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# The influence of $\beta$ -amyloid on [ $^{18}\text{F}$ ]AV-1451 in semantic variant of primary progressive aphasia

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## Abstract

### Objective

To compare [ $^{18}\text{F}$ ]AV-1451 uptake in the semantic variant of primary progressive aphasia (svPPA) to Alzheimer dementia, and determine whether increased uptake in svPPA is associated with the presence of  $\beta$ -amyloid ( $\text{A}\beta$ ).

### Methods

Thirty-one participants with svPPA underwent MRI and Pittsburgh compound B–PET scanning, and 17 of these also underwent [ $^{18}\text{F}$ ]AV-1451 tau-PET. A global Pittsburgh compound B standardized uptake value ratio was calculated for all participants, with a cutoff of 1.42 used to define  $\text{A}\beta(+)$  participants. We assessed region and voxel-level [ $^{18}\text{F}$ ]AV-1451 uptake in the whole svPPA cohort and separately in  $\text{A}\beta(+)$  and  $\text{A}\beta(-)$  svPPA groups, compared to 12  $\text{A}\beta(+)$  participants with Alzheimer dementia and 170 cognitively normal,  $\text{A}\beta(-)$  controls.

### Results

Of the entire cohort of participants with svPPA, 26% were  $\text{A}\beta(+)$ . The  $\text{A}\beta(+)$  participants were older at scan compared to the  $\text{A}\beta(-)$  participants. svPPA showed elevated [ $^{18}\text{F}$ ]AV-1451 uptake in anteromedial temporal regions but the degree of uptake was lower than in Alzheimer dementia. After controlling for age,  $\text{A}\beta(+)$  status in svPPA was associated with significantly higher uptake in all anteromedial and inferior/middle lateral temporal regions, but uptake was still lower than in Alzheimer dementia.

### Conclusion

Although [ $^{18}\text{F}$ ]AV-1451 uptake is focally elevated in svPPA, the level of uptake is much less than what occurs in Alzheimer dementia and appears to be at least partially related to  $\text{A}\beta$ . Therefore, it is possible that some of the increased uptake of [ $^{18}\text{F}$ ]AV-1451 in svPPA is related to binding paired helical filament tau.

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

## Glossary

**A $\beta$**  =  $\beta$ -amyloid; **FDG** = [ $^{18}\text{F}$ ]-fluorodeoxyglucose; **MCALT** = Mayo Clinic Adult Lifespan Template; **MP-RAGE** = magnetization-prepared rapid-acquisition gradient echo; **PART** = primary age-related tauopathy; **PiB** = Pittsburgh compound B; **ROI** = region of interest; **SUVR** = standardized uptake value ratio; **svPPA** = semantic variant of primary progressive aphasia; **TDP-43** = TAR DNA binding protein of 43 kDa.

The semantic variant of primary progressive aphasia (svPPA)<sup>1</sup> is characterized by anomia and the loss of conceptual knowledge pertaining to the meaning of words and results from neurodegeneration of the anteromedial temporal lobes. It is most frequently associated with deposition of the TAR DNA binding protein of 43 kDa (TDP-43) at autopsy,<sup>2–8</sup> although svPPA cases have been reported with Alzheimer disease<sup>3,6,9,10</sup> and definite or possible primary age-related tauopathy (PART).<sup>11,12</sup> PET ligands, such as [ $^{18}\text{F}$ ]AV-1451,<sup>13</sup> are now available that allow the detection of the paired helical filament 3R + 4R tau associated with Alzheimer disease and show little or no binding to TDP-43.<sup>14–16</sup> Despite this, elevated uptake of [ $^{18}\text{F}$ ]AV-1451 has been reported in patients with svPPA, with uptake observed in anteromedial temporal lobes concordant with the topographic distribution of neurodegeneration.<sup>17–19</sup> It is, however, unclear whether the degree of uptake observed with [ $^{18}\text{F}$ ]AV-1451 is comparable to the degree of uptake observed in Alzheimer disease. In addition, the biological basis for [ $^{18}\text{F}$ ]AV-1451 uptake in svPPA is currently unknown.<sup>17–19</sup>

We aimed to determine whether the degree of [ $^{18}\text{F}$ ]AV-1451 uptake in svPPA was similar to that observed in Alzheimer dementia, and whether the pattern or degree of uptake in svPPA differs according to the presence of  $\beta$ -amyloid (A $\beta$ ) deposition on PET imaging. The presence of A $\beta$  deposition on PET is typically considered a biomarker for Alzheimer disease, and hence we will be able to evaluate the evidence that [ $^{18}\text{F}$ ]AV-1451 uptake in A $\beta$ (+) participants with svPPA may be related to the presence of paired helical filament tau pathology.

## Methods

### Participants

Thirty-one participants who met clinical criteria for svPPA<sup>1</sup> were recruited from the Department of Neurology, Mayo Clinic, Rochester, MN, into an NIH-funded study (principal investigator K.A.J.) between October 28, 2010, and April 10, 2018. All 31 participants underwent standardized neurologic, speech and language, and neuropsychological assessments, Pittsburgh compound B (PiB)-PET, and a 3-tesla volumetric MRI. Twenty-five of the 31 participants with svPPA underwent APOE genotyping and 17 underwent [ $^{18}\text{F}$ ]AV-1451 PET.

The 17 participants with svPPA who underwent [ $^{18}\text{F}$ ]AV-1451 scans were matched 10:1 by age and sex to 170 A $\beta$ (–) cognitively normal controls (median [interquartile range] age at scan 66 [59–70] years, global PiB standardized uptake value ratio [SUVR] 1.31 [1.27–1.36], and 59% male) recruited into

the Mayo Clinic Study of Aging.<sup>20</sup> Twelve A $\beta$ (+) participants with typical amnesic Alzheimer dementia (median [interquartile range] age at scan 74 [70–76] years, global PiB SUVR 2.74 [2.57–2.92], Montreal Cognitive Assessment 13 [9–18], and 51% male) were also selected from the Mayo Clinic Alzheimer's Disease Research Center database matched 3:1 by age and sex to the 4 A $\beta$ (+) participants with svPPA who had [ $^{18}\text{F}$ ]AV-1451 scans. All controls and participants with Alzheimer dementia had undergone identical [ $^{18}\text{F}$ ]AV-1451, PiB-PET, and 3-tesla volumetric MRI acquisitions as the participants with svPPA.

All participants consented to having their data utilized for research, and the study was approved by the Mayo Clinic institutional review board.

### Clinical test battery

All participants with svPPA were administered identical neurologic, speech and language, and neuropsychological test batteries. The neurologic battery included tests of general cognitive function (Montreal Cognitive Assessment),<sup>21</sup> presence of psychiatric features (Neuropsychiatric Inventory–short version),<sup>22</sup> behavioral control (Cambridge Behavioral Inventory),<sup>23</sup> executive function (Frontal Assessment Battery), praxis (praxis subtest of the Western Aphasia Battery),<sup>24</sup> face recognition (10-item facial recognition task),<sup>25</sup> and motor parkinsonism (Movement Disorders Society–sponsored revision of the Unified Parkinson's Disease Rating Scale, Part III).<sup>26</sup> The speech-language battery included tests of aphasia severity (Western Aphasia Battery Aphasia Quotient), confrontation naming (the Sydney Language Battery for Naming),<sup>27</sup> single-word comprehension (Pyramids and Palm Trees Test, word-word version),<sup>28</sup> object knowledge (the Sydney Language Battery for Semantic Association Task),<sup>27</sup> phonemic fluency (Letter Fluency Test [FAS]), semantic fluency (Animal Fluency Test), syntactic ability (Northwestern Anagram Test),<sup>29</sup> sentence repetition (repetition subtest of the Boston Diagnostic Aphasia Examination and the repetition subtest of the Western Aphasia Battery),<sup>30</sup> surface vs deep dyslexia (Western Aphasia Battery reading irregular words and reading nonwords), and lexical processing (Peabody Picture Vocabulary Test). The neuropsychological battery included tests of visual perceptual abilities (the Visual Object and Space Perception Battery–fragmented letters),<sup>31</sup> visual spatial abilities (Visual Object and Space Perception Battery–cube analysis<sup>31</sup> and the Rey-Osterrieth Complex Figure),<sup>32</sup> psychomotor speed (Trail Making Test, Part A),<sup>32</sup> executive function (Trail Making Test, Part B),<sup>32</sup> working memory (Digit Span and Spatial Span),<sup>32</sup> verbal and visual episodic memory (the

