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APOE4 influences β -amyloid burden in primary progressive aphasia and speech apraxia

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Abstract

Background—Apolipoprotein E epsilon 4 (APOE4) is a risk factor for β -amyloid deposition in Alzheimer's dementia. Its influence on β -amyloid deposition in speech and language disorders, including primary progressive aphasia (PPA), is unclear.

Methods—One hundred and thirty subjects with PPA or speech apraxia underwent APOE genotyping and Pittsburgh compound B (PiB) PET scanning. The relationship between APOE4 and PiB status, as well as severity and regional distribution of PiB, was assessed.

Results—Forty-five subjects had an APOE4 allele and 60 subjects were PiB-positive. The odds ratio for a subject with APOE4 being PiB-positive compared to a subject without APOE4 being PiB-positive was 10.2 (4.4–25.5, $p < 0.0001$). APOE4 status did not influence regional PiB distribution or severity.

Conclusion—APOE4 increases the risk of β -amyloid deposition in PPA and speech apraxia, but does not influence regional β -amyloid distribution or severity.

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Keywords

Apolipoprotein; Pittsburgh Compound B; primary progressive aphasia; logopenic aphasia; speech apraxia

1. Introduction

The presence of the apolipoprotein E epsilon 4 (APOE4) allele is a risk factor for Alzheimer's disease (AD)[1–3] and hence for β -amyloid deposition. While β -amyloid deposition is usually associated with episodic memory loss and Alzheimer's dementia[4], patients with progressive speech or language disorders have also been reported to have AD or β -amyloid deposition. Patients with early and prominent deficits in language are generally diagnosed with one of three variants of primary progressive aphasia (PPA)[5]. The three variants include logopenic PPA (lvPPA) in which patients present with anomia, poor word retrieval in spontaneous speech, difficulty repeating sentences and phonological errors, semantic PPA (svPPA) in which patients present with anomia and loss of word knowledge, and agrammatic PPA (agPPA) in which patients have difficulty with grammar and syntax, and can also have a motor speech disorder known as apraxia of speech[6, 7]. In addition, patients with early and prominent deficits in speech in which the presenting disorder is dominated by apraxia of speech, or where apraxia of speech is the sole presenting feature[8], can be classified as progressive apraxia of speech (PAOS)[8, 9]. Hence progressive speech and language disorders can be broadly classified as PPA and PAOS. Beta-amyloid deposition is strongly associated with lvPPA[10–12], but has also been observed to occur in patients with svPPA[13], agPPA[11] and PAOS[8, 9], although these latter PPA variants and PAOS are usually associated with frontotemporal lobar degeneration pathologies[10, 14–16]. It is unclear whether the APOE4 allele is a risk factor for the presence of β -amyloid deposition in PPA or PAOS, or within the PPA variants. It is also unclear whether APOE4 influences the distribution or severity of β -amyloid deposition in these patients. Understanding the relationship between the APOE4 genotype and β -amyloid deposition in patients with speech and language disorders is important to better understand the underlying biological mechanisms that may account for pathological variability in these subjects.

The aim of this study was to use a large cohort of 130 patients with PPA or PAOS to determine the relationship between the APOE4 allele and β -amyloid deposition. We hypothesized that the presence of the APOE4 allele would strongly increase the odds of β -amyloid deposition, but would not influence β -amyloid severity or distribution.

2. Materials and Methods

2.1. Subjects

Between February 2010 and February 2013 we consecutively recruited subjects with a progressive speech or language disorder who presented to the Department of Neurology, Mayo Clinic, Rochester MN (n=130). All 130 subjects underwent APOE genotyping as previously described[17, 18] and completed ^{11}C Pittsburgh compound B (PiB) PET scanning for determination of β -amyloid status (see below).

