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Regional β-amyloid burden does not correlate with cognitive or language deficits in Alzheimer's disease presenting as aphasia

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Abstract

Background—A subset of patients with Alzheimer's disease (AD) present with early and prominent language impairment (aphasic AD). We previously reported an association between global β-amyloid burden measured on [^{11}C] Pittsburgh compound B PET (PiB) and general cognitive impairment, but not with aphasia, in such subjects. As a follow up, we assess whether there is any association between regional β-amyloid burden, atrophy on MRI, and global cognitive impairment, aphasia, or other cognitive and functional impairment in aphasic AD.

Methods—Forty-four aphasic AD subjects that underwent PiB scanning and volumetric MRI and were determined to be positive for β-amyloid deposition were analyzed. All had completed detailed neurological, neuropsychological and language batteries. Spearman's rank-order correlation was utilized to assess for associations.

Results—Greater visuospatial impairment was associated with increased β-amyloid burden in the primary visual cortex ($p = 0.001$). Although there were many trends for associations between neurocognitive and language deficits and regional β-amyloid burden, there were no strong associations that survived correction for multiple comparisons. However, neurocognitive and language impairment in these subjects strongly correlated with the degree of left lateral temporal and inferior parietal atrophy ($p < 0.004$).

Conclusions—The findings from this study suggest a close relation between the severity of regional atrophy and cognitive and language impairment, but argue against a strong association between regional β-amyloid burden and such deficits in aphasic AD subjects. Hence, other

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pathological factors may be driving the previously identified association between global β-amyloid deposition and general cognitive impairment in aphasic AD.

Keywords

Dementia; Aphasia; PET; Beta-amyloid; PiB

Introduction

Patients with Alzheimer's disease (AD) most often present with loss of episodic memory, and are referred to as having amnestic AD. However, early and prominent language deficits can be the presenting symptoms of a subset of AD patients [1]. We refer to such patients as having aphasic AD to differentiate them from patients with amnestic AD. Beta-amyloid deposition is a hallmark pathological feature of AD, which occurs in a stereotypic fashion over several distinctive phases in patients with amnestic AD [2]. Similar patterns of global amyloid accumulation have been observed in patients with aphasic AD [3–5]. In patients with amnestic AD, higher amyloid burden has been shown to inversely correlate with cognitive function [6]. Interestingly, β-amyloid deposition may also affect cognition in AD patients presenting with aphasia. We previously found an association between global β-amyloid burden and general cognitive impairment in aphasic AD subjects [7, 8]. However, it is unclear whether this association may have been driven by other factors. We argue that if our previously identified association was genuinely related to β-amyloid then there would also be strong associations between general cognitive impairment and β-amyloid burden for specific regions. Here, we examined the relationships between regional β-amyloid burden on [^{11}C] Pittsburgh compound B (PiB) PET, atrophy on volumetric MRI, and performances on various neurological, neuropsychological, and language metrics in a large cohort of AD patients who presented with early and prominent language impairment.

Methods

Forty-four subjects who presented to Mayo Clinic, Rochester, MN with prominent language deficits without preceding memory complaints that impaired activities of daily living and had β-amyloid deposition on [^{11}C] PiB-PET were prospectively enrolled in this study. All subjects had aphasia characterized by anomia, poor sentence repetition, and phonological errors without loss of single word comprehension or apraxia of speech. All subjects met the criteria for the logopenic variant of primary progressive aphasia (lvPPA) [9, 10]. Each subject underwent a neurological evaluation that included the Montreal Cognitive Assessment (MoCA) [11], the Frontal Assessment Battery (FAB) [12], the Frontal Behavior Inventory (FBI) [13], and the Clinical Dementia Rating (CDR) [14] by a behavioral neurologist (KAJ). In addition, a language evaluation that included the Western Aphasia Battery (WAB) [15], the Token Test [16], and the Boston Naming Test (BNT) [17] was performed by one of two speech pathologists (JRD & EAS). Each participant also had a neuropsychometric evaluation that included the Auditory Verbal Learning Test (AVLT) [18], the Sorting Test from the Delis-Kaplan Executive Function System (DKEFS) [19], and the Incomplete Letters and Cube Analysis subtests from the Visual Object and Space Perception Battery (VOSP) [20]. By design, all subjects had positive PiB-PET determined

