HHS Public Access

Author manuscript

Ann Neurol. Author manuscript; available in PMC 2017 March 01.

Published in final edited form as:

Ann Neurol. 2016 March ; 79(3): 496–501. doi:10.1002/ana.24566.

Is *in vivo* Amyloid Distribution Asymmetric in Primary Progressive Aphasia?

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Abstract

We aimed to determine whether ^{18}F-florbetapir amyloid PET imaging shows a clinically concordant, left hemisphere dominant, pattern of deposition in primary progressive aphasia (PPA). Elevated cortical amyloid (Aβ+) was found in 19/32 PPA patients. Hemispheric laterality of amyloid burden was compared between Aβ+ PPA and an Aβ+ amnestic dementia group (n=22). The parietal region showed significantly greater left lateralized amyloid uptake in the PPA group than the amnestic group ($p < 0.007$), consistent with the left lateralized pattern of neurodegeneration in PPA. These results suggest the cortical distribution of amyloid may have a greater clinical concordance than previously reported.

INTRODUCTION

Primary progressive aphasia (PPA) is a clinical dementia syndrome characterized by selective vulnerability of the language network, with salient deficits in domains of word

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Authorship

M.M., E.R., and S.W. contributed to conception and design of the study; A.M., C.M., A.R., C.W., K.C., S.W. and E.R. collected and analyzed the data; A.M. and E.R. wrote the manuscript.

Potential Conflicts of Interest

A.M., C.M., A.R., C.W., S.W., K.C., and M.M. have nothing to disclose. ^{18}F-florbetapir doses were provided as non-financial support by Avid Radiopharmaceuticals (awarded to E.R.).

finding, word usage, and word comprehension[1]. In the early stages, PPA is associated with a clinically concordant, typically left-lateralized, pattern of cortical atrophy[2,3].

The most common neuropathology reported for PPA is frontotemporal lobar degeneration (~60%) followed by Alzheimer's disease (AD; ~40%)[4]. PPA patients with postmortem AD generally show a leftward predominance of cortical neuropathology, an asymmetry that is more prominent for neurofibrillary tangles than beta-amyloid (Aβ) plaques[5]. This distribution of pathology is different from that of patients with typical amnestic dementia of the Alzheimer's type (DAT) who show symmetric plaque and tangle pathology. However, previous amyloid imaging with ^{11}C-Pittsburgh Compound B (PiB) has yielded conflicting conclusions concerning asymmetry of binding in PPA[6,7,8]. The present study examined whether amyloid positivity identified using florbetapir F18 (^{18}F-AV-45), which was obtained at relatively early disease stages, would reveal a left hemisphere dominant pattern of deposition that is more consistent with the clinical picture of PPA.

METHODS

Participants

Thirty-two individuals with a root diagnosis of PPA[1,3] (ages, 58–82 years; symptom duration, 4.6 ± 2.2 years) were screened for amyloid positivity using florbetapir F18 (^{18}F-AV-45) positron emission tomography (PET). PPA patients were further characterized as logopenic (PPA-L), agrammatic (PPA-G), or semantic (PPA-S) based on quantitative neuropsychological data and clinical judgment using previously reported guidelines[9]. Patients who did not meet the current subtyping criteria were labeled “unclassified” (PPA-U)[3,10]. All participants were right-handed.

PPA participants were recruited from the PPA Research Program at the Cognitive Neurology and Alzheimer's Disease Center at Northwestern University's Feinberg School of Medicine. Written informed consent was obtained from all PPA participants in the study. The Northwestern University Institutional Review Board approved the study.

The Alzheimer's Disease Neuroimaging Initiative (ADNI; http://adni.loni.usc.edu), a longitudinal multisite neuroimaging study supported by the National Institutes of Health, was utilized to identify an amnestic dementia comparison group. The group included twenty-two individuals with a clinical diagnosis of DAT or mild cognitive impairment (MCI)[11] who had an elevated amyloid (Aβ+) PET scan and demographics and Clinical Dementia Rating (CDR)[12] score similar to the PPA cohort.