All 130 subjects underwent detailed speech and language evaluations, as previously described[8], including the Western Aphasia Battery[19] in which the Aphasia Quotient is a measure of aphasia severity, and neurological testing that included the Mini-Mental State Examination[20] as a measure of global cognitive impairment. Subjects were classified as PAOS, or as one of the three well-recognized PPA variants (agPPA, svPPA or lvPPA), based on qualitative and quantitative speech and language data which was influenced by the PPA consensus guidelines[5], and on recommended criteria for the diagnosis of PAOS[8, 9]. Subjects who met criteria for PPA but could not be classified into one of the three PPA variants were labeled as unclassified (ucPPA).

The study was approved by the Mayo Clinic institutional review board and all patients consented for enrolment into the study.

2.2. Imaging analysis

All PiB-PET scans were performed using a PET/CT scanner (General Electric, Milwaukee, WI) operating in three-dimensional mode. Each subject was injected with approximately 614 MBq of PiB and after a 40 minute uptake period, a 20 minute PiB scan was obtained. All subjects also underwent MRI at 3.0 Tesla, which included a 3D magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence, within two days of the PiB-PET scan.

A global PiB ratio[21] was calculated for each subject in order to classify subjects as PiB-positive or PiB-negative. All PiB-PET images were co-registered to the MPRAGE for each patient, and the automated anatomical labeling atlas[22] was used to calculate median PiB uptake for the following 6 cortical regions-of-interest: temporal lobe, parietal lobe, posterior cingulate/precuneus, anterior cingulate, prefrontal cortex, and occipital lobe (left and right were combined for all regions). Median PiB uptake in each of the 6 regions was divided by median cerebellar uptake to create uptake ratios. A global cortical PiB retention summary was formed by calculating median uptake ratio values across all 6 regions. Patients were classified as PiB-positive using a cortical-to-cerebellar (SUVR) ratio cut-point of 1.5[21].

In addition, a voxel-level comparison of PiB-PET regional distribution was performed within all PiB-positive subjects. All voxels in the PiB-PET image were divided by median uptake of the cerebellum to form PiB uptake ratio images. The PiB-PET uptake ratio images were then normalized to a customized template using the normalization parameters from the MPRAGE normalization. Two-sided t-tests were used to compare all the PiB-positive subjects with an APOE4 allele and the PiB-positive subjects without an APOE4 allele to an age and gender matched control cohort. The control cohort consisted of 30 healthy subjects that had all undergone an identical PiB-PET and MRI acquisition and were all PiB-negative. Results were corrected for multiple comparisons using the family wise error (FWE) correction at $p < 0.05$. Direct comparisons were also performed between the APOE4 negative and positive disease groups, assessed uncorrected for multiple comparisons at $p < 0.001$ with an extent threshold of 100 voxels. These analyses were also repeated using only PiB-positive lvPPA subjects given that the number of PiB-positive lvPPA subjects were large enough for analysis, and that the vast majority of PiB-positive PPA subjects were in fact lvPPA. Age and gender was included as a covariate in all analyses.

2.3. Statistical analysis

Statistical analyses were performed utilizing JMP computer software (JMP Software, version 9.0.0; SAS Institute Inc., Cary, NC) with significance assessed at $p < 0.05$. Odds ratios and confidence intervals were calculated using logistic regression for PPA, PAOS, and for the secondary analysis for each PPA variant. For the svPPA group, in order to calculate a conservative odds ratio, we had to artificially replace the 0 cell count with a count of 1, based on published recommendation[23]. Mann-Whitney-U test was used to compare SUVR ratios between APOE4 positive PiB-positive subjects and APOE4 negative PiB-positive subjects. Given the strong association between lvPPA and β -amyloid deposition, we performed additional analyses for the lvPPA group. First, we compared the lvPPA group to all other PPA variants and PAOS. Secondly, within the lvPPA group, we compared demographic and clinical features for all the PiB-positive subjects, stratified by APOE4 status (i.e. APOE4 positive PiB-positive lvPPA versus APOE4 negative PiB-positive lvPPA).

