worse performance on cognitive testing, greater burden of microbleeds and WMH and different patterns of atrophy and hypometabolism. Despite worse cognitive impairment and higher PiB uptake, their language disturbance (aphasia) was not more severely impaired than those with typical patterns of PiB uptake.

The pattern of PiB uptake in the lvPPA-high subjects was unusual, with the occipital lobe showing strikingly high Z-scores compared to other regions of the brain. In contrast, the lvPPA-low subjects showed occipital Z-scores lower than all other regions of the brain; more consistent with group-level patterns of PiB uptake previously reported in DAT and lvPPA^{4, 8, 10, 11}. Given these patterns, it is unlikely that the high PiB uptake values observed in the occipital lobe and other posterior regions of the brain in lvPPA-high simply reflect a more severe or advanced disease process than lvPPA-low. If this were the case, one might still expect to see a similar regional profile of uptake in both groups, with differences only in severity. Instead, these groups showed topographically different regional patterns of PiB uptake. This heterogeneity in regional PiB uptake may help explain divergent results in previous studies, where one group observed lower occipital PiB uptake in lvPPA compared to DAT⁴, whereas another did not observe any differences in the occipital lobe between lvPPA and DAT⁸. It is possible that these studies contained different proportions of lvPPA-high and lvPPA-low subjects, resulting in slightly different group-level patterns. The findings of the later study do in fact support our results since they found that PiB uptake was lower in lvPPA than DAT in all regions except the occipital lobe, suggesting potential elevated occipital uptake in lvPPA⁸.

The lvPPA-high subjects showed poorer general cognitive function as measured by the MoCA, and poorer performance on calculations and executive and visuospatial neuropsychological testing, than the lvPPA-low subjects. Although there was a trend for lower education and older age in lvPPA-high, we accounted for any potential confounding effects of both age and education in our statistical analysis. The findings were also not confounded by disease duration which was comparable across groups. In contrast to the cognitive scores, performance on measures of aphasia severity did not differ between the two groups. The lvPPA-high group therefore appears to be characterized by language impairment in the context of more widespread cognitive impairment. These subjects happen to meet criteria for lvPPA, despite the widespread cognitive impairment, because language was the initial complaint and was the cause for impairment of activities of daily living. Furthermore, none of the lvPPA high subjects complained of early deficits in the other affected cognitive domains. Whether such patients should be lumped with, or separated from, lvPPA subjects with isolated or focal aphasia, requires further debate. On one hand, the underlying pathological process in both entities is AD which supports the notion not to separate such patients. On the other hand, although not captured by the CDR, those with widespread cognitive deficits are more likely to be functionally impaired on activities of daily living given the additional problems likely to occur with calculation-dependent and visuospatially mediated tasks, as well as problems with planning and organizing. In order to

identify such subjects we favor a modification to the lvPPA criteria with subcategories in order to distinguish those with pure or focal aphasia from those with aphasia embedded in the context of more widespread cognitive deficits. Regardless, our findings suggest an association between the presence of widespread cognitive impairment in lvPPA and elevated occipital lobe A β . Despite the widespread cognitive impairment, language impairment remained the predominant symptom, and therefore these subjects would not meet criteria for other variants of AD, such as DAT or posterior cortical atrophy (PCA). The patterns of atrophy and hypometabolism in lvPPA-high were indeed consistent with a diagnosis of lvPPA showing left temporoparietal involvement, and did not resemble findings in DAT or PCA⁴.

Striking differences across groups were also observed on MRI, with a greater proportion of lobar microbleeds and subcortical and periventricular WMHs observed in the lvPPA-high group. In fact, a number of the lvPPA-high subjects had multiple microbleeds. Microbleeds have previously been shown to correlate to the degree of global A β deposition³¹, and be associated with the presence of WMHs³⁴. It is possible that the higher burden of WMHs may be contributing to the cognitive decline observed in lvPPA-high, since WMHs have been shown to correlate with decline in executive function and other cognitive domains³⁵. The presence of microbleeds is not thought to be associated with cognitive decline³⁶. Microbleeds are thought to be related to the presence of cerebral amyloid angiopathy (CAA)³⁷, which may suggest that CAA could be present in the lvPPA-high group. Indeed, CAA can cause elevated PiB uptake³⁸, particularly in the occipital lobes³⁹. The one patient that had come to autopsy did, indeed, have CAA in the visual cortex in addition to AD pathology. The distribution of microbleeds does not, however, support this hypothesis since they were most commonly observed in the frontal lobes, and not the occipital lobe which showed the highest PiB uptake in lvPPA-high. A previous study similarly found topographic discordance between A β uptake and microbleed location in a DAT cohort³¹. Therefore, while the contribution of CAA to the elevated occipital PiB uptake in lvPPA-high cannot be ruled out, it may not fully explain the finding.

