Tau Uptake in Agrammatic Primary Progressive Aphasia with and without Apraxia of Speech

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ORIGINAL ARTICLE

Tau uptake in agrammatic primary progressive aphasia with and without apraxia of speech

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Background and purpose: The non-fluent/agrammatic variant of primary progressive aphasia (agPPA) is a heterogeneous diagnosis wherein some individuals have apraxia of speech (AOS). When agPPA includes AOS, a tauopathy is the likely underlying pathology. Recently, [18F]AV-1451 was developed for the *in-vivo* assessment of tau. In this study, we compared patterns of tau tracer uptake in patients with agPPA with and without AOS.

Methods: Nine patients with agPPA (four without AOS) underwent tau positron emission tomography imaging with [18F]AV-1451. Uptake of [18F]AV-1451 was assessed as cortical to cerebellar crus ratio (standard uptake value ratio) in cortical regions of interest measured using the MCALT atlas and compared voxel-wise in SPM12. Each patient was age- and sex-matched to three controls.

Results: The agPPA without AOS showed uptake in the left frontal and temporal lobes, whereas agPPA with AOS showed uptake in the bilateral supplementary motor areas, frontal lobes, precuneus and precentral gyrus relative to controls. The left precentral gyrus had uptake in agPPA with AOS relative to those without AOS.

Conclusions: This cross-sectional study suggests that [18F]AV-1451 uptake in the precentral gyrus is implicated in AOS in agPPA.

Introduction

Under current consensus criteria [1], patients with the non-fluent/agrammatic variant of primary progressive aphasia (agPPA) [2,3] may have either or both agrammatism and apraxia of speech (AOS). This inherent clinical heterogeneity is mirrored by pathological heterogeneity, more so than in other variants of primary progressive aphasia [4]. Prior imaging and pathologic evidence suggest that patients who are solely agrammatic may, in fact, be an entity distinct from those who present with concomitant AOS. Research has demonstrated that agPPA without AOS is associated with TAR DNA-binding protein 43 (TDP-43) pathology [5]. However, there were associations with 4-repeat (4R) tau pathology (e.g. progressive supranuclear palsy or a corticobasal syndrome) when AOS was also present [6,7]. These findings demonstrate the importance of clear characterization of this patient population.

In-vivo imaging of tau pathology, using [18F]AV-1451, may facilitate testing of hypotheses about the pathology underlying a given clinical presentation. A recent autoradiographic study demonstrated low-level [18F]AV-1451 uptake in the left temporal and left frontal lobes in a patient with agPPA without AOS [8]. In another case series, a patient who presented with agPPA, but later met criteria for progressive supranuclear palsy, demonstrated tracer uptake in the frontal and temporal lobes and cerebellar dentate, with more prominent signal in the basal ganglia and midbrain (it is not mentioned whether the patient also had AOS) [9]. We have recently demonstrated [18F]AV-1451 uptake in the prefrontal

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cortex in a group of subjects with agPPA [10] although it is unclear how patterns of uptake relate to the presence and absence of concomitant AOS.

Toward that end, the goal of the current study was to investigate differences in [18F]AV-1451 uptake patterns in patients with agPPA, with and without AOS. We hypothesized that the patterns of [18F]AV-1451 uptake would differ between the two groups, supporting an association between area of tau tracer uptake and clinical presentation, possibly reflecting more robust binding of [18F]AV-1451 in agPPA with AOS (a likely 4R tauopathy) compared with agPPA without AOS (a possible TDP-43 proteinopathy).

Methods

Participants

The study was approved by the Mayo Clinic Institutional Review Board and written consent was given by all participants. Between February 2015 and September 2017, tau positron emission tomography (PET) imaging was collected from nine patients with agPPA (four without AOS). All patients underwent a 3.0-Tesla volumetric head magnetic resonance imaging scan, [18F]AV-1451 tau PET scan, and neurological, speech and language evaluations. All patients were age- and sex-matched (1:3) to 27 cognitively unimpaired individuals from the Mayo Clinic Study of Aging cohort. All controls were amyloid negative (global Pittsburgh Compound B PET ratio < 1.42) [11] and underwent [18F]AV-1451 tau PET scans using acquisition parameters that were identical to those of the patient cohort.