3. Results

Results for APOE4 and PiB status by clinical diagnosis are shown in Table 1. Of the 130 subjects with a progressive speech and language disorder, 45 (34%) had at least one APOE4 allele while the remaining 85 did not. Sixty subjects (46%) were PiB-positive. Given an APOE4 positive status a subject was more than 10X more likely to be PiB-positive than if the APOE4 allele was not present ($p < 0.0001$). Seven subjects were APOE 4/4 homozygotes, and all 100% of these subjects were PiB-positive. After excluding the 53 lvPPA subjects, given an APOE4 positive status a subject was 13X more likely to be PiB-positive than if the APOE4 allele was not present (OR=13.0; CI: 3.3–51.0; $p < 0.0001$).

3.1. PPA

Of the 91 PPA subjects, 39 (43%) had at least one APOE4 allele and 53 (58%) were PiB-positive. Given an APOE4 positive status a PPA subject was almost 9X times more likely to be PiB-positive than if the APOE4 allele was not present ($p < 0.0001$).

Within the PPA variants, the proportion of subjects with at least one APOE4 allele was highest in lvPPA (57%), followed by svPPA (43%), ucPPA (25%) and agPPA (0%). Similarly, the proportion of PiB-positive subjects was highest in lvPPA (89%), followed by ucPPA (25%), svPPA (21%), and agPPA (0%). Given an APOE4 positive status, the svPPA and ucPPA subjects were more likely to be PiB-positive than if the APOE4 allele was not present ($p = 0.01$ and $p = 0.07$). The lvPPA subjects did not have significant odds ratios. Six of the lvPPA subjects were APOE 4/4 homozygotes, and all were PiB-positive. All agPPA subjects were APOE4 negative and all were PiB-negative.

Subjects with lvPPA were more likely to be APOE4 positive than all other speech or language subjects combined (57% vs. 23%; $p < 0.0001$). Subjects with lvPPA were also more likely to be PiB-positive compared to all other speech or language subjects combined (89% vs. 20%; $p < 0.0001$). After accounting for APOE4 status, the odds ratio for a subject with lvPPA to be PiB-positive compared to a subject with any of the other speech or language

syndromes being PiB-positive was 33 (CI: 11.7–113.6; $p < 0.0001$). Demographic and clinical features of all subjects by APOE4 status are shown in Table 2. Notable observations include the fact that the PiB-positive lvPPA subjects without an APOE4 allele were on average 10 years younger than the lvPPA PiB-positive subjects with an APOE4 allele ($p = 0.03$). No other demographic or clinical differences were observed between the PiB-positive subjects stratified by APOE4 status.

3.2. PAOS

Of the 39 PAOS subjects, six (15%) had at least one APOE4 allele and seven (18%) were PiB-positive. Given an APOE4 positive status, a PAOS subject was more than 7X more likely to be PiB-positive than if the APOE4 allele was not present ($p = 0.04$). One PAOS subject was APOE 4/4 homozygous and was PiB-positive. The APOE4 allele frequency in the PAOS group was significantly different from the frequency observed in PPA (43%) ($P = 0.002$) but was not different from the APOE4 allele frequency in PPA when the lvPPA subgroup was excluded from PPA (9/38=24%) ($p = 0.36$).

3.3. Imaging findings

In the voxel-level analyses, the regional distribution of PiB-PET uptake was very similar in the PiB-positive subjects with and without an APOE4 allele, with widespread PiB-PET uptake observed in prefrontal cortex, temporoparietal lobes, and posterior cingulate/precuneus in both groups compared to controls (Figure 1). No differences were observed between the APOE4 positive and negative groups on direct comparison. The median (interquartile range) global PiB ratio was 2.1 (2.0–2.3) in the PiB-positive APOE4 negative subjects and 2.1 (1.9–2.3) in the PiB-positive APOE4 positive subjects, with no difference observed across the groups ($p = 0.74$). Similarly, no differences were observed when the analyses were limited to only lvPPA subjects.