## Image acquisition

All PET scans were acquired using a PET/CT scanner (GE Healthcare, Milwaukee, WI) operating in 3-dimensional mode. For tau-PET, an IV bolus injection of approximately 370 MBq (range 333–407 MBq) of [<sup>18</sup>F]AV-1451 was administered, followed by a 20-minute PET acquisition performed 80 minutes after injection. For [<sup>18</sup>F]-fluorodeoxyglucose (FDG)-PET, participants were injected with <sup>18</sup>F-FDG of approximately 459 MBq (range 367–576 MBq), and after a 30-minute uptake period, an 8-minute <sup>18</sup>F-FDG scan was performed. For PiB-PET, participants were injected with PiB of approximately 628 MBq (range 385–723 MBq), and after a 40 minute uptake period, a 20-minute PiB scan was obtained consisting of four 5-minute dynamic frames. Standard corrections were applied. Emission data were reconstructed into a 256 × 256 matrix with a 30-cm field of view (pixel size = 1.0 mm, slice thickness = 1.96 mm). A global PiB SUVR was also generated for each patient in the study using the cerebellar crus gray matter as a reference region, and a cut point of 1.42 was used to establish Aβ positivity, as previously described.<sup>34</sup> All participants had a 3-tesla MP-RAGE sequence performed on the same day as the tau-PET, as previously described.<sup>34</sup>

## [<sup>18</sup>F]AV-1451 analysis

Patterns of [<sup>18</sup>F]AV-1451 uptake were assessed both at the region and voxel level using SPM12 (fil.ion.ucl.ac.uk/SPM). The [<sup>18</sup>F]AV-1451 images were each registered to the participant's MP-RAGE using 6 degrees-of-freedom registration. Normalization parameters were computed between each MP-RAGE and the Mayo Clinic Adult Lifespan Template (MCALT) (nitrc.org/projects/mcalt/) using ANTs.<sup>35</sup> With these parameters, the MCALT atlases were propagated to native MP-RAGE space and used to output region-level data from the following set of 10 regions of interest (ROIs): temporal pole (middle + superior temporal pole), inferior/middle temporal gyrus, superior temporal gyrus, amygdala, entorhinal cortex, fusiform gyrus, medial frontal lobe (frontal superior medial + anterior cingulate + supplementary motor area), orbitofrontal lobe (inferior, middle, superior, and medial orbitofrontal cortex + rectus gyrus), inferior parietal lobe (inferior parietal + supramarginal + angular gyrus), and precuneus. We specifically analyzed many subregions of the temporal lobe, as well as frontal regions, because of their involvement in svPPA and regions in the parietal lobe since [<sup>18</sup>F]AV-1451 uptake has been observed in these regions in Alzheimer dementia. Median [<sup>18</sup>F]AV-1451 was calculated from both gray and white matter voxels in each ROI and divided by median uptake in cerebellar crus gray matter to create SUVRs. For the voxel-level analyses, all voxels in the MP-RAGE-space [<sup>18</sup>F]AV-1451 images were divided by the median uptake in the cerebellar crus gray matter using the MCALT atlas to create SUVR images. These SUVR images were normalized to the MCALT and smoothed at 6 mm full-width at half maximum. Voxel-level comparisons

were performed assessing uptake in the Aβ(–) and Aβ(+) participants with svPPA compared to controls and the participants with Alzheimer dementia. Results were assessed using 2-sided *t* tests in SPM12, at *p* < 0.05 after correction for multiple comparisons using the family-wise error correction. Age and sex were included in all analyses as covariates.

## Statistical analysis

We fit a Bayesian hierarchical linear regression model using Markov Chain Monte Carlo simulation to estimate mean log-transformed [<sup>18</sup>F]AV-1451 uptake across the 10 ROIs separately for each of 4 diagnosis groups [Aβ(–) svPPA, Aβ(+) svPPA, Aβ(+) Alzheimer dementia, and controls] while adjusting for age and within-participant correlation. By estimating all regional quantities of interest within a single hierarchical model, we can borrow statistical strength across regions, stabilize our estimates via shrinkage, account for multiple comparisons, and reduce overall mean square error.<sup>36–38</sup>

Our model specified an overall mean within each group and assumed that regional values for the group were normally distributed with a group-specific SD, a distribution denoted by Normal( $\mu_{\text{group}}$ ,  $\sigma_{\text{group}}$ ). The means of the control and Alzheimer dementia groups were assumed independent of each other and of the 2 svPPA means while the Aβ(–) and Aβ(+) svPPA means were allowed to be correlated. Weakly informative priors were used for the group-wise means by specifying a Normal(0, 2) prior distribution. The group-wise SD for control and Alzheimer dementia groups were modeled as following a half-Normal(0, 2) distribution and the group-wise SD for both svPPA groups as following a half-Normal(1, 3). Our model also included a participant-specific intercept term modeled as Normal(0,  $\sigma_{\text{participant}}$ ). A priori, this participant-specific SD was given a weakly informative half-Normal(0, 3) distribution. To account for age, which we centered at 65 and scaled by 10 years, we included an age coefficient for controls, Alzheimer dementia, and svPPA. These 3 parameters were given weakly informative Normal(0, 1) priors.

Results were based on 100 parallel Markov Chain Monte Carlo chains with randomly generated initial values, each of length 200,000 and thinned to every 20th value, resulting in a posterior sample size of 1,000,000. We report interval estimates for regional means and group-wise differences in regional means based on quantiles of the samples. The posterior probability that a regional mean of one group is greater than that of another group is based on the proportion of posterior samples where a positive difference was observed. Analyses were performed with R<sup>39</sup> version 3.4.2 using the rjags package<sup>40</sup> version 4-6 running JAGS version 4.

## Standard protocol approvals, registrations, and patient consents

The study was approved by the Mayo Clinic institutional review board. All participants consented to participate in the research study.