We found some evidence, albeit relatively weak, that the lvPPA-high subjects had greater hypometabolism in posterior regions of the brain, particularly medial and lateral parietal lobe, compared to lvPPA-low. In contrast, the lvPPA-low subjects showed greater atrophy and hypometabolism in the anterior temporal lobes compared to lvPPA-high. Those subjects with higher occipital A β burden therefore appear to develop greater hypometabolism in parietal regions, whereas those with a more typical pattern of PiB uptake have a more temporal lobe predominant disease process. Greater involvement of the medial and lateral parietal lobe could be contributing to poorer performance on some of the cognitive tests in lvPPA-high. In fact, cube analysis, a test of spatial skills associated with occipitoparietal connections, was more affected in the lvPPA-high group, while fragmented letters, a tests of perceptual function associated with occipitotemporal connections, was not more affected⁴⁰. While our sample size was relatively small and our results generalizable only to lvPPA, it is tempting to speculate that A β deposition may influence brain metabolism and neurodegeneration.

While the biological mechanisms underlying the elevated occipital PiB uptake are unclear, our findings do suggest that there is a large subset of lvPPA subjects that have elevated occipital PiB uptake, widespread cognitive impairment, greater burden of microbleeds and WMH, and greater hypometabolism in the parietal lobe. These findings increase our understanding of the heterogeneity in lvPPA and could be helpful for patient prognosis and treatment.

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Figure 1.

Regional PiB-PET Z-scores for lvPPA-low and lvPPA-high groups. Individual subjects are shown in grey with group means shown in red. PiB-PET scans from two subjects in each group are shown on the right.

Figure 2.
Voxel-level maps of PiB-PET uptake in lvPPA-low and lvPPA-high groups compared to cognitively normal subjects and each other.

Figure 3.
Voxel-level maps of FDG-PET hypometabolism and MRI grey matter volume loss in lvPPA-low and lvPPA-high groups compared to cognitively normal subjects.

Figure 4. Unthresholded T-score effect maps showing differences between the lvPPA-low and lvPPA-high groups, for both FDG-PET hypometabolism and MRI grey matter volume loss.

Figure 5. Subcortical (A) and peri-ventricular (B) white matter hyperintensity burden in cognitively normal (CN), lvPPA-low and lvPPA-high groups. WMHp = white matter hyperintensity proportion, reflecting the percentage of white matter in each region that was affected by white matter hyperintensities. Error bars show standard deviation.

* Significantly different from CN at $p < 0.05$

** Significantly different from lvPPA-low at $p < 0.05$

Table 1

Clinical, demographic and imaging findings in lvPPA groups

	lvPPA-low (n=16)	lvPPA-high (n=17)	P values
Gender (% female)	7 (44%)	11 (65%)	0.23
Education, years	15.5 ± 2.6	13.8 ± 1.8	0.05
APOE e4 carriers (%)	9/16 (56%)	11/17 (65%)	0.62
APOE e2 carriers (%)	2/16 (13%)	1/17 (6%)	0.51
Hypertension (%)	6/14 (43%)	5/12 (42%)	0.95
Age at onset, years	61.1 ± 8.5	65.7 ± 9.7	0.21
Age at scan, years	64.8 ± 8.6	68.9 ± 10.5	0.21
Time from onset to scan, years	3.8 ± 1.7	3.3 ± 1.6	0.34
MoCA	16.4 ± 7.4	11.7 ± 5.6	0.03[‡]
Calculation from MoCA	1.9 ± 1.4	1.1 ± 1.0	0.01
Modified CDR sum of boxes	5.2 ± 4.3	6.6 ± 4.0	0.73
FBI	13.9 ± 10.1	13.4 ± 7.5	0.36
Limb apraxia subscale of WAB	53.2 ± 8.4	48.7 ± 14.7	0.51
WAB AQ	75.3 ± 16.4	75.8 ± 17.0	0.33
WAB repetition	7.2 ± 1.8	7.6 ± 1.9	0.27
Token Test	9.6 ± 6.9	8.7 ± 5.2	0.72
Boston Naming Test	7.6 ± 4.3	5.2 ± 4.9	0.51
Trail Making Test B (seconds) [‡]	5.3 ± 4.4	1.1 ± 0.5	0.0004
AVLT delayed recall [‡]	6.8 ± 4.4	4.6 ± 1.8	0.28
Rey-Osterrieth complex figure test [‡]	8.0 ± 4.6	3.2 ± 2.2	0.001
VOSP letters	16.4 ± 6.5	13.9 ± 7.1	0.23
VOSP cube	7.7 ± 3.4	5.3 ± 3.6	0.001
Global PiB ratio	2.05 ± 0.15	2.23 ± 0.25	0.007
Presence of lobar microbleeds (%)	1/10 (10%)	8/12 (67%)*	0.007
Presence of deep microbleeds (%)	1/10 (10%)	4/12 (33%)	0.19
Total WMHp	3.03 ± 2.30	5.00 ± 2.66	0.04

Data shown as mean ± standard deviation. APOE = apolipoprotein E; MoCA = Montreal Cognitive Assessment; FBI = Frontal Behavioral Inventory; WAB AQ = Western Aphasia Battery Aphasia Quotient; AVLT = Auditory Verbal Learning Test; WMHp = white matter hyperintensities proportion, expressed as percentage of total white matter; VOSP = Visual Object and Space Perception battery.

* One subject with microbleeds had frontal linear hypointense T2 signal likely reflecting hemosiderin due to possible trauma. This subject did not have any structural damage in the frontal lobe.

[‡] Age and education adjusted Mayo Older Americans Normative Studies (MOANS) scores. Two subjects were under the age range for MOANS.

[‡] P value for MoCA which includes an inherent education adjustment. Additional adjustment for education with regression yields p=0.12.