Amyloid deposition in semantic dementia: a positron emission tomography study

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Background: Pittsburgh compound B ([11C]-PIB) identifies amyloid-β (Aβ) deposition *in vivo*. Asymptomatic Aβ deposition has been reported consistently in some healthy older subjects. Of patients with frontotemporal dementia, those who have later onset have a higher potential for Aβ deposition.

Objective: Comparison of Aβ deposition in Alzheimer's disease (AD), healthy older controls, and patients with early- and late-onset semantic dementia (SD), a subtype of frontotemporal dementia.

Methods: Subjects were recruited from tertiary academic care centers specializing in assessment and management of patients with neurodegenerative disease. We used the radiotracer [11C]-PIB in a high-resolution positron emission tomography scanner to evaluate 11 participants with SD (six with onset before age 65 and five with later onset), 9 with probable AD, and 10 controls over age 60. The main outcome measures were frontal, temporal, parietal, and total [11C]-PIB standardized uptake value ratios to establish PIB-positive (PIB+) cutoff.

Results: The five patients with late-onset SD were PIB-negative. Two of six with early-onset SD, seven of nine with AD, and 1 of 10 controls were PIB+. The SD participants who were PIB+ did not have memory or visuospatial deficits that are typical in AD.

Conclusions: Aβ deposition does not seem to be associated with late-onset SD. Future larger studies might confirm whether a significant minority of early-onset SD patients exhibit Aβ deposition. Copyright © 2016 John Wiley & Sons, Ltd.

Introduction

Frontotemporal dementia (FTD) is an umbrella term that includes the clinical diagnoses behavioral variant FTD and primary progressive aphasia. Neuropathologically confirmed frontotemporal lobar dementia (FTLD) is associated with heterogeneous underlying proteinopathies, all of which are distinct from the β-amyloidosis of Alzheimer's disease (AD) (Giacobini and Gold, 2013; Riedl *et al.*, 2014). As pathology-specific treatments such as anti-amyloid or anti-tau medications are developed, patients with FTD and their care providers will benefit from more individualized proteomic therapies (Giacobini and Gold, 2013).

Current clinical criteria for behavioral variant FTD have improved on clinicopathological correlation with sensitivity reported at 0.85 (Rascovsky *et al.*, 2011). Nonetheless, diagnostic dilemmas are common when trying to differentiate atypical presentations of AD from late-onset FTD (Galton *et al.*, 2000). Patients meeting some FTD criteria, but with symptom onset after age 70 years and with memory loss as a significant feature, raise the possibility of AD in the differential diagnosis. However, the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria (McKhann *et al.*, 2011) for AD are inclusive enough to have only 23% specificity among FTD cases (Varma *et al.*, 1999). Furthermore, at least in early case series reports, semantic dementia (SD), a subtype of primary progressive aphasia, has revealed underlying AD pathology, rather than FTLD, in up to 80% of cases (Kertesz *et al.*, 1997; Knibb *et al.*, 2006; Chow *et al.*, 2010).

The benzothiazole radiotracer Pittsburgh compound B ([11C]-PIB) allows *in vivo* assessment of cerebral amyloid-β (Aβ) burden (Wang *et al.*, 2002; Ikonomovic *et al.*, 2008; Leinonen *et al.*, 2008). High [11C]-PIB retention has been shown reliably in AD (Klunk *et al.*, 2004; Price *et al.*, 2005). However, a proportion of older individuals without dementia also shows Aβ deposition *in vivo* and by post-mortem immunostaining (Price and Morris, 1999; Pike *et al.*, 2007; Rowe *et al.*, 2007; Sojkova *et al.*, 2008). In some, this may have no clinical significance, or it may reflect preclinical AD (Price and Morris, 1999; Villemagne *et al.*, 2011): high [11C]-PIB retention in healthy individuals predicts memory decline better than apolipoprotein E4 (APOE E4) allele status (Lim *et al.*, 2012).

Prior reports of Aβ imaging in FTD have shown little or no Aβ in early-onset FTD (Drzezga *et al.*, 2007; Rabinovici *et al.*, 2007; Rowe *et al.*, 2007; Engler *et al.*, 2008; Rabinovici *et al.*, 2008), but because there are reports of Aβ in participants with late-onset FTD (Rabinovici *et al.*, 2007; Engler *et al.*, 2008), it has remained unclear whether these patients have AD pathology manifesting as FTLD syndromes or coincidental age-related Aβ plaques (Rabinovici *et al.*, 2007; Engler *et al.*, 2008). If this were the case, late-onset FTD might be more frequently associated with Aβ pathology than early-onset FTD.