**Table 1** Demographics and clinical features of the full svPPA cohort of 31 participants

	Aβ(−) (n = 23)	Aβ(+) (n = 8)	Total (n = 31)
<b>Demographic features</b>			
Sex, male, n (%)	13 (56.5)	3 (37.5)	16 (51.6)
Age at scan, y	65 (58–69)	75 (70–78)	68 (60–72)
Global PiB SUVRs	1.28 (1.24–1.32)	1.99 (1.66–2.17)	1.31 (1.26–1.48)
Right-handedness, n (%) <sup>a</sup>	18 (78.3)	8 (100.0)	26 (83.9)
Disease duration, y	4 (2–5)	4 (3–6)	4 (2–5)
Education, y	16 (16–18)	13 (12–14)	16 (14–18)
APOE ε4 carriers, n (%) <sup>b</sup>	6 (29)	5 (63)	11 (38)
Family history, n (%) <sup>c</sup>	4 (18)	0 (0)	4 (13)
<b>Neurologic measures</b>			
MoCA (/30)	22 (18–24)	20 (14–23)	21 (18–24)
MDS-UPDRS III (/132)	1 (0–2)	4 (0–7)	1 (0–2)
WAB praxis (/60)	59 (58–60)	59 (54–59)	59 (58–60)
NPI-Q (/36)	4 (2–8)	4 (3–5)	4 (2–7)
Cambridge Behavioral Inventory (/180)	38 (19–63)	46 (39–58)	41 (29–63)
Facial recognition (/10)	7 (5–10)	2 (1–4)	7 (3–10)
Frontal Assessment Battery (/18)	16 (14–17)	15 (13–15)	15 (14–17)
<b>Speech and language measures</b>			
Animal Fluency	8 (4–10)	6 (3–9)	7 (4–10)
Letter Fluency (FAS)	19 (15–37)	22 (16–26)	19 (15–30)
SYDBAT Naming (/30)	6 (3–10)	7 (5–10)	6 (3–10)
SYDBAT Semantic Association (/30)	15 (10–20)	15 (10–18)	15 (10–19)
Repetition Boston Diagnostic (/10)	10 (8–10)	8 (8–9)	9 (8–10)
PPT word-word (/52)	41 (35–44)	41 (37–43)	41 (35–44)
Northwestern Anagram Test (/10)	9 (8–10)	10 (9–10)	10 (8–10)
WAB Aphasia Quotient (/100)	86 (80–93)	88 (79–92)	86 (80–93)
WAB repetition (/10)	9 (9–10)	9 (8–10)	9 (9–10)
WAB reading irregular words (/10)	8 (4–9)	10 (6–10)	8 (4–10)
WAB reading nonwords (/10)	9 (6–10)	8 (8–9)	9 (6–10)

**Table 1** Demographics and clinical features of the full svPPA cohort of 31 participants (*continued*)

	Aβ(−) (n = 23)	Aβ(+) (n = 8)	Total (n = 31)
PPVT <sup>d</sup>	68 (61–83)	74 (68–78)	71 (61–80)
<b>Neuropsychological measures</b>			
Trail Making Test, Part A, s	36 (28–47)	56 (43–68)	40 (29–56)
Trail Making Test, Part B, s	90 (69–122)	136 (114–170)	106 (74–141)
Rey-Osterrieth (/36)	33 (30–35)	32 (30–34)	33 (30–35)
VOSP letters (/20)	20 (19–20)	20 (19–20)	20 (19–20)
VOSP cubes (/10)	10 (9–10)	10 (10–10)	10 (9–10)
Digit Span	15 (13–20)	16 (16–16)	15 (14–19)
Spatial Span	14 (11–17)	12 (12–14)	13 (11–15)
Camden faces (/25)	20 (17–23)	20 (18–22)	20 (18–23)
Camden words (/25)	16 (14–21)	20 (18–22)	18 (14–22)

Abbreviations: Aβ = β-amyloid; MDS-UPDRS III = Movement Disorders Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (Motor Examination); MoCA = Montreal Cognitive Assessment Battery; NPI-Q = brief questionnaire version of the Neuropsychiatric Battery; PiB = Pittsburgh compound B; PPT = Pyramids and Palm Trees; PPVT = Peabody Picture Vocabulary Test; SUVR = standardized uptake value ratio; svPPA = semantic variant of primary progressive aphasia; SYDBAT = Sydney Language Battery; VOSP = Visual Object and Space Perception Battery; WAB = Western Aphasia Battery.

Data shown as median (25th–75th quartile) or n (%), and where applicable, the maximum score is shown after a slash in parentheses.

<sup>a</sup> Two Aβ(−) participants were ambidextrous.

<sup>b</sup> APOE data available in 29 participants, 21 Aβ(−) svPPA and 8 Aβ(+) svPPA.

<sup>c</sup> Information on the presence/absence of family history of a neurologic disease in immediate family members (children, parents, siblings, grandparents) was available in 30 of the 31 participants.

<sup>d</sup> Standard score (100 = average, 85 is −1 SD, 115 is +1 SD).

## Data availability

All data from the study will be shared in an anonymized format to any qualified investigator on request from the corresponding author.

## Results

The cohort of 31 participants with svPPA had a median (25th quartile, 75th quartile) age at scan of 67 (60–72) years and consisted of 52% males (table 1). Eight of the 31 (26%) were Aβ(+) and 11 of 29 (38%) were APOE ε4 carriers. The Aβ(+) participants consisted of 38% male, had median age at scan of 75 (69–77) years, and 63% were APOE ε4 carriers. The Aβ(−) participants consisted of 57% male, had median age at scan of 64 (58–69) years, and 29% were APOE ε4 carriers. Family history of a neurologic disease in immediate family members was present in 4 of 30 participants (13%) (unknown in the last case); all 4 were Aβ(−) and one was an APOE ε4 carrier. In the [<sup>18</sup>F]AV-1451 cohort, 4 of 17 (24%) were Aβ(+) and 5 of



**Table 2** Demographics and clinical features of the [<sup>18</sup>F] AV-1451 svPPA cohort

	Aβ(−) (n = 13)	Aβ(+) (n = 4)	Total (n = 17)
<b>Demographic features</b>			
Sex, male, n (%)	9 (69.2)	1 (25.0)	10 (58.8)
Age at scan, y	64 (57–68)	76 (72–78)	65 (60–70)
Global PiB SUVR	1.27 (1.20–1.32)	1.99 (1.80–2.19)	1.31 (1.23–1.41)
Right-handedness, n (%)	12 (92.3)	4 (100.0)	16 (94.1)
Disease duration, y	4 (2–5)	2 (2–4)	3 (2–5)
Education, y	16 (14–16)	12 (12–13)	16 (14–16)
APOE ε4 carriers, n (%) <sup>b</sup>	3 (27)	2 (50.0)	5 (33.3)
Family history, n (%) <sup>c</sup>	3 (25)	0 (0)	3 (18.8)
<b>Neurologic measures</b>			
MoCA (/30)	20 (18–24)	20 (18–21)	20 (18–24)
MDS-UPDRS III (/132)	0 (0–2)	8 (5–8)	0 (0–3)
WAB praxis (/60)	60 (58–60)	60 (59–60)	60 (59–60)
NPI-Q (/36)	7 (4–9)	4 (3–6)	7 (3–9)
Cambridge Behavioral Inventory (/180)	38 (19–63)	46 (39–58)	41 (29–63)
Facial recognition (/10)	7 (4–10)	2 (1–3)	7 (2–10)
Frontal Assessment Battery (/18)	14 (13–16)	16 (15–16)	15 (14–16)
<b>Speech and language measures</b>			
Animal Fluency	7 (4–10)	6 (5–8)	7 (4–9)
Letter Fluency (FAS)	19 (15–37)	22 (16–26)	19 (15–30)
SYDBAT Naming (/30)	6 (3–10)	7 (5–10)	6 (3–10)
SYDBAT Semantic Association (/30)	15 (10–20)	15 (10–18)	15 (10–19)
Repetition Boston Diagnostic (/10)	10 (8–10)	8 (8–9)	9 (8–10)
PPT word-word (/52)	38 (32–43)	41 (40–42)	39 (38–42)
Northwestern Anagram Test (/10)	9 (8–10)	10 (9–10)	10 (8–10)
WAB Aphasia Quotient (/100)	86 (80–91)	88 (84–93)	86 (82–92)
WAB repetition (/10)	9 (9–10)	9 (9–9)	9 (9–10)
WAB reading irregular words (/10)	5 (4–8)	10 (8–10)	7 (4–9)
WAB reading nonwords (/10)	8 (5–10)	10 (9–10)	8 (6–10)
PPVT <sup>a</sup>	68 (61–83)	74 (68–78)	71 (61–80)