Amyloid PET imaging acquisition and analysis

PET imaging for the PPA group was performed on a Siemens Biograph 40 TruePoint/TrueV PET-CT system located at Northwestern Memorial Hospital in Chicago, IL. Participants were administered a bolus intravenous injection of 370 MBq (10 +/− 1.0 mCi) florbetapir-F18. A CT scan was acquired for attenuation correction within 10 minutes before the beginning of PET imaging. Exactly 50 minutes post-injection, dynamic 3D imaging was continuously acquired for 20 minutes. The first 10 minutes of PET acquisition was reconstructed into 2×5 minute frames.

The ADNI participants completed an identical florbetapir PET imaging protocol at hospital and university sites nationwide. The 22 ADNI amnestic group subjects used in this study were scanned on Siemens, Phillips, and GE PET scanners.

Because of the inherent differences in PET scanners, smoothness of florbetapir signal was carefully estimated and matched for each amnestic and PPA subject. Smoothness was estimated with the Advanced Normalization Tools (ANTs; http://stnava.github.io/ANTs)[13] and Analysis of Functional NeuroImages (AFNI; http://afni.nimh.nih.gov)[14] software. Specifically, the Automated Anatomical Labeling (AAL) atlas[15] left and right hemisphere masks were reverse normalized with ANTs from a ^{18}F-AV-45 PET template[16] to native subject space. The AAL binarized volume, in native space, was used to mask the motion corrected 2×5 minute mean PET volume with AFNI's 3dFWHMx, which estimated smoothness using a combination of first and second neighbor differences. A Gaussian kernel with varying levels of global smoothness (between 2-4mm FWHM) was applied to each amnestic subject's PET volume to achieve the same spatial smoothness of the Aβ+ PPA group. This method is ideal because it minimizes the amount of smoothing compared to typical ADNI processing, which blurs to a uniform 8mm FWHM.

For comparisons with other florbetapir studies, pre-processing methods and *a priori* regions from a previous report of DAT patients with pathologically confirmed AD were used[17]. Briefly, SPM 8 (http://www.fil.ion.ucl.ac.uk) was used to spatial normalize each subject's florbetapir scan to a common stereotaxic space[16]. An average cortical cerebral-to-cerebellar standard uptake value ratio (mean cortical SUVR) was calculated using a single SUVR mask consisting of six *a priori* bilateral volumes of interest (VOIs) in the frontal, temporal, parietal, anterior cingulate, posterior cingulate, and precuneus regions[17, 18]. Elevated amyloid (Aβ+) was defined as mean cortical SUVR ≥ 1.10. This threshold has been validated by florbetapir imaging of participants with confirmed AD histopathology[17].

The laterality analysis compared scans from 19 Aβ+ PPA participants to that of 22 Aβ+ amnestic participants. For this analysis, the mean SUVR mask described above was segmented by region and by hemisphere, resulting in six regional SUVR pairs. Laterality scores were calculated (see formula below) for each VOI pair to determine asymmetry among the Aβ+ subjects. A positive laterality score indicates left hemisphere (LH) greater than right hemisphere (RH) amyloid burden.

$$\text{Laterality Score} = \frac{LH\ \ VOI\ \ SUVR - RH\ \ VOI\ \ SUVR}{LH\ \ VOI\ \ SUVR + RH\ \ VOI\ \ SUVR}$$

Statistical analysis

Differences in demographics and neuropsychological performance among groups (Aβ+ PPA, Aβ- PPA, and Aβ+ amnestic) were assessed with independent two-sample *t*-tests or χ^2 using PASW 22.0 (SPSS Inc., Chicago, IL). Laterality of amyloid burden was compared between Aβ+ PPA and Aβ+ amnestic groups for each of the six VOI using independent samples *t*-tests and a Bonferroni criterion of $p < 0.007$. Within-group differences of the laterality score were assessed with a one-sample *t*-test.