4. Discussion

This study demonstrates that the APOE4 allele is associated with β -amyloid deposition in subjects with speech and language disorders, including PPA, but APOE4 does not appear to affect the severity and regional distribution of β -amyloid deposition in these subjects.

The APOE4 allele was associated with an increased risk of β -amyloid deposition across all subjects. The risk was, in fact, highest in subjects homozygous for the APOE 4/4 allele, since all these subjects had β -amyloid deposition on PiB-PET. Interestingly, the association between APOE4 and β -amyloid deposition was also found for most of the clinical groups that are typically associated with FTLD pathologies, i.e. svPPA, ucPPA and PAOS. This finding demonstrates that patients with any of these syndromic variants are at increased risk of having β -amyloid deposition in the brain if they have an APOE4 allele; a finding that would affect patient management and treatment strategies, particularly if amyloid imaging is unavailable. These findings do not, however, imply that β -amyloid deposition is the primary pathological process accounting for the presenting syndrome. Instead, β -amyloid deposition may represent a secondary pathology in these subjects. In fact, in a recent case report, a PPA patient that was PiB-positive was found to have FTLD pathology, as well as β -amyloid

deposition[24]. Therefore, the APOE4 allele may be increasing the risk of β -amyloid being co-deposited, as opposed to increasing the risk of AD being the primary pathology accounting for these syndromes. Tau assessment either via CSF analysis or tau-PET imaging could be helpful in this regard. Our findings also fit with the fact that the APOE4 allele has been shown to be associated with β -amyloid deposition in diseases characterized pathologically by FTLT-tau, as well as FTLT characterized by deposition of the TAR DNA binding protein of 43kDa (TDP-43)[17, 25]. The PAOS, agPPA and svPPA syndromes are indeed most commonly pathologically characterized by tau and TDP-43 deposition, respectively[10, 14–16].

The association between APOE4 and β -amyloid deposition in agPPA was difficult to assess since all agPPA subjects were PiB-negative and all were APOE4 negative. The findings indicate however that agPPA subjects are much less likely to have β -amyloid deposition. It is possible that the absence of β -amyloid deposition in agPPA is a direct result of the fact that none of the agPPA subjects had an APOE4 allele. It is, however, unclear why none of the 12 agPPA subjects had an APOE4 allele, since the APOE4 allele occurs in approximately 25–30% in the healthy population[26–28]. It is possible that the absence of the APOE4 allele in the agPPA was due to a relatively small sample size.

This is the first study to report the APOE4 allele frequency in patients with PAOS. Interestingly, the frequency of APOE4 was low, with only 15% of PAOS subjects having an APOE4 allele. With that said, however, PAOS is strongly associated with tau pathology, with almost 100% of such subjects having tau pathology; with the majority having progressive supranuclear palsy pathology[14, 15, 29]. Although our PAOS sample size was less than half the sample size of our PPA group, the APOE4 allele frequency in PAOS was significantly lower than the frequency observed in PPA. This difference was however driven by the lvPPA subgroup.

The APOE4 allele was most frequent in the lvPPA variant. Similarly, lvPPA had the highest frequency of positive PiB-PET scans with almost 90% being positive, similar to previous reports[11, 30]. Interestingly, there was an almost equal chance of being PiB-positive whether the subject did, or did not have, an APOE4 allele, although of note was the fact that 100% of the APOE 4/4 homozygotes were PiB-positive. Therefore, the striking association of lvPPA with β -amyloid deposition remained strong even after taking into account APOE4. It appears that although we cannot entirely exclude APOE4 as having a role in β -amyloid deposition in lvPPA, there may be another unknown factor or factors, which is playing a role. Of note is the fact that the PiB-positive lvPPA subjects without an APOE allele were unusually young. While it is possible that older age played a role in the PiB-positive status of some of the non-lvPPA subjects without an APOE4 allele, older age cannot explain the high frequency of PiB-positivity in APOE4 negative lvPPA subjects and the lack of association with APOE4. Given the young age at evaluation, and even younger age at onset, it would be reasonable to postulate a genetic factor playing some type of a role in these subjects. One limitation of the study is the lack of screening for dominantly inherited Alzheimer's or FTLT genes[31], although none of our PiB-positive subjects had a positive family history. We have however recently screened the six PiB-negative lvPPA subjects for

FTLD gene mutations and identified a progranulin gene mutation in three of the six subjects[32].