**Table 2** Demographics and clinical features of the [<sup>18</sup>F]AV-1451 svPPA cohort (*continued*)

	Aβ(−) (n = 13)	Aβ(+) (n = 4)	Total (n = 17)
<b>Neuropsychological measures</b>			
Trail Making Test, Part A, s	42 (29–50)	56 (48–61)	46 (29–58)
Trail Making Test, Part B, s	106 (78–134)	126 (102–152)	110 (78–138)
Rey-Osterrieth (/36)	33 (31–35)	28 (24–32)	33 (30–35)
VOSP letters (/20)	20 (20–20)	20 (19–20)	20 (20–20)
VOSP cubes (/10)	10 (9–10)	10 (10–10)	10 (9–10)
Digit Span	15 (13–20)	16 (16–16)	15 (14–19)
Spatial Span	14 (11–17)	12 (12–14)	13 (11–15)
Camden faces (/25)	20 (17–23)	20 (18–22)	20 (18–23)
Camden words (/25)	16 (14–21)	20 (18–22)	18 (14–22)

Abbreviations: Aβ = β-amyloid; MDS-UPDRS III = Movement Disorders Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (Motor Examination); MoCA = Montreal Cognitive Assessment Battery; NPI-Q = brief questionnaire version of the Neuropsychiatric Battery; PiB = Pittsburgh compound B; PPT = Pyramids and Palm Trees; PPVT = Peabody Picture Vocabulary Test; SUVR = standardized uptake value ratio; svPPA = semantic variant of primary progressive aphasia; SYDBAT = Sydney Language Battery; VOSP = Visual Object and Space Perception Battery; WAB = Western Aphasia Battery.

Data shown as median (25th–75th quartile) or n (%), and where applicable, the maximum score is shown after a slash in parentheses.

<sup>a</sup> Standard score (100 = average, 85 is −1 SD, 115 is +1 SD).

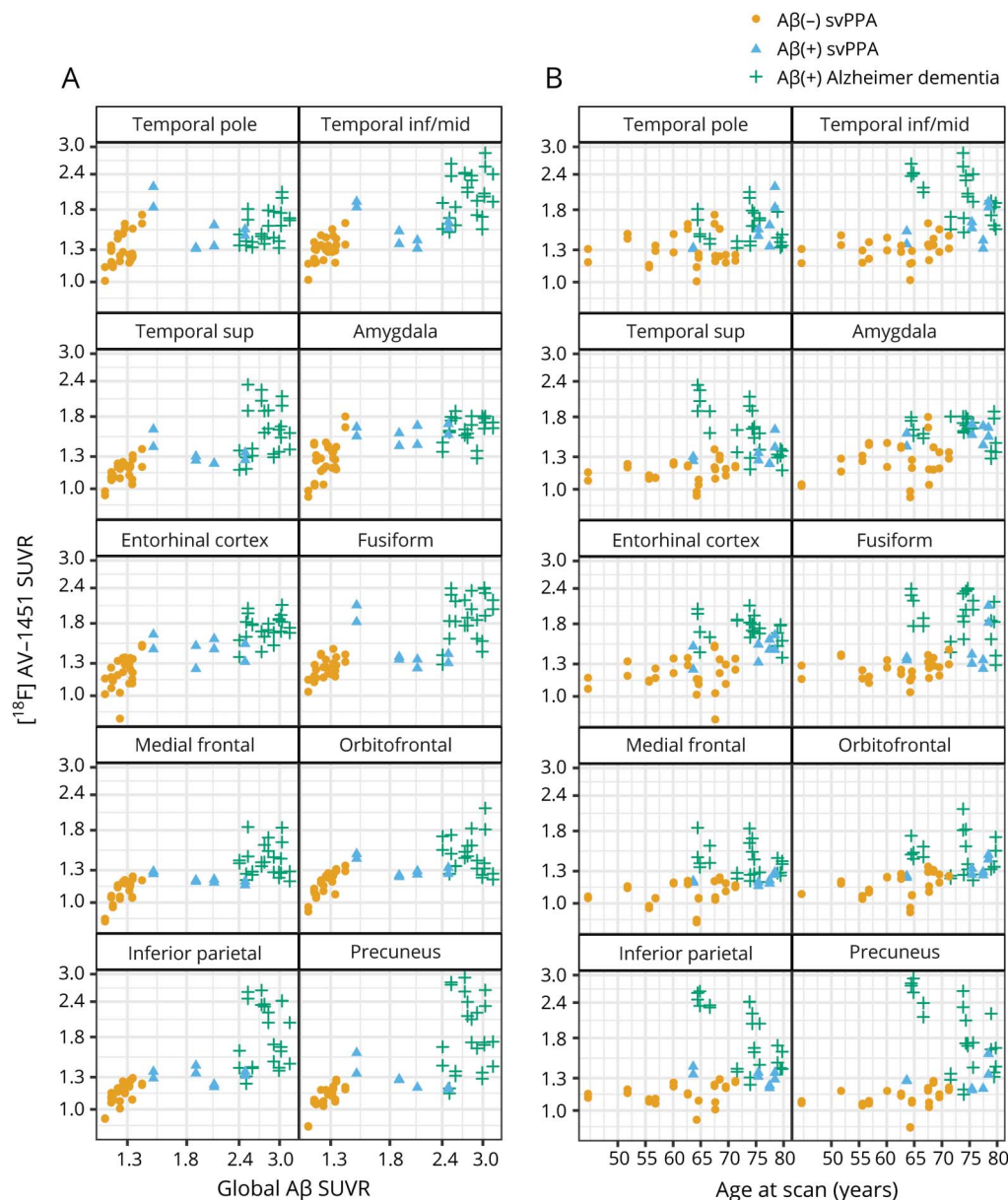
<sup>b</sup> APOE data available in 15 participants, 11 Aβ(−) svPPA and 4 Aβ(+) svPPA.

<sup>c</sup> Information on the presence/absence of family history of a neurologic disease in immediate family members (children, parents, siblings, grandparents) was available in 16 of the 17 participants.

15 (33%) were APOE ε4 carriers. Demographic and clinical features of the [<sup>18</sup>F]AV-1451 cohort were no different from the larger cohort and are shown in table 2. The Aβ(+) participants were older at the time of scan and had slightly shorter disease duration compared to the Aβ(−) participants, but performed comparably on clinical testing. The global PiB SUVRs in the Aβ(+) participants ranged from 1.50 to 2.48, and were noticeably lower than the global PiB SUVRs observed in Alzheimer dementia (figure 1).

[<sup>18</sup>F]AV-1451 uptake across all ROIs was higher in the Alzheimer dementia group compared to the svPPA group (figure 2). When the participants with svPPA were divided by Aβ status, we found that both the Aβ(−) and Aβ(+) participants showed greater uptake in the temporal pole, inferior/middle temporal gyrus, amygdala, entorhinal cortex, and fusiform cortex compared to controls in the ROI-level analysis, with the Aβ(+) participants also showing greater uptake in the superior temporal gyrus and across the parietal and frontal ROIs compared to controls (figures 2 and 3). The Aβ(+) participants showed generally higher uptake across all ROIs compared to