RESULTS

Nineteen PPA participants (7 PPA-L, 8 PPA-G, and 4 PPA-U) and 22 amnestic participants (7 DAT and 15 MCI) showed elevated florbetapir burden (mean cortical SUVR ≥ 1.10) and were included in the laterality analysis (Fig 1). There was no difference in dementia severity, as measured by the Clinical Dementia Rating (CDR) between the Aβ+ PPA group and Aβ+ amnestic group. However, the Aβ+ PPA group scored significantly lower than the amnestic group on the mini-mental state examination (MMSE; $p < 0.05$). This is not surprising since the MMSE is highly dependent on language ability and can overestimate dementia severity in PPA patients[19]. There were no significant differences in demographics or neuropsychological performance between the 19 Aβ+ and 13 Aβ− PPA patients (Table 1). Demographic and neuropsychological test scores by PPA subtype for the 19 Aβ+ participants are provided in Table 2.

Laterality scores for the 19 Aβ+ PPA and 22 amnestic participants across all six individual VOI regions (anterior cingulate, posterior cingulate, precuneus, frontal, temporal, parietal) and the laterality of the mean cortical SUVR are provided in Figure 2a. Laterality scores from the parietal region of the Aβ+ PPA participants showed a significantly greater left-lateralized uptake compared to the Aβ+ amnestic group ($p < 0.007$). The laterality score of the parietal region was significantly asymmetric (different from zero) in the Aβ+ PPA group ($p < 0.001$). In contrast, the Aβ+ amnestic group showed no significant asymmetry of the parietal region ($p = 0.827$). There were no significant differences in the parietal laterality score between PPA-L (mean laterality score = 0.152 ± 0.122) and PPAG (mean laterality score = 0.153 ± 0.118; $p = 0.639$). Furthermore, parietal laterality scores were not correlated with age (Pearson's r = −0.056; $p = 0.821$). An Aβ+ PPA participant with clear asymmetric parietal uptake and an Aβ+ DAT participant with symmetric burden are provided for demonstrative purposes in Figure 2b.

DISCUSSION

This study applied the standard florbetapir methods[17] for quantification to a well-characterized cohort of 32 PPA participants. In keeping with autopsy series, approximately half of PPA patients (59%) showed elevated β-amyloid binding. The differential percentage of participants with elevated amyloid in the PPA-L (78%) and PPA-S (0%) groups is consistent with prior amyloid PET imaging studies[6,7]. The number of PPA-G participants with elevated amyloid was higher than in previous reports. However, the fact that both PPA-L and PPA-G phenotypes showed elevated amyloid is consistent with clinicopathologic reports showing there is no one-to-one correspondence between clinical phenotypes and underlying pathology[4]. One of the PPA-L subjects with elevated amyloid in this study has come to autopsy and showed congruent AD pathology.

For PPA participants with elevated amyloid, greater left-lateralized Aβ asymmetry was detected in the parietal region compared to Aβ+ amnestic subjects. This left-lateralized parietal florbetapir signal is consistent with the clinical phenotype and the left-lateralized pattern of atrophy in early-stage PPA.

The few quantitative reports of *in vivo* amyloid PET imaging in PPA have exclusively used PiB and shown conflicting results. A single PPA case was compared to 10 DAT participants using a whole brain approach and found left-lateralized frontotemporal PiB retention[8]. However, two group comparison studies between PPA and DAT using PiB showed no significant differences in the hemispheric distribution of amyloid[6,7]. While both ^{11}C-PiB and ^{18}F-florbetapir identify amyloid with high reliability[21,17, 20], slight differences in nonspecific white matter signal or differential binding profiles between the two amyloid radiotracers may influence quantitative metrics[21].