Clinical data

All patients with agPPA had a thorough neurological examination and did not meet criteria for another neurodegenerative disease. All patients completed a test of general cognition (Montreal Cognitive Assessment battery, with a score of ≥ 26 considered normal). Non-verbal oral apraxia was assessed (a score ≤ 29 suggested the presence of non-verbal oral apraxia [12]). Several speech and language measures were administered, as previously reported [13–15]. The Western Aphasia Battery (WAB) aphasia quotient served as a composite measure of global language ability (a score ≥ 93.8 was considered normal). Grammar was assessed by review of conversational speech and verbal and written picture descriptions. The Northwestern Anagram test, a non-speech sentence production task, was also administered [16]. As previously described [13–15], judgments about motor speech abilities were based on spoken language tasks of the WAB and supplementary speech tasks (including speech alternating and sequential motion rates). Aphasia and AOS severity were rated on a scale of 0–4 (1, mild; 4, severe). Due to the sample size, descriptive rather than inferential statistics were utilized.

Neuroimaging acquisition and analysis

Neuroimaging acquisition parameters were identical to those previously reported [17]. Briefly, all analyses were performed using two-compartment partial volume-corrected tau PET standard uptake value ratio images with the cerebellar crus gray matter reference region, using the MCALT atlas (https://www.nitrc.org/projects/mcalt/) in SPM12. The cohorts of patients with agPPA without AOS ($n = 4$) and those with AOS ($n = 5$) were compared with their respective matched subgroup of controls. Age and sex were not included in the models, as comparisons were made between age- and sex-matched groups. The patients with agPPA without AOS and those with AOS were directly compared with each other. Voxel-level comparisons were performed using SPM12, with results assessed at $P < 0.001$ (uncorrected) for the direct group comparison and $P < 0.05$ (false discovery rate corrected) for the patient to control comparison, both with an extent threshold of 50 voxels.

Results

Clinical findings

Demographic and clinical data are summarized in Table 1. The patients with agPPA without AOS (two females) had a median age of 64.5 years, median education of 13.5 years, median disease duration of 2.25 years and median aphasia severity of 2.25 (consistent with median WAB aphasia quotient score of 80.45 and Northwestern Anagram test score of 4). The patients with agPPA with AOS (one female) had a median age of 68 years, median education of 16 years, median disease duration of 4 years and median aphasia severity of 3 (consistent with median WAB aphasia quotient score of 70.05 and Northwestern Anagram test score of 5). Median AOS severity was 1 (mild). Montreal Cognitive Assessment battery scores were lower (worse) in the patients with agPPA with AOS; three patients in each group were below the recommended cutoff of 26. All nine patients with agPPA, regardless of AOS, had non-verbal oral apraxia.

[18F]AV-1451 findings

At the voxel level, the agPPA without AOS cohort showed increased tau PET uptake in the left inferior

Table 1 Demographic, neurological, speech and language information for all patients

Patient	Sex	Age at evaluative (years)	Time since onset (years)	Education (years)	MOCA score (/30)	WAB-AQ score (/100)	Agrammatism in writing	Agrammatism in speaking	NAT score (/10)	NVOA (/32)	Aphasia severity (/4)	Apraxia severity (/4)
agPPA without AOS												
1	F	55	3	12	23	75.4	Yes	Yes	4	29	3	0
2	F	65	4.5	13	18	66.5	Yes	Yes	DNT	25	3	0
3	M	64	1.5	14	27	90	Yes	Yes	5	29	1	0
4	M	72	1.5	16	23	85.5	Yes	No	2	21	1.5	0
agPPA with AOS												
5[a]	M	51	4.5	20	DNT	DNT	Yes	Yes	0	0	4	0.5
6	M	61	3	16	28	89	Yes	No	10	17	1.5	1
7	M	73	6	12	5	53.1	Yes	Yes	DNT	16	3	3
8	F	68	4	12	13	58.2	Yes	Yes	DNT	13	3	3
9	M	87	2	16	21	81.9	Yes	Yes	5	24	1.5	1

agPPA, agrammatic variant of primary progressive aphasia; AOS, apraxia of speech; DNT, did not test; F, female; M, male; MOCA, Montreal Cognitive Assessment; NAT, Northwestern Anagram Test; NVOA, non-verbal oral apraxia; WAB-AQ, Western Aphasia Battery Aphasia Quotient. Where appropriate, maximum score is noted in column header. [a]Left handed.

temporal region, left inferior, middle and superior frontal gyri, and left supplementary motor area relative to controls (Fig. 1). The agPPA with AOS cohort showed bilateral but greater left than right increased tau PET uptake in the supplementary motor area, inferior, middle and superior frontal gyri, precentral gyrus and left precuneus relative to controls (Fig. 1). [18F]AV-1451 uptake was never greater in controls than in patients with agPPA (with or without AOS).