**Figure 1** [ $^{18}\text{F}$ ]AV-1451 SUVR by global PiB SUVR (A) and age (B)



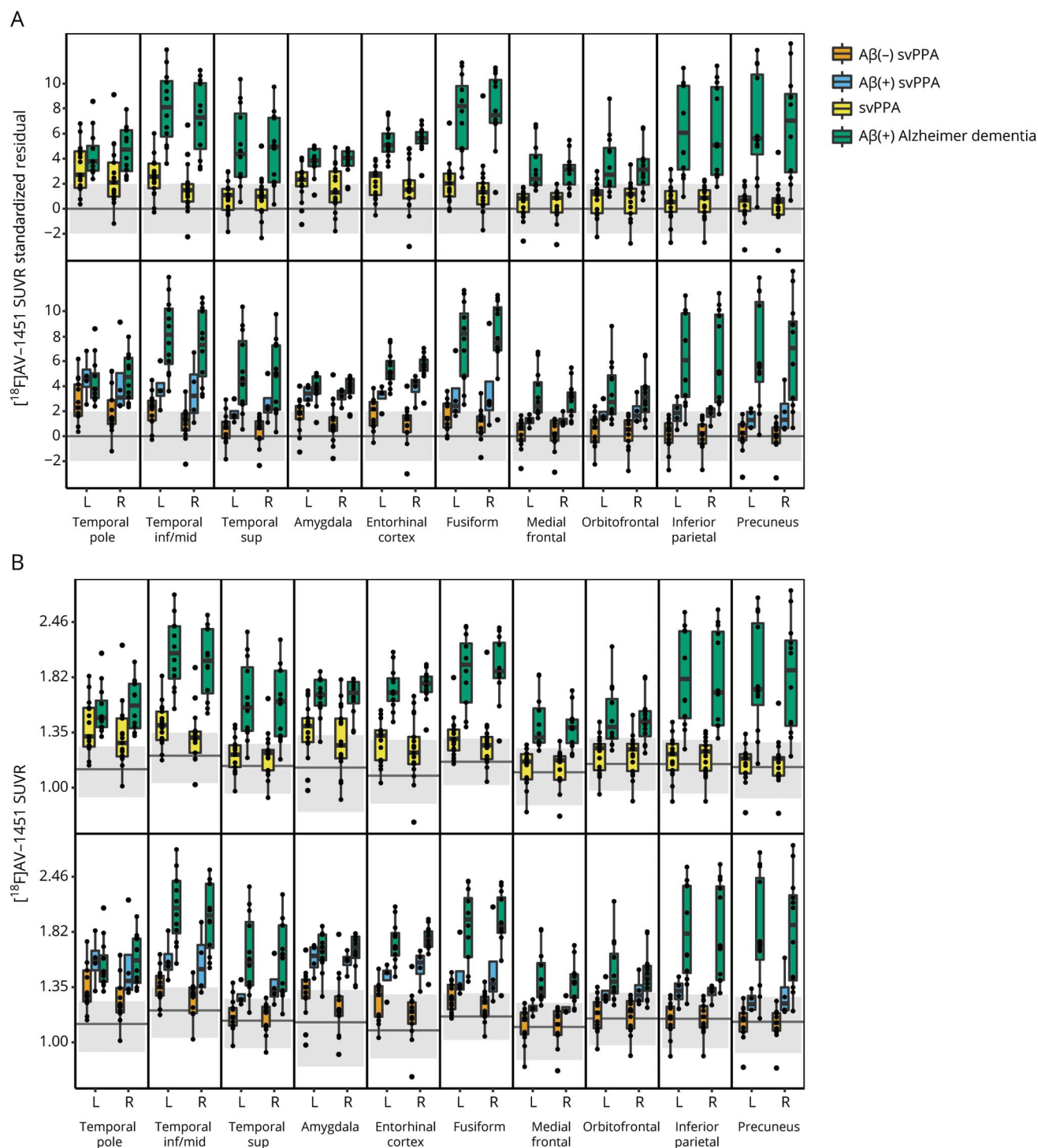
[ $^{18}\text{F}$ ]AV-1451 SUVR and global PiB SUVR are shown on a log scale. There are 2 points per patient in each facet, one for each hemisphere. A $\beta$ (-) participants with svPPA are represented by yellow circles, A $\beta$ (+) patients with svPPA by blue triangles, and A $\beta$ (+) participants with Alzheimer dementia by green crosses. A $\beta$  =  $\beta$ -amyloid; inf = inferior; mid = middle; sup = superior; SUVR = standardized uptake value ratio; svPPA = semantic variant of primary progressive aphasia.

the A $\beta$ (-) participants (figure 2), with the probabilities that A $\beta$ (+) participants had higher uptake  $\geq 0.97$  for all temporal and parietal ROIs, with the greatest differences observed for the temporal pole, inferior/middle temporal gyrus, amygdala, entorhinal cortex, and fusiform (figure 3). Uptake in the A $\beta$ (+) participants was lower than uptake observed in the Alzheimer dementia cohort across all ROIs (figures 2 and 3). The tau-PET SUVRs in all 4 of the A $\beta$ (+) participants was generally at the lower range of SUVRs observed in Alzheimer dementia, and did not appear to be associated with PiB-PET SUVR or age (figure 1). The tau-PET SUVRs in the A $\beta$ (-) participants also did not appear to increase with age, but did show a possible relationship

with PiB-PET SUVR, with tau-PET SUVRs increasing with increasing PiB-PET SUVRs (figure 1).

In the voxel-level analysis (figure 4), the A $\beta$ (-) participants with svPPA showed elevated uptake compared to controls in the left inferior and middle temporal gyri, fusiform, amygdala, parahippocampal gyrus, hippocampus, temporal pole, right inferior temporal gyrus, and right temporal pole, with an additional area of increased uptake encompassing the left rectus gyrus, orbitofrontal cortex, anterior putamen, nucleus accumbens, olfactory cortex, and anterior insula. The A $\beta$ (+) participants showed similar, although more bilateral and widespread,

**Figure 2** Boxplots of [ $^{18}\text{F}$ ]AV-1451 uptake by region and hemisphere



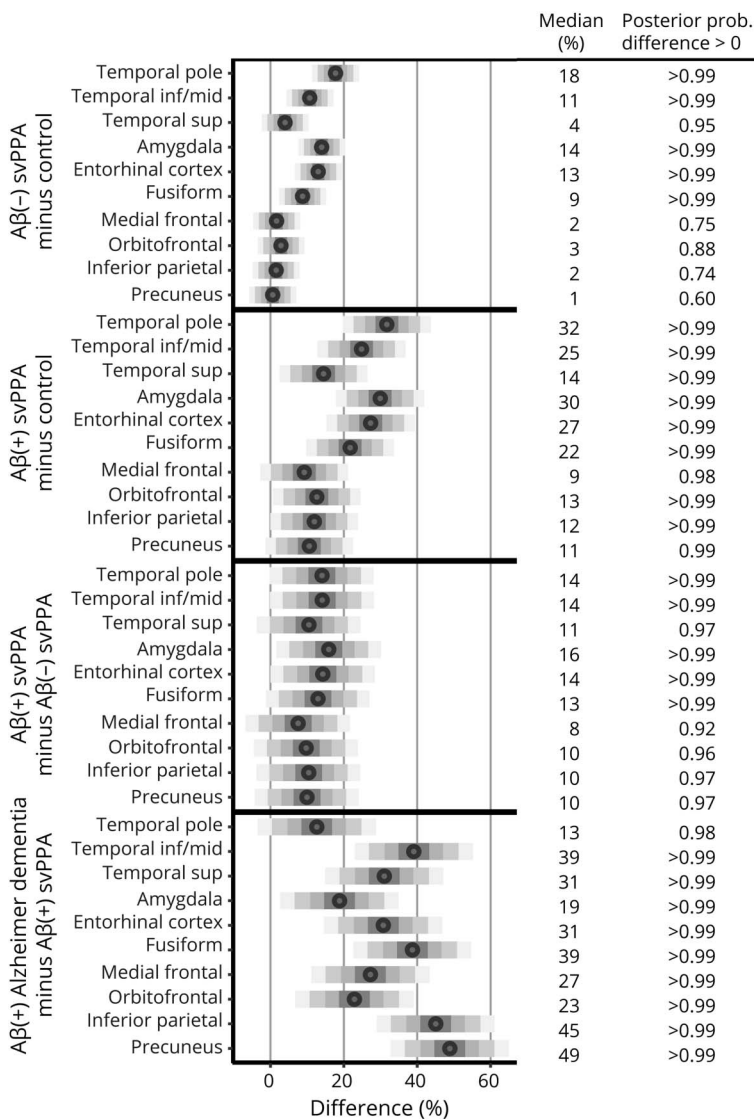
Data are shown as age-corrected residuals (A) and SUVR (B). For the age-corrected residuals, participants with svPPA and Alzheimer dementia were standardized using a simple regression of tau predicted by age at scan within each region in the 170 controls. Within each region, a gray blush is drawn to cover approximately 95% of a cognitively normal, Aβ(-) control population, with the line representing mean values in the controls. In the top part of the plots, the svPPA cohort is compared to the Aβ(+) participants with Alzheimer dementia. In the bottom half of the plots, the Aβ(-) and Aβ(+) participants with svPPA are compared to each other and the Aβ(+) participants with Alzheimer dementia. Aβ = β-amyloid; inf = inferior; mid = middle; sup = superior; SUVR = standardized uptake value ratio; svPPA = semantic variant of primary progressive aphasia.