by a global PiB ratio cut-point of 1.5, as previously described [21]. Seven areas of interest, including Broca's area, insular, prefrontal, parietal, medial and lateral temporal, and visual cortex, were selected. Regional PiB uptake ratios were calculated for each region as previously described [8]. Briefly, PiB-PET images were co-registered to 3D magnetisation prepared rapid acquisition gradient echo (MPRAGE) using 6 degrees-of-freedom affine registration. The automated anatomical labelling (AAL) atlas was used to calculate median PiB uptake for the regions of interest. The uptake ratios were calculated by dividing median PiB uptake in each region by median uptake in cerebellar gray matter. In addition, left lateral temporal, inferior parietal, and hippocampal atrophy on MRI was calculated as previously described [22]. The association between regional PiB uptake ratio, atrophy on MRI, and performances on neurological, neuropsychological, and language metrics was examined using Spearman's rank-order correlation. Statistical analyses were performed using JMP software, version 9.0 (SAS Institute Inc, Cary, NC). In order to correct for multiple comparisons, Bonferroni correction was applied to each set of comparisons among the 12 regional variables and individual neurological, neuropsychological, and language measures (Tables 3 – 5) and vice versa (Table 6) with a desired α of 0.05. Therefore, a p value < 0.004 was considered statistically significant for our regional analyses.

This study was approved by the Mayo Clinic IRB. Informed consent was obtained from the patients and their family members or significant others.

Results

The subjects included 22 men and 22 women. The demographic characteristics of the subjects are shown in Table 1. Of the 44 subjects, two were left-hand dominant, and one was ambidextrous. The median age of the participants was 68 (interquartile range [IQR], 59 – 73). The median age at disease onset was 64 (IQR, 55 – 70). The median disease duration at the time of evaluation was 3.5 years (IQR, 1.5 – 5). The median years of education were 16 (IQR, 12.5 – 18). The severity of cognitive impairment and aphasia measured by neurological, neuropsychological, and language metrics were variable in these subjects (Table 1).

The seven cortical regions of interest, including Broca's area, insular, prefrontal, parietal, medial and lateral temporal, and visual cortex, displayed varying degrees of β-amyloid accumulation (Table 2). Beta-amyloid burdens were similar between the left and right hemisphere. Highest β-amyloid burdens were observed in the prefrontal and parietal cortex followed by the lateral temporal cortex, Broca's area, insula, and primary visual cortex. The lowest β-amyloid deposition was observed in the medial temporal cortex. Global and regional amyloid burdens were positively correlated ($p<0.004$, data not shown). In addition, positive associations were seen between regional amyloid burdens in most areas of interest ($p<0.004$, data not shown) with exception to the association between medial temporal and primary visual cortex amyloid burden.

Correlations between regional β-amyloid burden and performances on neurological, neuropsychological, and language assessments are shown in Tables 3 – 5. Global cognitive function as measured by the MoCA showed trends for associations with β-amyloid

deposition in multiple cortical regions, including the right prefrontal, right lateral temporal, right parietal, and primary visual cortex. A similar trend was noted for scores on the FAB, a measure of executive function, and β-amyloid burden in the right lateral temporal cortex. However, none of the associations reached significance, including other associations between FBI and CDR and any regional β-amyloid burden in our regions of interest.

The only strong association observed on the neuropsychological measures was between visuospatial function measured by the Cube Analysis subtest of the VOSP battery and β-amyloid burden in the primary visual cortex. Short-term and long-term memory impairment measured by the AVLT and concept formation and problem-solving skills measured by DKEFS Sorting were not associated with regional β-amyloid deposition.

With our language measures, there was a trend for an association between overall aphasia severity measured by the WAB and β-amyloid burden in the right prefrontal region. In addition, aphasia severity and deficits in receptive language and auditory processing measured by the Token Test showed a trend for an inverse correlation with β-amyloid burden in the bilateral prefrontal cortex. However, none of these associations reached significance. Impaired repetition and confrontation naming measured by the WAB repetition subscores and the BNT, respectively, showed no trend for any associations with regional β-amyloid burden.

On the other hand, left lateral temporal and inferior parietal atrophy on MRI strongly correlated with impairment in global cognitive function (i.e. MoCA) and executive function (i.e. FAB), as well as aphasia severity (i.e. WAB, Token Test) (Table 6). None of these measures had significant associations with left hippocampal atrophy.

Conclusions

This study demonstrated associations between atrophy in the left lateral temporal and inferior parietal cortex, regions that are known to be affected in aphasic AD [1, 22, 23], and measures of general cognitive and language impairment, but failed to identify any convincing evidence for associations between regional β-amyloid burden and such deficits in aphasic AD subjects except for a biologically plausible association between visuospatial impairment and increased β-amyloid burden in the primary visual cortex.