We used [11C]-PIB-positron emission tomography (PET) to test whether Aβ deposition occurs in late-onset FTD (onset after age 65), and if so, whether it is more similar to normal aging or AD. Our participants with FTD (both behavioral variant and primary progressive aphasia) included only those with predominant temporal lobe atrophy, which the Hodges lab has referred to as

SD regardless of right- or left-predominant asymmetry (Garrard and Hodges, 2000; Thompson *et al.*, 2003; Kamminga *et al.*, 2015). The clinical course of FTD is determined more by the location of pathology not by the heterogeneous proteinopathy. Because AD and SD both focus on temporal lobe structures, we felt our yield for [11C]-PIB uptake would be optimized by these sample inclusion criteria. The hypothesis for this study was that patients with late-onset, temporal lobe-predominant FTD would be more likely to show [11C]-PIB uptake than those with early-onset FTD, whether due to the effect of age on β-amyloidosis or due to coincident AD.

Materials and methods

Recruitment

Participants were recruited from March 2009 to April 2013 in the Memory Disorders Clinics at three academic centers in Toronto: the Centre for Addiction and Mental Health (CAMH), University Health Network, and Baycrest. Participants with FTD or AD assented to the study, and written informed consent was obtained from their substitute decision-makers. This study received Research Ethics Board approval at CAMH and at Baycrest.

All participants were at least 60 years old and ambulatory. Although SD most frequently begins before age 60, Aβ deposition occurs mainly among healthy elderly over the age of 60, and we chose to increase our yield on [11C]-PIB scanning among the few participants funded for this study. Participants with SD met the McKhann consensus clinical criteria for FTD (McKhann *et al.*, 2001), which accommodates both behavioral variant FTD and SD subtypes; in addition, participants had to have more temporal than frontal atrophy on diagnostic structural imaging (see the preceding discussion). At the time of their participation in the study, participants with right-sided SD showed more behavioral disturbances than aphasic features. The left-sided SD participants had, as required for the diagnosis of the semantic variant of primary progressive aphasia (Gorno-Tempini *et al.*, 2011), lost word meaning and manifested surface dyslexia among other clinical criteria for SD that are not seen in typical AD.

Participants with AD met Diagnostic and Statistical Manual IV Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000) for Dementia of the Alzheimer Type. Healthy control (HC) participants reported independence for activities of daily living and no cognitive impairment. Exclusion criteria included: DSM-IV-TR criteria for vascular dementia;

delirium or substance-induced persisting dementia; a score of greater than 3 on the depression items of the Neurobehavioral Rating Scale; unstable systemic disease or neurological disorder (e.g., stroke); any positive response on the CAGE questionnaire (Ewing, 1984); or a history of a psychotic or bipolar disorder. In addition, participants were excluded if they had significant renal dysfunction, a contraindication to magnetic resonance imaging (MRI) (e.g., claustrophobia), severe agitation, or were premenopausal women.

Cognitive and behavioral assessment

All participants were assessed using the Mini–Mental State Examination (MMSE) (Folstein *et al.*, 1975), the Clinical Dementia Rating scale modified for FTD (Knopman *et al.*, 2008), the Neurobehavioral Rating Scale validated for the detection of behavioral and psychiatric symptoms of dementia in the context of all dementia aetiologies (Folstein *et al.*, 1975; Ewing, 1984), the Frontal Behavioral Inventory (FBI) (Kertesz *et al.*, 1997), and the Neuropsychiatric Inventory (Cummings *et al.*, 1994).

Apolipoprotein E4 genotype

Participants' APOE E4 status was obtained after recruitment and group allocation by combining genotypes at rs7412 and rs429358. Single nucleotide polymorphisms were genotyped in duplicate by polymerase chain reaction using standard TaqMan Assay-on-Demand genotyping protocols (10 ul reaction volume), and allelic discrimination was performed using the Applied Biosystems (Foster City, CA, USA) ViiA 7 Real-Time polymerase chain reaction system.

Positron emission tomography and magnetic resonance imaging

Positron emission tomography scans were performed with the CAMH high-resolution research tomography (HRRT) (Siemens Medical Imaging, Knoxville, TN), which measures radioactivity in 207 brain slices with a thickness of 1.2 mm each. The intrinsic in-plane resolution of the scanner was approximately 2.8 mm full width at half maximum. Each participant underwent a 10-min transmission scan using a single photon point source of 137Cs for attenuation correction. List mode emission was acquired for approximately 100 min after a bolus injection of [11C]-PIB (mean dose 9.4 ± 0.8 mCi) via antecubital intravenous line (Verhoeff *et al.*, 2004). Data were reconstructed offline

in 22 frames that consisted of five 1-min, ten 2-min, and then seven 5-min frames.