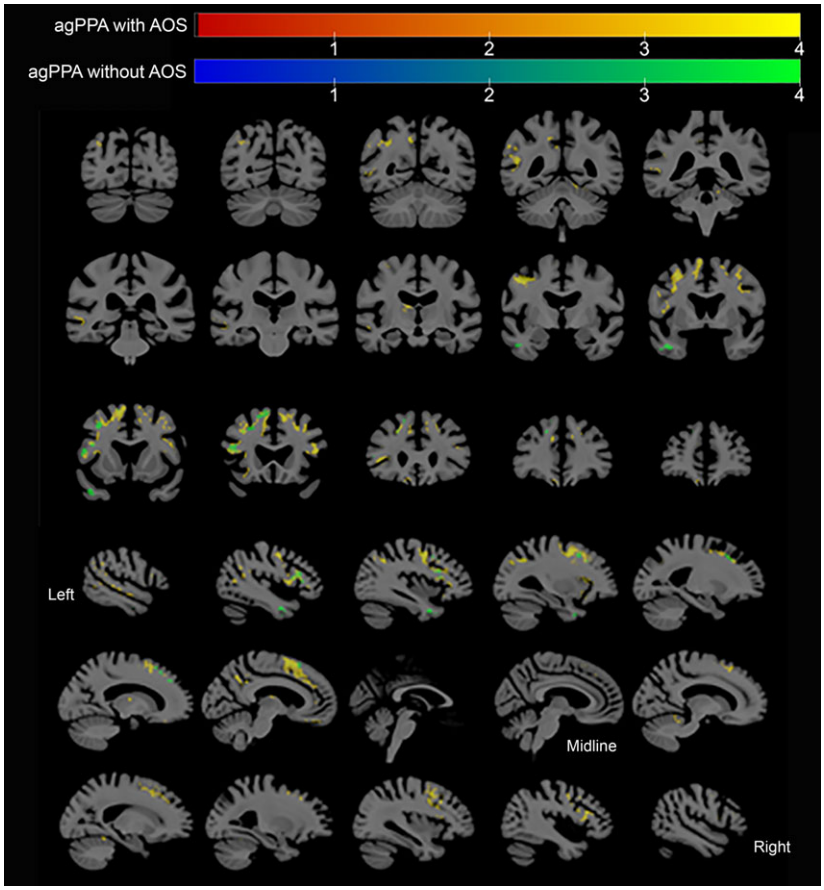


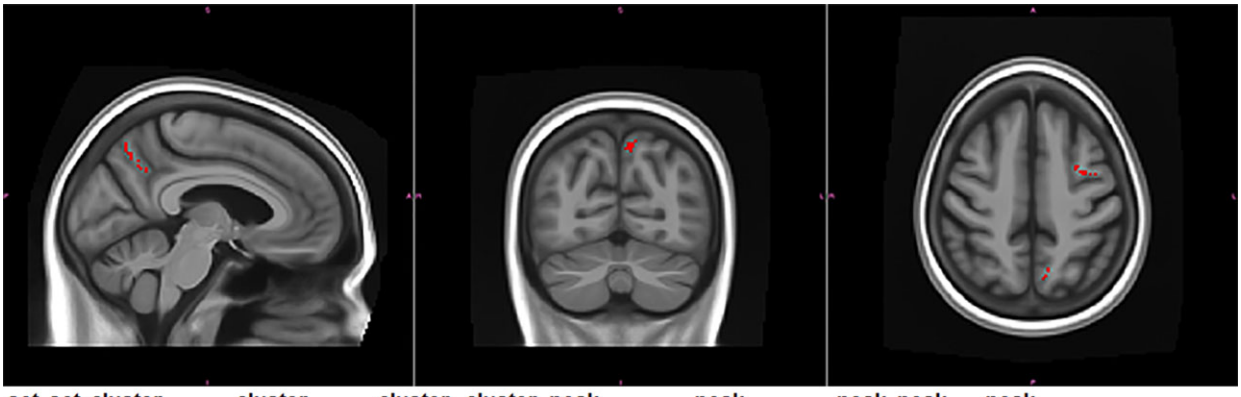
Figure 1 Regions where partial volume-corrected AV-1451 tau positron emission tomography standard uptake value ratio was significantly larger (false discovery rate corrected, $P < 0.05$, extent > 50 voxels) in patients with agrammatic variant of primary progressive aphasia (agPPA), with and without apraxia of speech (AOS), than in controls. Results visualized using MRIcroGL (Chris Rorden, University of South Carolina, Columbia, SC, USA). [Colour figure can be viewed at wileyonlinelibrary.com]