patterns of uptake throughout the temporal lobes compared to controls, with greater involvement of the left hemisphere, and uptake also observed in a bilateral area encompassing the

anterior insula, anterior cingulum, orbitofrontal cortex, rectus gyrus, nucleus accumbens, and olfactory cortex. On direct comparison between the Aβ(-) and Aβ(+) groups, the Aβ(+)



**Figure 3** Posterior densities representing mean differences in [ $^{18}\text{F}$ ]AV-1451 uptake between diagnoses in each region



The bars are centered at the median and drawn to cover 50%, 80%, 95%, and 99% of differences from the posterior sample, with the median printed on the right. The posterior probability of a positive difference, i.e., the probability the first diagnosis has higher [ $^{18}\text{F}$ ]AV-1451 uptake than the second diagnosis, is next to the median. Aβ = β-amyloid; inf = inferior; mid = middle; prob. = probability; sup = superior; svPPA = semantic variant of primary progressive aphasia.

participants showed greater uptake in the right amygdala, hippocampus, entorhinal cortex, fusiform gyrus, inferior, middle, and superior temporal gyri and temporal pole, and left fusiform, inferior, middle, and superior temporal gyri, and temporal pole compared to the Aβ(-) participants. No regions showed greater uptake in the Aβ(-) participants compared to the Aβ(+) participants. The Alzheimer dementia cohort showed greater uptake in bilateral entorhinal cortices, posterior regions of the inferior and middle temporal gyri, and throughout the parietal, occipital, and frontal lobes compared to the Aβ(+) svPPA participants.

Figure 5 shows individual [ $^{18}\text{F}$ ]AV-1451, MRI, and FDG-PET images for the 4 Aβ(+) participants with svPPA. All 4 participants showed predominant anteromedial temporal hypometabolism and atrophy on FDG-PET and MRI, respectively, consistent with the diagnosis of svPPA. Elevated [ $^{18}\text{F}$ ]AV-1451

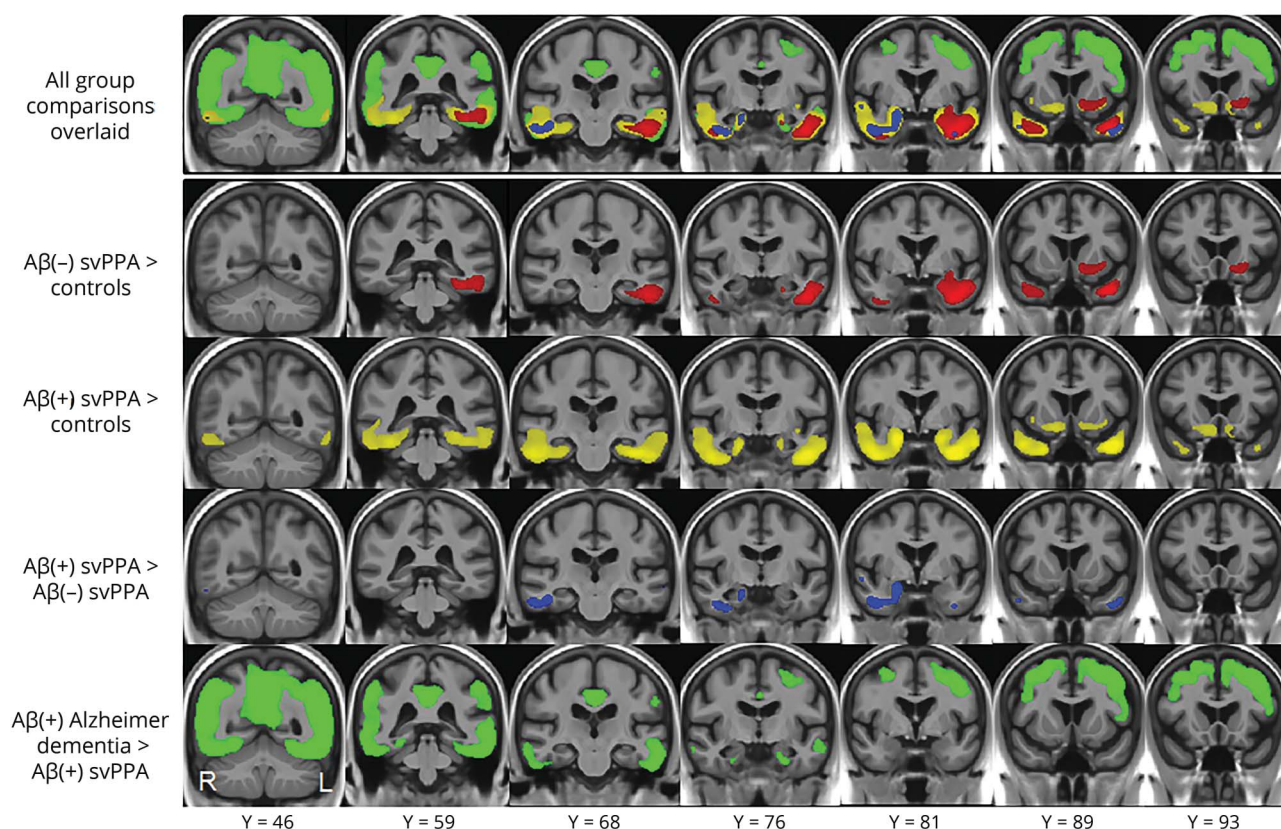
uptake was observed in the temporal lobes of all 4 participants, with additional involvement of the precuneus in participant 1 and lateral parietal lobe in participant 2.

## Discussion

This study demonstrates that the degree of uptake of [ $^{18}\text{F}$ ]AV-1451 in svPPA is lower than that observed in Alzheimer dementia, a disease that has paired helical filament tau deposition at autopsy. However, the degree of uptake was greater in participants with svPPA who were Aβ(+), suggesting some contribution of paired helical filament tau in these participants.

A high proportion of our svPPA cohort showed Aβ deposition on PET, with a frequency of 26% Aβ(+) observed in our larger

**Figure 4** Results of the voxel-level comparisons between A $\beta$ (-) svPPA, A $\beta$ (+) svPPA, and A $\beta$ (+) Alzheimer dementia cohorts



Each row represents results of a different group contrast, with all of these contrasts shown overlaid on the same brain images in the top row of the figure. Red represents regions with greater uptake in A $\beta$ (-) svPPA compared to controls; yellow represents regions with greater uptake in A $\beta$ (+) svPPA compared to controls; blue represents regions with greater uptake in A $\beta$ (+) svPPA compared to A $\beta$ (-) svPPA; green represents regions with greater uptake in A $\beta$ (+) Alzheimer dementia compared to A $\beta$ (+) svPPA. All results are shown corrected for multiple comparisons using the false discovery rate correction at  $p < 0.05$ . A $\beta$  =  $\beta$ -amyloid; svPPA = semantic variant of primary progressive aphasia.