It will be important to determine how atrophy, partial volume effects, disease stage, and PET tracers influence the detection of amyloid deposition in the cerebral cortex so that we can more accurately explain the relationship between amyloid PET measures and the pathophysiologic AD process. The asymmetry of pathology in PPA offers a unique setting for addressing this question since the right hemisphere acts as a control for the left, thus eliminating the complications inherent in inter-subject comparisons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank Amanda Rezutek, Kristen Whitney, and Joseph Boyle for neuropsychological test administration of the primary progressive aphasia (PPA) participants. PET imaging for the PPA group was performed at the Northwestern Memorial Hospital Department of Nuclear Medicine.

This project was supported by DC008552 from the National Institute on Deafness and Other Communication Disorders, M.M.; AG13854 (Alzheimer Disease Center) from the National Institute on Aging, M.M.; NS075075 from the National Institute of Neurological Disorders and Stroke (NINDS), E.R.; this is not an industry-sponsored study.

Florbetapir F18 (^{18}F-AV-45) doses for the PET imaging performed at Northwestern Memorial Hospital (Chicago, IL), as part of the primary progressive aphasia program at Northwestern University, were provided by Avid Radiopharmaceuticals a wholly owned subsidiary of Eli Lilly and Company.

A subset of data used in preparation of this article was obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI; adni.loni.usc.edu). For a full list of ADNI acknowledgements, see the online Supplementary File 1.

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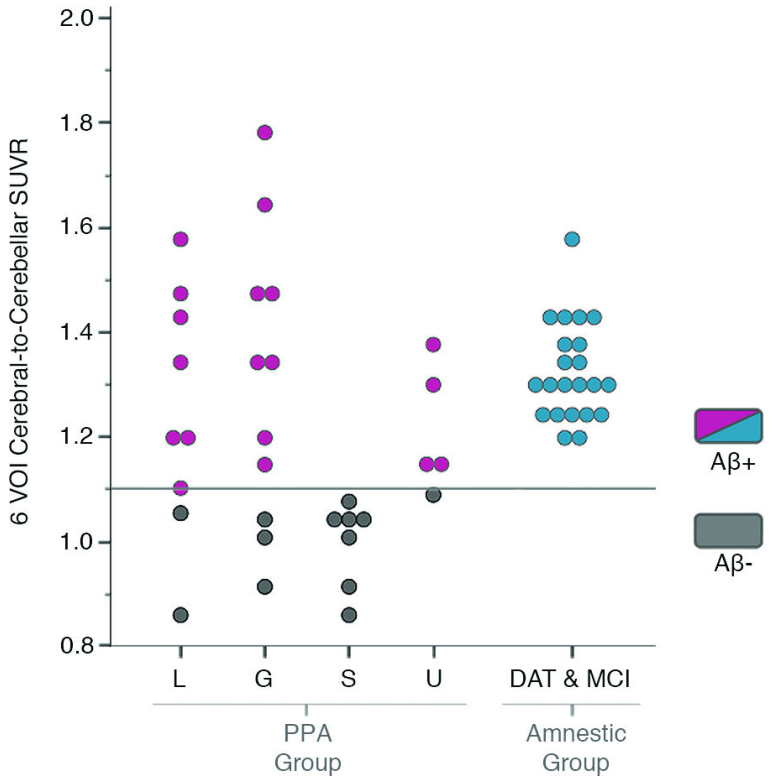

Figure 1. Mean cortical SUVR values for PPA and amnestic participants by clinical subtype

Amyloid burden for individual participants based on the mean cortical cerebral-to-cerebellar standard uptake value ratio (global mask of anterior cingulate, posterior cingulate, precuneus, frontal, temporal, and parietal regions). Nineteen PPA and 22 DAT/MCI amnestic subjects were above the 1.10 threshold and showed elevated florbetapir burden. *Abbreviations*: Aβ+ = elevated amyloid, mean cortical SUVR ≥ 1.10; Aβ– = Amyloid below threshold, mean cortical SUVR < 1.10; PPA = primary progressive aphasia; PPA-G = agrammatic subtype of PPA; PPA-L = logopenic subtype of PPA; PPA-S = semantic subtype of PPA; PPA-U = unclassifiable subtype of PPA; DAT = dementia of the Alzheimer's type; MCI = mild cognitive impairment; SUVR = standard uptake value ratio; VOI = volume of interest.