At the voxel level, the agPPA with AOS cohort showed increased tau PET uptake in the left precentral gyrus and left precuneus relative to the agPPA without AOS cohort (Fig. 2). [18F]AV-1451 uptake was never greater in patients with agPPA without AOS than in patients with agPPA with AOS. Although region of interest-level analyses were not formally conducted, standard uptake value ratios were calculated for each participant for selected regions of interest. This allowed for a qualitative assessment of whether individuals reflected the pattern seen in the group-level voxel analysis (Fig. 3).

Discussion

This study demonstrated that [18F]AV-1451 uptake was seen in patients with agPPA in regions known to be involved with speech and language, with differing patterns of tracer uptake relative to the presence of AOS. [18F]AV-1451 uptake was observed in the left precentral gyrus and left precuneus in agPPA when AOS was also present, compared with agPPA alone. This is similar to previous research, where [18F]AV-1451 uptake in the precentral gyrus has been demonstrated in a patient with a dominant AOS and aphasia, who ultimately had corticobasal degeneration pathology at autopsy [18]. Additionally, the precentral gyrus was implicated in stroke-induced pure AOS, with additional areas of involvement accounting for concomitant aphasia [19]; importantly, the speech and language network may respond differently to a degenerative process rather than a focal event, such as stroke. [18F]AV-1451 uptake in the precuneus was previously associated with cognitive impairment associated with Alzheimer's disease, Parkinson's disease and Lewy Body dementia [20]. Although we did not compute correlations, there were overall lower Montreal Cognitive Assessment battery scores in the group with higher [18F]AV-1451 uptake in the precuneus (i.e. agPPA with AOS). It is possible that tracer uptake in this region is associated with longer disease duration in the patients with AOS and more widespread disease, but it does not appear to be associated with AOS severity. Importantly, when examining the individual data (Fig. 3), it is noticeable that only one patient (Patient 8) had noticeably higher tracer uptake in the precuneus. It is possible that this patient is driving this result; nonetheless, there are no clinical or imaging concerns that warrant excluding this participant.

When comparing the patient groups with controls, the results suggest that [18F]AV-1451 uptake in the bilateral supplementary motor areas and left precentral gyrus is associated with AOS in the context of more severe aphasia (i.e. agPPA with AOS). Interestingly, this pattern of [18F]AV-1451 uptake is consistent with findings in patients with a predominant AOS and co-occurring aphasia [17]. Whether the AOS or aphasia dominates, there is a consistent relationship between [18F]AV-1451 uptake and the clinical



set P	set c	cluster p(FWE-corr)	cluster p(FDR-corr)	cluster equivk	cluster p(unc)	peak p(FWE-corr)	peak P(FDR-corr)	peak T	peak equivZ	peak P(unc)	x	y	z {mm}
0	2	0		91	0	0.032	0.003	5.82	5.27	0	−30	−2	42
						0.05	0.003	5.71	5.18	0	−39	0	34
						1	0.027	4.77	4.44	0	−28	6	46
		0		53	0	0.985	0.019	4.96	4.6	0	−6	−64	45
						1	0.032	4.63	4.32	0	−4	−52	32