Participants had one MRI scan of the brain without gadolinium for co-registration with the PET image. Fourteen MRI scans were conducted at CAMH in a 3 Tesla GE Discovery MR750 scanner, and the remainder at Toronto General Hospital captured with a 3 Tesla Siemens Magnetom Trio whole-body scanner. For co-registration, a Sagittal T1 BRAVO (FSPGR) image (time repetition = 6.7 s; time echo = 3.0 s; flip angle = 8200 sagittal slices with a 1-mm 3 voxel size; field of view: 24.0 cm; acquisition matrix: 256×256) was acquired.

Calculation of gray matter volume

Magnetic resonance imaging data were analyzed using SPM8 (Wellcome Trust Centre for Neuroimaging) running on MATLAB (version R2010a). Each T1-weighted structural image was preprocessed using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra method following steps suggested by Ashburner (Ashburner, 2010). T1-weighted images were manually reoriented to the Montreal Neurological Institute space with the coordinate of the anterior commissure as close as possible to the origin. The images were classified into gray matter, white matter, and cerebrospinal fluid (CSF) using the 'new segment' routine per Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra. The flow fields and the final template image contributed to create smoothed (8 mm), modulated, spatially normalized, and Jacobian-scaled gray matter images resliced to 1.5 mm isotropic voxel size in Montreal Neurological Institute space. Finally, gray matter volumes for the frontal, temporal, and parietal lobes were obtained using the Automated Anatomical Labeling template (Tzourio-Mazoyer *et al.*, 2002).

[11C]-PIB-specific binding

The MRI images were co-registered to the PET space image using the normalized mutual information algorithm (Studholme *et al.*, 1997) included in SPM2, and accuracy was checked visually. Regions of interest (ROIs) were manually and systematically drawn onto the co-registered T1-weighted MRI using a Wacom tablet (TWC and EEB). Each ROI combined the [11C]-PIB signal from both hemispheres. White matter was excluded. The cerebellum was drawn from the most caudal slice containing cerebellar tissue and the four consecutive rostral slices. The temporal lobe was drawn caudal to rostral until orbitofrontal cortex was

visible. The parietal lobe was also drawn rostral to caudal using lateral ventricles as a landmark. The frontal lobe was drawn anterior to the pre-central gyrus from the slice on which the optic chiasm could be clearly seen, then working toward the vertex and avoiding insular cortex until midway to the vertex, at which point we restarted drawing the frontal lobe from the vertex, working caudally for greater ease of structural identification.

Time activity curves (TACs) from frontal, temporal, parietal, and cerebellar ROIs were extracted from the dynamic [11C]-PIB PET images in native space co-registered to the corresponding MRI image using Analyze software (version 10.0).

Our primary outcome measure to compare [11C]-PIB specific retention between diagnostic groups was standardized uptake value ratio (SUVR), which has been shown to be valid and have good test–retest reliability (Lopresti *et al.*, 2005). SUVRs were calculated first by converting TACs from nCi/cc to standard uptake values (SUV) with the formula: $SUV = [\text{mean radioactivity (nCi/cc)}]/[\text{radiotracer dose (mCi)/body weight (Kg)}]$. Secondly, $SUVR_{TACs}$ were calculated dividing the SUV-normalized TAC from a given ROI by the SUV-normalized TAC from the cerebellum. Thirdly, the final SUVR was calculated as the mean of the $SUVR_{TACs}$ from minutes 40 to 90. The cerebellum was used as reference, because even in patients with suspected pathology, it has low [11C]-PIB specific binding (Klunk *et al.*, 2004; Lopresti *et al.*, 2005).

Our secondary outcome measure was the distribution volume ratio (DVR) for each ROI (Lopresti *et al.*, 2005; Price *et al.*, 2005; Aizenstein *et al.*, 2008). DVRs were derived as implemented in PMOD (version 3.1) software to provide an estimate of radiotracer-specific retention using Logan graphical analysis with the cerebellum as reference.