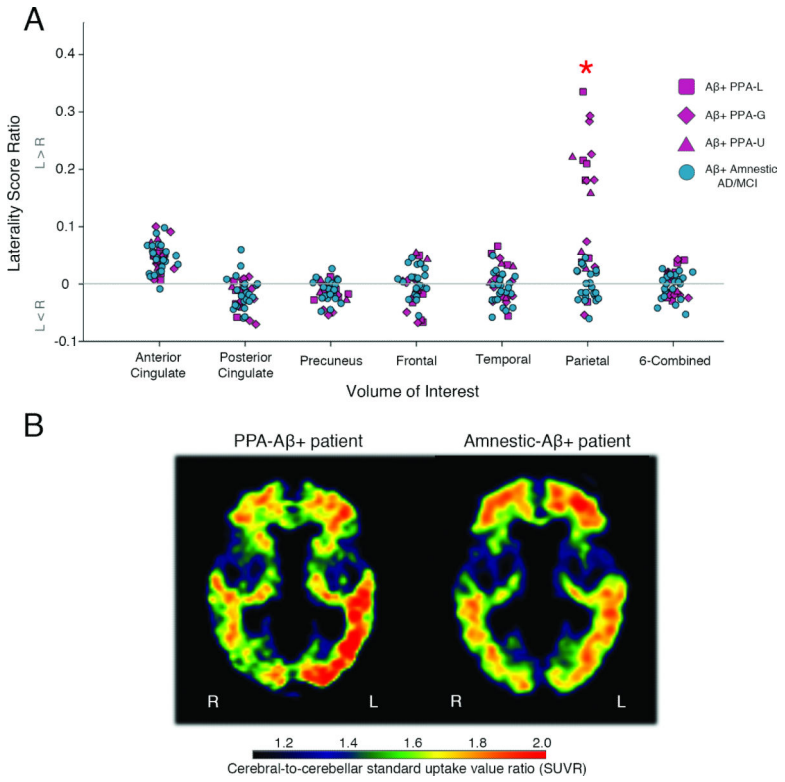

Figure 2. Laterality of the florbetapir PET signal for PPA and amnestic individuals with elevated amyloid

(A) Laterality scores of each Aβ+ PPA (n = 19) and amnestic (n = 22) subject in each of six volumes of interest (VOI) and the mean SUVR, which is the average SUVR of the 6 VOIs. A positive laterality score indicates left > right asymmetry. * The parietal VOI showed significant differences between groups (PPA-Aβ+ mean laterality score = 0.146 ± 0.110; amnestic-Aβ+ group mean laterality score = – 0.001 ± 0.028).

(B) An Aβ+ PPA patient (CDR = 0.5; MMSE = 28; mean cortical Aβ SUVR = 1.436) with an asymmetric left lateralized distribution of cortical amyloid in comparison to an amnestic DAT patient at similar stage of disease and amyloid load (CDR = 0.5; MMSE = 28; mean cortical Aβ SUVR = 1.437). Axial slices (radiological orientation) for visualization are provided (MNI-Talairach z = 5) and scaled at the same SUVR. The flame scale (1.1 to 2.0 SUVR) is provided, with warmer colors representing higher cerebral-to-cerebellar SUVR values.

Abbreviations: PPA = primary progressive aphasia; PPA-L = logopenic subtype of PPA; PPA-G = agrammatic subtype of PPA; PPA-U = unclassifiable subtype of PPA; Aβ+ = elevated amyloid, mean cortical SUVR ≥ 1.10; L = Left hemisphere; R = right hemisphere; MMSE = mini-mental state examination; DAT = dementia of the Alzheimer's type; SUVR = standard uptake value ratio.