There were trends for an association between degree of impairment in general cognitive function and β-amyloid burden in several cortical regions, including the prefrontal, temporal, parietal, and primary visual cortex. However, none of these associations were strong, and hence none survived our correction for multiple comparisons. The findings have implications on our previous study that showed increased global β-amyloid burden was associated with worse cognition in aphasic AD subjects [7]. A reasonable deduction, given the lack of robust findings, is that factors other than β-amyloid are the driving force behind cognitive impairment in aphasic AD subjects. Furthermore, it would not be unreasonable to consider the possibility that these other factors may have confounded our previous results. On the other hand, taking into account the findings from both studies, including the many trends identified in this study, it still remains possible that β-amyloid could partly be

contributing to cognitive impairment in aphasic AD subjects. Hence, we are unable to determine whether β-amyloid is playing a definitive role in the cognitive impairment that occurs in aphasic AD subjects.

Short-term and long-term memory measures did not correlate with β-amyloid accumulation in the seven cortical areas of interest. Similarly, the overall severity of aphasia, the most prominent symptom observed in these subjects, showed a trend for an association with prefrontal β-amyloid burden without reaching significance. This is not a particularly expected association, and could have been observed by chance given the many comparisons performed. Previously, the Token test has been shown to be associated with involvement of a number of left hemisphere regions, including Broca's area, but not the prefrontal cortex or right hemisphere regions [24]. More specific aphasia related deficits, such as impaired repetition and naming, also did not correlate with increased regional β-amyloid burden, although this was not surprising since our previous study failed to demonstrate any association between global β-amyloid burden and these deficits [7].

The confounding effects of other proteins, such as tau and TDP-43, could not be examined in this study. Several studies have shown regional discrepancy between β-amyloid deposition, cortical atrophy, and hypometabolism in AD [25–27]. Similarly, we did not find clinical correlations with increased β-amyloid deposition in the parietal cortex, an area associated with atrophy and hypometabolism in lvPPA [1, 22, 28]. The accumulation of β-amyloid is thought to occur in early stages of AD [29]. Therefore, it could be that β-amyloid is deposited early before the onset of the aphasia and the cognitive deficits in aphasic AD subjects. It is possible that β-amyloid plaques then initiate downstream pathways involving these other pathologic proteins that then directly cause further insults leading to the aphasia and the later general cognitive impairment. In fact, tau pathology was shown to correlate with the degree of gray matter atrophy in AD [30], and recently TDP-43 was shown to correlate with measures of memory loss and measures of language, such as naming, as previously discussed [31, 32]. Therefore, downstream effects of β-amyloid deposition cannot be ignored in aphasic AD subjects, and serial followup and correlation with future disease progression may be helpful to inform us in this regard.

The relationship between β-amyloid and clinical phenotypes of AD remains unclear. Diffuse β-amyloid deposition has been seen in AD regardless of its phenotypes, including amnestic, aphasic, and visuospatial/perceptual AD [3–5]. It is also unclear whether the role of β-amyloid in aphasic AD subjects is different from its role in amnestic AD subjects. The results of this study, therefore, do not substantiate our previous finding of an association between β-amyloid burden and general cognitive impairment. Further studies that simultaneously assess for other pathologic proteins involved in AD are needed to define their roles and relationship to β-amyloid in the clinical manifestations of aphasic AD.

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Table 1

Demographic, neurological, language, and neuropsychological characteristics

Demographics	**Median (interquartile range)**
Gender (M/F)	22/22
Handedness (R/L/ambidextrous)	41/2/1
Age, y	68 (59 – 73)
Age at disease onset, y	64 (55 – 70)
Disease duration, y	3.5 (1.5 – 5)
Education, y	16 (12.5 – 18)
Neurological evaluation	Median (interquartile range)
MOCA	16 (9 – 20.8)
FAB	12 (7.3 – 14)
FBI	10.5 (7 – 19.8)
CDR-SB	3.5 (1.5 – 6)
Neuropsychological evaluation	
AVLT trial 1 MOANS	5 (2 – 7.5)
AVLT LT % retention MOANS	6 (3 – 10)
DKEFS sorting scaled score	7 (4 – 9)
VOSP cube raw score	9 (5 – 10)
Language evaluation	
WAB AQ	83 (70.6 – 88.1)
WAB repetition	7.8 (7 – 8.6)
Token test	11 (5.3 – 14)
BNT	7 (3 – 11)