Our finding that APOE4 was associated with increased odds of having β -amyloid deposition persisted within the PPA cohort as a whole. This finding differs from another study that did not observe an association between APOE4 and the presence of Alzheimer's disease in 31 PPA subjects[33]. While it is possible that this other study suffered from a lack of power, the APOE4 frequencies were slightly different between studies (32% versus 43%) and the outcome measures also differed across studies with our study using β -amyloid deposition measured on PiB-PET and the previous study diagnosing Alzheimer's disease by assessing the presence of both β -amyloid and tau on autopsy.

We found no evidence that the APOE4 allele influences the severity of β -amyloid deposition measured by the global PiB ratio, or the distribution of β -amyloid deposition, in subjects that are PiB-positive. These findings were consistent across all PiB-positive subjects and within the lvPPA group only. A typical distribution of β -amyloid deposition was observed both in subjects with and without the APOE4 allele, with greatest PiB-PET uptake observed in the prefrontal cortex, temporoparietal lobes, and posterior cingulate/precuneus. This topographic pattern concurs with the distribution of β -amyloid deposition observed at autopsy in AD[34], and with the distribution of PiB-PET uptake typically reported in subjects with Alzheimer's dementia[21, 35] and lvPPA[11, 12, 36, 37]. Therefore, while APOE4 may increase the odds of developing β -amyloid deposition, once β -amyloid deposition is present the APOE4 allele does not appear to influence the spread or amount of β -amyloid deposition. Previous imaging studies in Alzheimer's dementia have reported conflicting findings concerning whether the APOE4 allele influences the degree of β -amyloid deposition in subjects that are PiB-positive, with some showing increased β -amyloid deposition associated with the APOE4 allele[38], while others found decreased β -amyloid deposition associated with the APOE4 allele[39, 40], and others found no differences according to APOE4 genotype[41, 42]. Pathological studies have similarly observed conflicting findings with some not observing any relationship between the burden of β -amyloid senile plaques and the APOE4 allele in AD[43], and others finding a greater burden of plaques in APOE4 carriers[44, 45]. Discrepancies across studies may be due to heterogeneous clinical and pathological cohorts and methodological differences. Our study is, however, the first to assess this issue in PiB-positive subjects with speech and language disorders, and in subjects specifically with lvPPA, and in this cohort APOE4 does not appear to be associated with the severity of β -amyloid deposition.

Our findings suggest that determining the APOE4 allele status in subjects with PPA and PAOS may help to shed light on why β -amyloid deposition is observed in some subjects, despite an expected isolated FTLD pathology. Autopsy studies will, however, be needed to determine whether the β -amyloid deposition reflects a primary or secondary pathology in these cases.

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Abbreviations

AD	Alzheimer's disease
PPA	primary progressive aphasia
PAOS	progressive apraxia of speech
lvPPA	logopenic variant of PPA
svPPA	semantic variant of PPA
agPPA	agrammatic variant of PPA
ucPPA	unclassified PPA
PiB	Pittsburgh Compound B
PET	positron emission tomography
APOE4	apolipoprotein e4
MPRAGE	3D magnetization prepared rapid acquisition gradient echo
FTLD	frontotemporal lobar degeneration

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Research in Context

Systematic review

We performed a pubmed search for articles published in English with search terms “apolipoprotein”, “amyloid”, “Pittsburgh Compound B”, “Alzheimer’s disease”, “apraxia of speech” and “aphasia”, in order to identify manuscripts that had assessed apolipoprotein genotyping and β -amyloid deposition in speech and language disorders and Alzheimer’s disease.