Figure 2 Regions where partial volume-corrected AV-1451 tau positron emission tomography standard uptake value ratio was significantly larger (uncorrected $P < 0.001$, extent > 50 voxels) in patients with agrammatic variant of primary progressive aphasia (agPPA) with apraxia of speech (AOS) than in patients with agPPA without AOS. SPM results included; coordinates correspond to the MCALT template (Schwarz *et al*., 2017) (https://www.nitrc.org/projects/mcalt/). Results visualized using fslview. [Oxford FMRIB (Functional Magnetic Resonance Imaging of the Brain), Oxford, UK] [Colour figure can be viewed at wileyonlinelibrary.com]

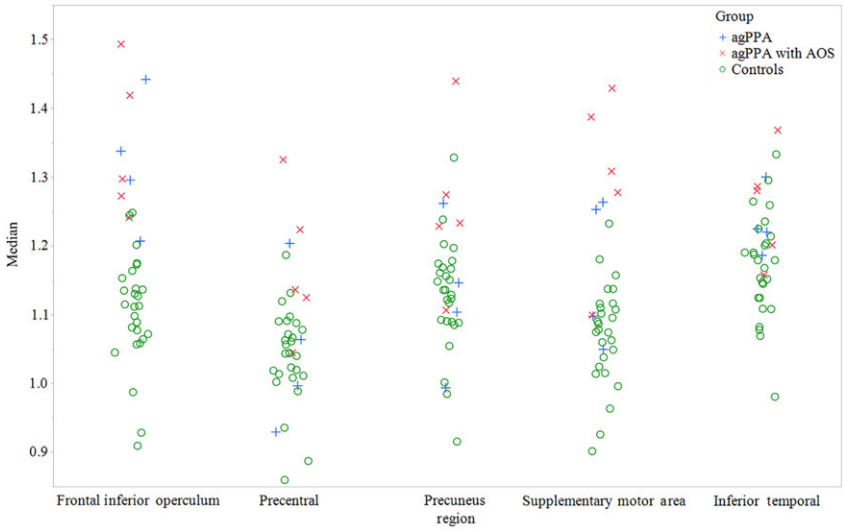


Figure 3 Partial volume-corrected tau positron emission tomography standard uptake value ratios (SUVrs), normalized by the median uptake in the cerebellar crus gray matter to create SUVr images for left-sided regions of interest. Green circles, controls; blue crosses, agrammatic variant of primary progressive aphasia (agPPA) without apraxia of speech (AOS); red Xs, agPPA with AOS. [Colour figure can be viewed at wileyonlinelibrary.com]

appearance; both presentations have been associated with an underlying 4R tauopathy (e.g. corticobasal degeneration or progressive supranuclear palsy).

There are limitations to the current study. Although the sample size was small, it is relatively large for the study of [18F]AV-1451 uptake in agPPA. Although the comparison of tau tracer uptake in agPPA with AOS to agPPA without AOS did not survive stringent correction for multiple comparisons (i.e. false discovery rate), a more stringent threshold ($P < 0.001$) was used to assess statistical significance. These findings lay the foundation for future hypothesis-driven studies in agPPA. This study demonstrates the importance of clear characterization of participants for the study of this patient population. Longitudinal confirmation of these cross-sectional findings is necessary to support or reject their clinical significance. We hypothesize that patients with agPPA at initial presentation who develop AOS will demonstrate [18F]AV-1451 uptake in the precentral gyrus and have an underlying 4R tauopathy. Of course, past research suggests caution in interpreting results of [18F]AV-1451 uptake, in that there is weak binding with 4R tauopathies and TDP-43 [8]. The [18F]AV-1451 signal in agPPA without AOS is possibly off-target binding and the same is true, perhaps to a lesser extent, for the patients with agPPA with AOS. A portion of these results could be attributable to artifact; nonetheless, their relationship to clinical correlates is impressive. Ultimately, autopsy confirmation will be needed to determine the root pathology in these patients.

In conclusion, there is a relationship between location of [18F]AV-1451 uptake and clinical presentation in agPPA. Although a direct association between [18F]AV-1451 uptake in agPPA and pathology is unclear, [18F]AV-1451 uptake in the precentral gyrus is suggestive of the concomitant presence of AOS, suggestive of a 4R tauopathy.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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