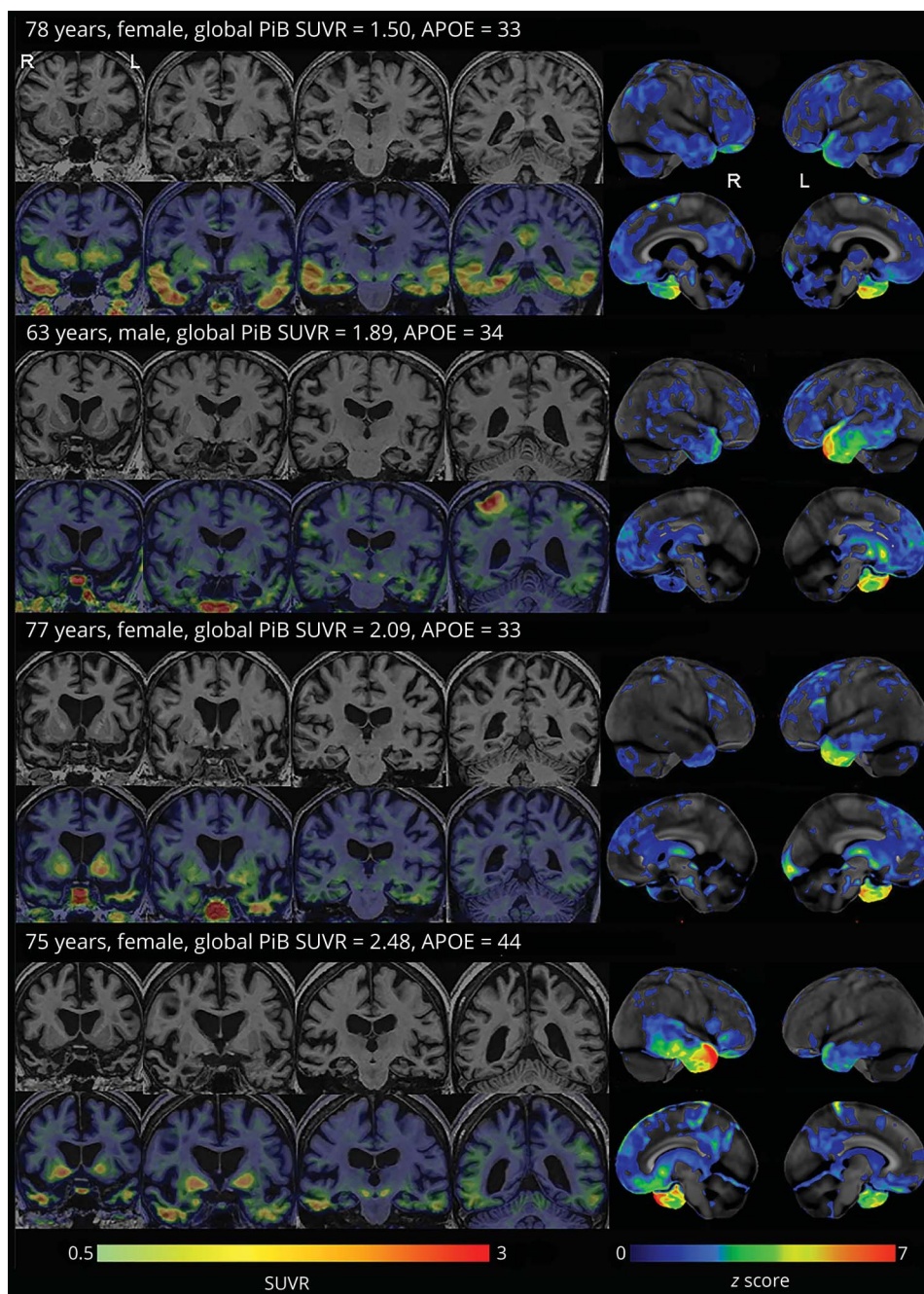
cohort of 31 participants. This is on the higher end of the frequencies previously published, which range from 0% to 25%.<sup>12,41–43</sup> Differences across studies could be attributable to different techniques used to determine A $\beta$  status. We used a quantitative derived cut point while visual ratings were used in other studies. Another explanation could be attributable to different tracers as we used PiB-PET while florbetapir has been used in other studies. Differences in the age distribution of svPPA cohorts across studies could also be contributing. All studies have found a decade difference in age between those who are A $\beta$ (+) and those who are A $\beta$ (-), and hence studies with more older participants will likely get a higher proportion of A $\beta$ (+) cases.

We and others have previously reported patterns of [ $^{18}\text{F}$ ]AV-1451 in svPPA compared to controls,<sup>17–19</sup> but now we expand on our previous study by reporting findings according to A $\beta$  status and comparing findings in svPPA to Alzheimer dementia. We confirm that elevated [ $^{18}\text{F}$ ]AV-1451 uptake is observed in A $\beta$ (-) participants with svPPA. These participants showed mild patterns of uptake that was highly asymmetric involving the anteromedial temporal lobe, as well as regions in the basal frontal lobes, insula, and putamen. It

remains unclear what the ligand is binding to in these cases. It has been hypothesized that it may represent spill out from increased binding in white matter due to the expression of monoamine oxidase B by reactive astrocytes,<sup>18</sup> may bind to low levels of abnormal tau that coexists with TDP-43,<sup>17,18</sup> to some cellular marker of neurodegeneration,<sup>17–19</sup> or may even represent low-level binding to TDP-43.<sup>18,19</sup> However, when A $\beta$  deposition was present in svPPA, we observed more striking uptake with higher SUVRs particularly in medial and lateral temporal regions, but also in parietal regions, compared to the A $\beta$ (-) participants. These differences were observed despite the fact that the sample size was smaller in the A $\beta$ (+) group and remained after correction for age differences between the groups; hence, in a more highly powered study, the differences could have been more pronounced. These results could be interpreted to suggest that paired helical filament tau may be present in at least some of the A $\beta$ (+) participants, contributing to the higher [ $^{18}\text{F}$ ]AV-1451 uptake. It is possible that Alzheimer disease is the only pathology in these cases, but it is also possible that Alzheimer disease pathology may coexist with TDP-43 pathology. One autopsy study reported 2 A $\beta$ (+) svPPA patients with TDP-43 pathology as the primary pathology, with concomitant Alzheimer disease pathology,



**Figure 5** MRI, [ $^{18}\text{F}$ ]AV-1451, and FDG-PET images for the 4 A $\beta$ (+) participants with svPPA



FDG-PET images were normalized to the pons and are shown as surface projection z score maps representing regions of abnormalities compared to controls (right side of the figure). [ $^{18}\text{F}$ ]AV-1451 standardized uptake value ratio images are shown overlaid on coronal MRI. A $\beta$  =  $\beta$ -amyloid; FDG = [ $^{18}\text{F}$ ]fluorodeoxyglucose; svPPA = semantic variant of primary progressive aphasia.

although one of these cases had a Braak neurofibrillary tangle stage of only II.<sup>12</sup> Clinicopathologic studies on svPPA have, however, very rarely reported any other pathology except TDP-43. Of 55 cases of svPPA reported with autopsy from 4 centers,<sup>3,4,6,9</sup> 3 (5%) had Alzheimer disease pathology and 3 (5%) had TDP-43 pathology with coexistent Alzheimer disease. In this study, we found that 31% of our participants with svPPA showed A $\beta$  deposition on PET. Given the general rarity of Alzheimer disease in clinicopathologic series of svPPA, it seems unlikely that all of our A $\beta$ (+) cases will have underlying Alzheimer disease pathology at autopsy. In other

words, there could be alternative explanations for the elevated A $\beta$  and elevated [ $^{18}\text{F}$ ]AV-1451 observed on PET imaging and it may not be correct to diagnose these participants as having Alzheimer disease based on PET findings. One possibility is that the PET scans are correctly binding to their identified targets, but that some of these participants have PART that is being detected by [ $^{18}\text{F}$ ]AV-1451. Possible PART can be diagnosed in the presence of A $\beta$  deposition, as long as the A $\beta$  Thal phase is low (1–2).<sup>11</sup> Consistent with our findings, PART occurs most frequently in older people and typically targets the temporal lobes, and an autoradiographic study has

shown [ $^{18}\text{F}$ ]AV-1451 binding to tau proteins in brain tissue in PART.<sup>14</sup> The older age could also be the explanation for the presence of A $\beta$  deposition; the fact that the global PiB SUVRs were lower in the participants with svPPA compared to those with Alzheimer dementia could support this theory. Another possibility is that [ $^{18}\text{F}$ ]AV-1451 is binding to another unexpected target. It could be binding in low levels to neuritic tau present in the A $\beta$  plaques in the A $\beta$ (+) participants.<sup>14,15</sup> Other tauopathies have, however, also been observed in svPPA at autopsy that could also be contributing to our findings, such as Pick disease,<sup>3,8</sup> globular glial tauopathies,<sup>3,44</sup> and argyrophilic grain disease.<sup>45</sup>