Abbreviations: MOCA = the Montreal Cognitive Assessment; FAB = the Frontal Assessment Battery; FBI = the Frontal Behavior Inventory; CDR-SB = Clinical Dementia Rating Sum of Boxes; AVLT = Auditory Verbal Learning Test; MOANS = Mayo Clinic's Older Americans Normative Studies; LT = long term delayed recall; DKEFS = Delis-Kaplan Executive Function System; VOSP = the Visual Object and Space Perception Battery; WAB = Western Aphasia Battery; AQ = aphasia quotient; BNT = the Boston Naming Test

Table 2

Regional PiB distribution

Area	PiB uptake ratio Median (interquartile range)
Left prefrontal	2.18 (2.06 – 2.41)
Left medial temporal	1.39 (1.29 – 1.44)
Left lateral temporal	2.08 (1.92 – 2.27)
Left parietal	2.19 (1.99 – 2.31)
Left insula	1.97 (1.85 – 2.09)
Broca's	2.01 (1.87 – 2.15)
Primary visual cortex	1.76 (1.55 – 2.07)
Right prefrontal	2.18 (2.00 – 2.36)
Right medial temporal	1.38 (1.31 – 1.46)
Right lateral temporal	1.98 (1.86 – 2.21)
Right parietal	2.12 (1.99 – 2.31)
Right insula	1.90 (1.77 – 2.04)

Table 3

Correlations between regional amyloid burden and neurological scores

	ρ value (p value)			
	MOCA	**FAB**	**FBI**	**CDR-SB**
L prefrontal	−0.30 (0.04)	−0.31 (0.04)	−0.03 (0.85)	0.32 (0.04)
L medial temporal	−0.11 (0.47)	−0.10 (0.51)	−0.09 (0.57)	0.08 (0.44)
L lateral temporal	−0.27 (0.08)	−0.23 (0.13)	−0.17 (0.28)	0.24 (0.11)
L parietal	−0.21 (0.18)	−0.20 (0.20)	−0.14 (0.35)	0.23 (0.13)
L insula	−0.21 (0.18)	−0.16 (0.31)	−0.25 (0.10)	0.18 (0.26)
Broca's	−0.19 (0.21)	−0.11 (0.47)	−0.21 (0.18)	0.16 (0.31)
Primary visual	−0.40* (0.01)	−0.27 (0.08)	−0.17 (0.28)	0.29 (0.06)
R prefrontal	−0.37* (0.01)	−0.36 (0.02)	−0.02 (0.92)	0.32 (0.04)
R medial temporal	−0.29 (0.06)	−0.30 (0.05)	−0.14 (0.38)	0.19 (0.22)
R lateral temporal	−0.41* (0.01)	−0.37* (0.01)	−0.10 (0.51)	0.33 (0.17)
R parietal	−0.37* (0.01)	−0.31 (0.04)	−0.04 (0.81)	0.33 (0.03)
R insula	−0.29 (0.05)	−0.28 (0.06)	−0.15 (0.34)	0.20 (0.21)

* Trend for significance ($p \leq 0.01$)

Abbreviations: L = left; R = right; MOCA = the Montreal Cognitive Assessment; FAB = the Frontal Assessment Battery; FBI = the Frontal Behavior Inventory; CDR-SB = Clinical Dementia Rating Sum of Boxes

Table 4

Correlations between regional amyloid burden and neuropsychological scores

	ρ value (p value)			
	AVLT trial 1 MOANS	**AVLT LT % ret MOANS**	**DKEFS sorting scaled score**	**VOSP cube raw score**
L prefrontal	−0.03 (0.87)	−0.07 (0.68)	−0.23 (0.15)	−0.26 (0.09)
L medial temporal	−0.06 (0.70)	−0.18 (0.26)	−0.01 (0.94)	0.12 (0.44)
L lateral temporal	0.10 (0.51)	−0.01 (0.93)	−0.19 (0.26)	−0.24 (0.13)
L parietal	0.12 (0.44)	0.01 (0.94)	−0.13 (0.44)	−0.37 (0.02)
L insula	0.04 (0.78)	0.10 (0.84)	−0.05 (0.78)	−0.25 (0.11)
Broca's	0.02 (0.91)	0.12 (0.44)	−0.04 (0.81)	−0.26 (0.09)
Primary visual	0.18 (0.25)	−0.17 (0.28)	−0.24 (0.15)	−0.49** (0.001)
R prefrontal	−0.01 (0.93)	−0.07 (0.65)	−0.25 (0.12)	−0.28 (0.07)
R medial temporal	−0.12 (0.45)	−0.10 (0.54)	−0.14 (0.41)	−0.09 (0.56)
R lateral temporal	0.09 (0.56)	−0.15 (0.36)	−0.30 (0.06)	−0.32 (0.03)
R parietal	0.07 (0.68)	−0.07 (0.65)	−0.28 (0.09)	−0.36 (0.02)
R insula	−0.02 (0.89)	−0.05 (0.74)	−0.07 (0.70)	−0.19 (0.23)