Cutoff value for [11C]-PIB-positive status

Total neocortical SUVR was estimated for each participant by combining the frontal, temporal, and parietal ROIs. As per Aizenstein *et al.* (2008), the cutoff for [11C]-PIB-positive (PIB+) status was estimated using the sample of HC total neocortical SUVRs. HCs with SUVR outside 1.5 SD from the mean (1.25) were excluded: two HC participants were excluded only from calculations for a cutoff value. The cutoff of 1.40 marked the upper inner fence of the remaining participants. Participants with a total neocortical SUVR of 1.40 or greater were deemed PIB+. A receiver

operating characteristic curve was generated using the total neocortical SUVR to stratify HC and participants with clinical AD (Pike *et al.*, 2007). The total area under the curve was 0.78, $p = 0.041$. The optimal cutoff was 1.42, with a sensitivity of 0.79 and a specificity of 0.90 (Figure 1).

Statistical analyses

Statistical analyses were performed using SPSS version 22.0. Each scalar clinical variable, lobar volume, and the SUVR data were tested for a statistical main effect of group using a one-way analysis of variance. Where the group effect was significant at alpha = 0.05, individual independent-samples *t*-tests were performed. We performed Levene's test for equality of variances and assumed equal variances only when this test did not reach significance of 0.05. No correction for multiple comparisons is reflected in the reported *p*-values. To assess significance of correlations, two-tailed Pearson r tests were performed. To assess significance of the categorical PIB+ classification, a Pearson chi-square test was performed.
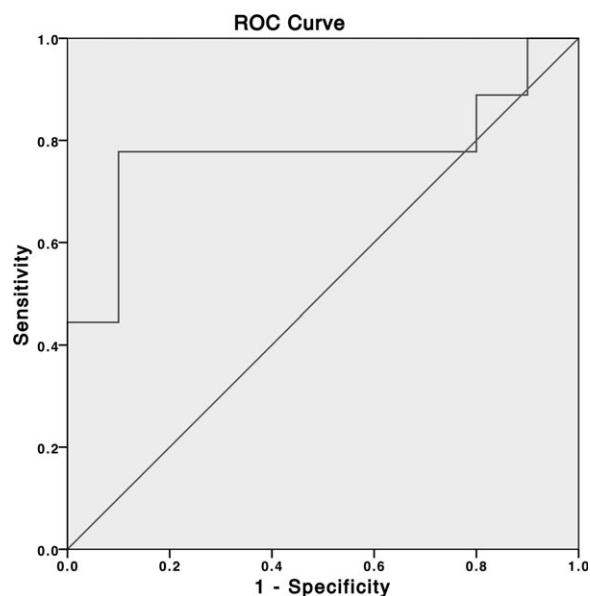
Figure 1 Receiver operating characteristic curve to segregate healthy controls from participants with Alzheimer's disease. A diagonal reference line is present. The test variable is the total neocortical standardized uptake value ratio (a combination of frontal, temporal, and parietal lobes). The total area under the curve was 0.778, $p = 0.041$. The optimal cutoff for [11C]-PIB+ status was 1.42, with a sensitivity of 0.788, and a specificity of 0.9. ROC, receiver operating characteristic.

Table 1 Demographic and clinical characteristics of study participants

	HC	SD			AD	p-value
	$n=10$	EO $n=6$	LO $n=5$	Pooled $n=11$	$n=9$	
Male sex, n, (%)	7 (70)	4 (67)	4 (80)	8 (73)	5 (56)	Among three groups $X^2 = 0.732$, d.f. = 2, $p=0.694$[c]
Age years, mean (standard deviation)	72.2 (8.1)	63.2 (2.3)	74.0 (6.0)	68.1 (7.0)	79.2 (7.3)	Among four groups: 0.002[a] AD versus HC: 0.065[b] EO SD versus HC: 0.007[b] LO SD versus HC: 0.670[b] EO SD versus LO SD: 0.013[b] AD versus EO SD: <0.001[b] AD versus LO SD: 0.201[b]
Education years, mean (standard deviation)	14.5 (2.4)	15.3 (2.7)	15.6 (5.7)	15.5 (4.1)	13.9 (2.6)	Between four groups: 0.752[a]
APOE4 allele status N (%)	1 (10) single	1 (17) single	0 (0)	1 (9) single	2 (22) double 2 (22) single	Among three groups (presence of at least one APOE4 allele): $X^2 = 7.034$, d.f. = 2, $p=0.030$[c]
Neuropsychiatric inventory (NPI)	1.8 (4.1)	36.7 (27.6)	25.0 (14.2)	31.4 (22.3)	18.6 (10.7)	Among four groups: 0.001[a] AD versus HC: 0.001[b] EO SD versus HC: 0.027[b] LO SD versus HC: <0.020[b] AD versus EO SD: 0.176[b] AD versus LO SD: 0.353[b] EO SD versus LO SD: 0.416[b]
Mini-mental Status Exam (MMSE)	29.3 (0.7)	23.8 (7.2) ($n=5$)	12.7 (4.5) ($n=3$)	19.6 (8.3) ($n=8$)	19.2 (6.9) ($n=8$)	Among four groups: <0.001[a] AD versus HC: 0.004[b] EO SD versus HC: 0.161[b] LO SD versus HC: <0.023[b] AD versus EO SD: 0.277[b] AD versus LO SD: 0.165[b] EO SD versus LO SD: 0.055[b]
Frontal Behavioral Inventory (FBI)	0.4 (1.0) ($n=9$)	32.2 (7.6)	28.4 (14.0)	30.5 (10.5)	17.1 (6.3)	Among four groups: <0.001[a] AD versus HC: <0.001[b] EO SD versus HC: <0.001[b] LO SD versus HC: 0.011[b] AD versus EO SD: 0.001[b] AD versus LO SD: 0.148[b] EO SD versus LO SD: 0.609[b]
Clinical Dementia Rating Scale (CDR) modified for FTD	0.15 (0.24)	2.00 (0.82) ($n=4$)	2.00 (0.71)	2.00 (0.71) ($n=9$)	2.11 (0.33)	Among four groups: <0.001[a] AD versus HC: <0.001[b] EO SD versus HC: <0.001[b] LO SD versus HC: <0.001[b] AD versus EO SD: 0.725[b] AD versus LO SD: 0.692[b]