The distribution of [ $^{18}\text{F}$ ]AV-1451 uptake in the A $\beta$ (+) participants was relatively typical for svPPA, involving the anteromedial temporal lobes, left and/or right, and did not show a widespread distribution through the brain that has been observed in Alzheimer dementia.<sup>46–48</sup> In addition, the degree of [ $^{18}\text{F}$ ]AV-1451 uptake across all regions was lower than that observed in Alzheimer dementia. It is certainly possible that Alzheimer disease pathology could have an atypical medial temporal distribution<sup>48</sup> or have a low Braak stage,<sup>49</sup> although if the cases had a pure Alzheimer disease pathology, one might expect the [ $^{18}\text{F}$ ]AV-1451 uptake values to be higher and more in the range observed in Alzheimer dementia. The A $\beta$ (+) participants did show a more bilateral pattern of uptake compared to the more asymmetric pattern observed in the A $\beta$ (-) participants—perhaps a feature that could help predict A $\beta$  deposition. Little is known about [ $^{18}\text{F}$ ]AV-1451 in vivo in PART, but the temporal predominance would fit with the possible explanation that these participants have TDP-43 pathology with PART. The A $\beta$ (+) participants also had a higher APOE  $\epsilon$ 4 frequency compared to the A $\beta$ (-) participants (50% vs 14%), which suggests APOE  $\epsilon$ 4 may have a role in driving the presence of A $\beta$  deposition and could possibly support an underlying Alzheimer disease mechanism, although one study has suggested that APOE is not a risk factor for Alzheimer disease across all variants of PPA.<sup>4</sup> Ultimately, however, we can only hypothesize about the underlying pathology, and autopsy confirmation will be needed on these participants in order to determine the underlying pathologic substrate for the increased [ $^{18}\text{F}$ ]AV-1451 uptake. It is quite possible of course that the underlying pathology will differ across the 4 A $\beta$ (+) participants. In fact, 2 of the A $\beta$ (+) participants showed quite striking and focal regions of elevated [ $^{18}\text{F}$ ]AV-1451 uptake in the parietal lobe while the other 2 did not, perhaps pointing to an underlying Alzheimer disease pathology in the 2 with parietal uptake.

Of note, all 4 of the A $\beta$ (+) participants fulfilled diagnostic criteria for svPPA and performed comparably to the A $\beta$ (-) participants with svPPA on tests of naming and semantic association. All 4 also performed within the normal range on tests of sentence repetition, and none met clinical criteria for the logopenic variant of PPA.<sup>1</sup> Findings on FDG-PET also supported a diagnosis of svPPA in all cases.

Although not an aim of our study, we also observed some interesting relationships of [ $^{18}\text{F}$ ]AV-1451 uptake in the A $\beta$ (-) participants with svPPA. [ $^{18}\text{F}$ ]AV-1451 uptake may be associated with global PiB SUVR, rather than age, in these participants, with [ $^{18}\text{F}$ ]AV-1451 uptake across all ROIs tending to increase with global PiB SUVR, albeit below our cutoff of abnormality. A relationship between [ $^{18}\text{F}$ ]AV-1451 uptake and global PiB SUVR was not observed in the A $\beta$ (+) participants, although this could have been because of the small number of A $\beta$ (+) participants. It is currently unclear why this relationship was observed in the A $\beta$ (-) participants, although it mirrors relationships observed between increasing [ $^{18}\text{F}$ ]AV-1451 and global PiB SUVR that have been observed in A $\beta$ (-) cognitively normal people.<sup>50</sup> Further work is needed to assess this relationship in larger numbers of participants in order to determine a potential biological explanation.

Strengths of our study were in our well-characterized cohort, which all underwent extensive clinical testing, including an assessment with a speech/language pathologist, as well as scanning with multiple brain imaging modalities. Our single Bayesian model increased our statistical strength in this small sample by simultaneously estimating all regional quantities of interest and accounting for age, resulting in more stable estimates while accounting for multiple comparisons. A limitation of the study was the small number of participants with svPPA in our [ $^{18}\text{F}$ ]AV-1451 cohort. The lack of autopsy confirmation, which will be critical to determine the pathologic basis of the PET findings, was also a limitation.

The findings from this study add to our limited understanding of [ $^{18}\text{F}$ ]AV-1451 uptake in svPPA. We show strong evidence using Bayesian modeling that [ $^{18}\text{F}$ ]AV-1451 uptake is greater in A $\beta$ (+) compared to A $\beta$ (-) svPPA, although not to the degree observed in Alzheimer dementia. While more work is needed to confirm the underlying pathology in these cases, our findings do suggest that strong bilateral anteromedial temporal [ $^{18}\text{F}$ ]AV-1451 signal, perhaps also with involvement of the parietal lobes, could help clinically to increase suspicion that a person with svPPA may have A $\beta$  deposition and, hence, influence patient prognosis and potential treatment.

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## Disclosure

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## Appendix 1 Author contributions

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<b>Peter R. Martin, MS</b>	Mayo Clinic, Rochester, MN	Author	Major role in data analysis, interpreted the data, revised the manuscript for intellectual content
<b>Joseph R. Duffy, PhD</b>	Mayo Clinic, Rochester, MN	Author	Acquisition of data, revised the manuscript for intellectual content
<b>Heather M. Clark, PhD</b>	Mayo Clinic, Rochester, MN	Author	Acquisition of data, revised the manuscript for intellectual content
<b>Mary M. Machulda, PhD</b>	Mayo Clinic, Rochester, MN	Author	Acquisition of data, revised the manuscript for intellectual content
<b>Christopher G. Schwarz, PhD</b>	Mayo Clinic, Rochester, MN	Author	Data analysis, revised the manuscript for intellectual content
<b>Stephen D. Weigand, MS</b>	Mayo Clinic, Rochester, MN	Author	Data analysis, revised the manuscript for intellectual content
<b>Irene Sintini, PhD</b>	Mayo Clinic, Rochester, MN	Author	Data analysis, revised the manuscript for intellectual content
<b>Matthew L. Senjem, MS</b>	Mayo Clinic, Rochester, MN	Author	Data analysis, revised the manuscript for intellectual content
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<b>Hugo Botha, MD</b>	Mayo Clinic, Rochester, MN	Author	Acquisition of data, revised the manuscript for intellectual content
<b>Rene L. Utianski, PhD</b>	Mayo Clinic, Rochester, MN	Author	Acquisition of data, revised the manuscript for intellectual content
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## Appendix 1 (continued)

Name	Location	Role	Contribution
<b>Clifford R. Jack, MD</b>	Mayo Clinic, Rochester, MN	Author	Acquisition of data, revised the manuscript for intellectual content
<b>Val J. Lowe, MD</b>	Mayo Clinic, Rochester, MN	Author	Acquisition of data, revised the manuscript for intellectual content
<b>Keith A. Josephs, MD, MST, MSc</b>	Mayo Clinic, Rochester, MN	Author	Design and conceptualized the study, acquisition of data, analyzed the data, study funding, interpreted the data, revised the manuscript for intellectual content

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