Table 1

Demographic features of the amnestic group and PPA participants with and without elevated amyloid.

	PPA-Aβ+	PPA-Aβ–	Amnestic-Aβ+
N	19	13	22
Age, years (SD)	68.3 (± 6.2)	68.5 (± 6.2)	67.7 (± 5.5)
Gender, % male	42.1%	61.5%	27.3%
Education, years (SD)	16.0 (± 2.5)	15.1 (± 2.7)	15.5 (± 2.6)
CDR = 0, N	2	8	0
CDR = 0.5, N	14	4	17
CDR = 1.0, N	3	1	5
MMSE, 0-30 (SD)	20.9 (± 7.1)	25.0 (± 5.8)	26.0 (± 3.0) *
WAB-AQ, % (SD)	81.9 (± 11.0)	77.9 (± 16.0)	N/A

Age, and education are provided in years. WAB-AQ, and gender are provided as percent out of 100. MMSE, out of a total of 30, with higher scores representing preserved cognition. CDR is ranked out of 3, with higher scores representing greater dementia severity.

There were no significant differences in demographics or neuropsychological performance between PPA-Aβ+ and PPA-Aβ–.

Abbreviations: PPA = primary progressive aphasia; Aβ+ = elevated amyloid, mean cortical SUVR ≥ 1.10; Aβ– = Amyloid below threshold, mean cortical SUVR < 1.10; CDR = Clinical Dementia Rating global measure; MMSE = mini-mental state examination; WAB-AQ = aphasia quotient of the Western Aphasia Battery; N/A = not available; SUVR = standard uptake value ratio.

* MMSE performance was significantly better for the amnestic group compared to the PPA-Aβ+ group ($p < 0.05$).

Table 2

Neuropsychological features of the PPA participants with elevated amyloid by subtype.

	Aβ+ PPA-L	Aβ+ PPA-G	Aβ+ PPA-U
N	7	8	4
Age, years (SD)	68.0 (± 7.5)	66.5 (± 4.5)	72.3 (± 6.7)
Gender, % male	42.9%	37.5%	50.0%
Education, years (SD)	17.4 (± 1.8)	15.5 (± 2.8)	14.5 (± 1.9)
WAB-AQ (SD)	82.2% (± 13.7)	80.8% (± 11.4)	83.6% (± 5.9)
WAB-repetition (SD)	57.0% (± 24.1)	64.2% (± 18.6)	72.3% (± 8.4)
PPVT (SD)	91.3% (± 6.3)	88.9% (± 7.7)	68.8% (± 37.0)
BNT (SD)	71.1% (± 20.3)	62.6% (± 32.3)	48.3% (± 28.0)
NAT-nc (SD)	76.7% (± 22.6)	55.0% (± 26.7)	66.7% (± 21.1)

Age, and education were provided in years. Gender, WAB-AQ, WAB-repetition PPVT, BNT, and NAT-nc are provided as percent out of 100. There were no significant differences in demographics or neuropsychological performance between the elevated amyloid PPA-L and PPA-G groups.

Abbreviations: PPA = primary progressive aphasia; PPA-L = logopenic subtype of PPA; PPA-G = agrammatic subtype of PPA; PPA-U = unclassifiable subtype of PPA; Aβ+ = elevated amyloid, mean cortical SUVR ≥ 1.10; WAB = Western Aphasia Battery; WAB-AQ = aphasia quotient from the WAB; WAB-repetition = the 6 most difficult items (#10-15) from the WAB Repetition subtest; PPVT = a subset of 36 moderately difficult items (#157-192) from the Peabody Picture Vocabulary Test, Fourth Edition; BNT = Boston Naming Test; NAT-nc = 15 noncanonical sentence items from the Northwestern Anagram Test. Neuropsychological tests WAB-AQ, WAB-repetition, PPVT, BNT, and NAT previously described[3].