** Statistically significant ($p < 0.004$)

Abbreviations: L = left; R = right; AVLT = Auditory Verbal Learning Test; MOANS = Mayo Clinic's Older Americans Normative Studies; LT = long term delayed recall; DKEFS = Delis-Kaplan Executive Function System; VOSP = the Visual Object and Space Perception Battery

Table 5

Correlations between regional amyloid burden and language scores

	ρ value (p value)			
	WAB AQ	**WAB repetition**	**Token test**	**BNT**
L prefrontal	−0.33 (0.03)	−0.24 (0.12)	−0.37* (0.01)	−0.27 (0.08)
L medial temporal	−0.07 (0.64)	−0.03 (0.87)	−0.16 (0.29)	−0.06 (0.69)
L lateral temporal	−0.24 (0.12)	−0.13 (0.40)	−0.25 (0.11)	−0.28 (0.07)
L parietal	−0.20 (0.18)	−0.17 (0.26)	−0.23 (0.14)	−0.20 (0.18)
L insula	−0.33 (0.03)	−0.29 (0.05)	−0.28 (0.06)	−0.21 (0.17)
Broca's	−0.24 (0.11)	−0.25 (0.11)	−0.22 (0.15)	−0.22 (0.15)
Primary visual	−0.05 (0.74)	0.03 (0.87)	−0.10 (0.51)	−0.16 (0.31)
R prefrontal	−0.39* (0.01)	−0.30 (0.04)	−0.39* (0.01)	−0.31 (0.04)
R medial temporal	−0.23 (0.13)	−0.19 (0.21)	−0.22 (0.16)	−0.18 (0.24)
R lateral temporal	−0.36 (0.02)	−0.24 (0.12)	−0.35 (0.02)	−0.32 (0.04)
R parietal	−0.33 (0.03)	−0.26 (0.09)	−0.34 (0.03)	−0.29 (0.06)
R insula	−0.32 (0.04)	−0.31 (0.04)	−0.25 (0.11)	−0.18 (0.23)

* Trend for significance ($p \leq 0.01$)

Abbreviations: L = left; R = right; WAB = Western Aphasia Battery; AQ = aphasia quotient; BNT = the Boston Naming Test

Table 6

Correlations between regional atrophy and neurocognitive and language measures

MRI volume (median [IQR])			
	L hippocampus	**L lateral temporal**	**L inferior parietal**
	0.26 (0.23 – 0.27)	**1.83 (1.65 – 1.96)**	**0.77 (0.69 – 0.84)**
Correlation (ρ value [p value])			
	L hippocampus	**L lateral temporal**	**L inferior parietal**
MOCA	0.11 (0.47)	0.46** (0.002)	0.60** (<0.0001)
FAB	0.18 (0.24)	0.45** (0.002)	0.52** (0.0001)
FBI	0.22 (0.15)	0.08 (0.59)	−0.06 (0.68)
CDR-SB	−0.11 (0.47)	−0.26 (0.09)	−0.38 (0.03)
AVLT trial 1	−0.17 (0.28)	0.01 (0.95)	0.04 (0.79)
AVLT LT % retention	0.24 (0.13)	0.38* (0.01)	0.38* (0.01)
DKEFS sorting	−0.09 (0.57)	0.13 (0.44)	0.26 (0.11)
VOSP cube	0.24 (0.12)	0.42* (0.01)	0.37* (0.01)
WAB AQ	0.19 (0.23)	0.44** (0.003)	0.45** (0.002)
WAB repetition	−0.12 (0.43)	0.26 (0.09)	0.33 (0.03)
Token test	0.13 (0.41)	0.44** (0.003)	0.47** (0.001)
BNT	0.23 (0.13)	0.29 (0.05)	0.26 (0.08)

* Trend for significance ($p \leq 0.01$)

** Statistically significant ($p < 0.004$)

Abbreviations: L = left; R = right; MOCA = the Montreal Cognitive Assessment; FAB = the Frontal Assessment Battery; FBI = the Frontal Behavior Inventory; CDR-SB = Clinical Dementia Rating Sum of Boxes; AVLT = Auditory Verbal Learning Test; MOANS = Mayo Clinic's Older Americans Normative Studies; LT = long term delayed recall; DKEFS = Delis-Kaplan Executive Function System; VOSP = the Visual Object and Space Perception Battery; WAB = Western Aphasia Battery; AQ = aphasia quotient; BNT = the Boston Naming Test