Interpretation

This is the first study to show that the apolipoprotein e4 (APOE4) allele increases the risk of β -amyloid deposition in primary progressive aphasia and progressive apraxia of speech. We also show that APOE4 does not influence the severity or distribution of β -amyloid deposition in subjects in which β -amyloid deposition is present. Previous studies have reported conflicting results regarding the relationship between APOE4 and the severity of β -amyloid deposition, and have focused only on subjects with Alzheimer’s dementia.

Future directions

Autopsy studies will be needed to determine whether β -amyloid deposition present in speech and language subjects reflects a primary or secondary pathology.

PiB-positive/APOE4 negative

PiB-positive/APOE4 positive

Figure 1. Voxel-level maps of PiB-PET uptake in PiB-positive APOE4 negative and PiB-positive APOE4 positive subjects compared to controls

Results are shown after correction for multiple comparisons at $p < 0.05$. Renders were generated using the BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>).

Table 1
Percentages of subjects with PAOS and PPA variants with the APOE4 allele stratified by PiB status

Diagnosis	All		APOE4 +		APOE4 -		Odds ratio & p-values*
	APOE4 +	PiB-positive	PiB-negative	PiB-positive	PiB-negative	PiB-positive	
All subjects (n=130)	45 (34%)	60 (46%)	9 (20%)	36 (80%)	61 (72%)	24 (28%)	10.2 (CI: 4.4 – 25.5); p<0.0001
PAOS (n=39)	6 (15%)	7 (18%)	3 (50%)	3 (50%)	29 (88%)	4 (12%)	7.3 (CI: 1.1 – 54.1); p=0.04
PPA (n=91)	39 (43%)	53 (58%)	6 (15%)	33 (85%)	32 (62%)	20 (38%)	8.8 (CI: 3.3 – 26.8); p<0.0001
agPPA (n=12)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	12 (100%)	0 (0%)	N/A
[†] svPPA (n=14)	6 (43%)	3 (21%)	3 (50%)	3 (50%)	8 (100%)	0 (0%)	8.0 (CI: 2.2 – 203.3); p=0.01
lvPPA (n=53)	30 (57%)	47 (89%)	2 (7%)	28 (93%)	4 (17%)	19 (83%)	2.9 (CI: 0.5 – 22.8); p=0.22
ucPPA (n=12)	3 (25%)	4 (33%)	1 (33%)	2 (67%)	8 (89%)	2 (11%)	16.0 (CI: 0.8 – 73.0); p=0.07

* Odds ratio's and p values are for subjects with APOE4 being PiB-positive compared to subjects without APOE4 being PiB-positive.

[†] To calculate odds ratio and CI for this group we artificially added 1 APOE4 negative PiB-positive subject as a conservative option.

PPA = primary progressive aphasia; agPPA = agrammatic variant of primary progressive aphasia; lvPPA = logopenic variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia; ucPPA = unclassified PPA; PAOS = progressive apraxia of speech; CI = confidence interval

Table 2

Demographics and clinical features of all subjects and by APOE4 status

Diagnosis	All	APOE4 +		APOE4 –	
		PIB-negative	PIB-positive	PIB-negative	PIB-positive
Age, years					
All (n=130)	69 (62–74)	62 (59–68)	70 (65–74)	70 (65–75)	66 (56–74)
PAOS (n=39)	73 (64–78)	67 (63–71)	74 (67–74)	73 (65–79)	76 (70–78)
PPA = (n=91)	68 (62–73)	61 (58–67)	70 (65–73)	69 (65–72)	62 (56–72)
agPPA (n=12)	70 (65–72)	–	–	70 (65–72)	–
svPPA (n=14)	69 (63–72)	60 (59–61)	70 (69–73)	71 (69–73)	–
lvPPA (n=53)	68 (70–73)	63 (60–65)	70 (65–73)	66 (63–68)	60 (56–71)
ucPPA (n=12)	70 (67–73)	70	66 (64–73)	70 (65–73)	76
Gender, % F					
All (n=130)	67 (52%)	4 (44%)	18 (50%)	31 (51%)	14 (58%)
PAOS (n=39)	20 (51%)	1 (33%)	1 (33%)	14 (48%)	4 (100%)
PPA = (n=91)	47 (52%)	3 (50%)	17 (52%)	17 (53%)	10 (50%)
agPPA (n=12)	8 (67%)	–	–	8 (67%)	–
svPPA (n=14)	7 (50%)	2 (67%)	1 (33%)	4 (50%)	–
lvPPA (n=53)	26 (49%)	0 (0%)	14 (50%)	2 (50%)	10 (53%)
ucPPA (n=12)	6 (50%)	1 (100%)	2 (100%)	3 (38%)	0 (0%)
Illness duration, years					
All (n=130)	3.0 (2.0–4.5)	2.0 (2.0–4.0)	4.0 (3.0–5.0)	3.0 (2.0–4.0)	3.3 (2.4–4.3)
PAOS (n=39)	3.5 (2.2–4.8)	4.0 (3.8–5.0)	4.0 (3.0–7.0)	3.0 (2.0–4.8)	3.5 (3.0–5.0)
PPA = (n=91)	3.0 (2.0–4.0)	2.0 (1.6–2.0)	4.0 (3.0–5.0)	2.8 (1.9–4.0)	3.3 (2.0–4.3)
agPPA (n=12)	2.5 (1.4–3.6)	–	–	2.5 (1.4–3.6)	–
svPPA (n=14)	4.0 (2.3–5.0)	1.5 (1.3–3.3)	8.0 (6.0–11.0)	3.5 (2.8–4.3)	–
lvPPA (n=53)	3.5 (2.0–5.0)	2.0 (2.0–2.0)	4.0 (3.0–5.0)	2.5 (2.0–3.0)	3.5 (2.3–4.5)
ucPPA (n=12)	2.0 (1.4–3.0)	2.0	2.5 (2.3–2.8)	1.8 (1.0–3.3)	2.0
MMSE (/30)					
All (n=130)	27 (23–29)	27 (26–29)	24 (15–27)	29 (27–30)	25 (21–28)
PAOS (n=39)	29 (28–30)	29 (28–29)	27 (25–28)	29 (28–30)	29 (28–29)
PPA = (n=91)	25 (22–28)	27 (25–28)	23 (15–27)	28 (26–29)	24 (20–25)
agPPA (n=12)	29 (24–29)	–	–	29 (24–29)	–

Diagnosis	All	APOE4 +		APOE4 -	
		PIB-negative	PIB-positive	PIB-negative	PIB-positive
svPPA (n=14)	28 (26-29)	28 (27-29)	16 (15-23)	29 (28-29)	-
lvPPA (n=53)	24 (15-27)	27 (26-27)	24 (15-26)	27 (19-28)	24 (18-26)
ucPPA (n=12)	28 (24-28)	14	26 (24-27)	28 (27-29)	21
WAB AQ (/100)	All (n=130)	90 (73-96)	83 (73-88)	93 (85-96)	84 (72-89)
	PAOS (n=39)	96 (87-97)	83 (82-89)	96 (93-97)	87 (82-91)
	PPA = (n=91)	85 (73-92)	83 (73-84)	90 (79-93)	83 (63-89)
	agPPA (n=12)	84 (72-89)	-	84 (72-89)	-
	svPPA (n=14)	92 (80-95)	64 (54-79)	92 (89-94)	-
	lvPPA (n=53)	83 (73-88)	83 (73-87)	77 (66-81)	83 (62-89)
	ucPPA (n=12)	93 (90-95)	55	94 (94-95)	78

Data shown as median and interquartile range

PPA = primary progressive aphasia; agPPA =agrammatic variant of primary progressive aphasia; lvPPA = logopenic variant of primary progressive aphasia; svPPA = semantic variant of primary progressive aphasia; ucPPA = unclassified PPA; PAOS = progressive apraxia of speech