AD, Alzheimer's disease; EO, early-onset; HC, healthy controls; LO, late-onset; SD, semantic dementia.
[a] One way analysis of variance, comparing HC, EOSD, LOSD, and AD.
[b] Independent samples *t*-test, two-tailed, equal variance assumed when Levene's test fails to reject null hypothesis
[c] Pearson chi-square.

Results

Sample characterization

Participant demographics, clinical characteristics, diagnostic group, and APOE genotype summary are presented in Table 1. One participant with AD, one with early-onset SD, and two with late-onset SD were unable to complete the MMSE, but even when excluding these participants from the analysis, mean MMSE score was lower in each dementia group than in the controls with no difference between dementia groups. Total scores on the Neuropsychiatric Inventory and Clinical Dementia Rating modified for FTLD were more severe in each of the dementia groups than HC, again with no difference between the dementia groups. The mean FBI score for the early-onset SD group was significantly higher than that of the AD group ($t = 4.192$, d.f. = 13, $p = 0.001$). There was no significant difference in FBI scores between early-onset and late-onset SD.

[11C]-PIB uptake

The PIB+ cutoff determined by the 1.5 standard deviations upper limit of SUVR in HC and receiver operating characteristic analysis produced similar thresholds of 1.40 and 1.42, respectively, and identical classification. Among the 10 HC, one 78-year-old man was PIB+; as compared with seven of nine participants with AD,

two of six with early-onset SD, and none with late-onset SD (Table 1 and Figure 2). Data for individual participants are presented in the Supplement. The overall group effect was seen in the frontal, temporal, and parietal ROIs and in the pooled total neocortical SUVR (Table 2). Total neocortical SUVR did not correlate with age, MMSE, or lobar volume.

The total neocortical SUVR was 0.40 higher in the AD group than in HC (equal variances not assumed, $t = 2.399$, d.f. = 10.356, $p = 0.037$). The AD regional SUVR was higher than for HC in frontal (equal variances not assumed, $t = 2.367$, d.f. = 10.427, $p = 0.039$) and parietal (equal variances not assumed, $t = 2.803$, d.f. = 10.125, $p = 0.018$) ROIs. Each of the three regional SUVRs was significantly higher in AD than SD groups.

The late-onset SD group showed [11C]-PIB retention similar to the HC and the early-onset SD groups. The temporal SUVR was lower in SD than in HC ($t = 2.503$, d.f. = 19, $p = 0.022$). With PIB+ participants removed from the analysis, compared with HCs, the SD group had lower frontal ($t = 2.26$, d.f. = 16, $p = 0.038$) and temporal SUVRs ($t = 2.542$, d.f. = 16, $p = 0.022$).

One-way analysis of variance revealed no significant group effect of the reference signal, cerebellar SUV.

Cortical gray matter volume

The next analysis sought an effect of regional atrophy on the SUVRs earlier. Consistent with the clinical diagnosis of SD, this group had 15.9% ($t = 2.804$, d.f. = 19,
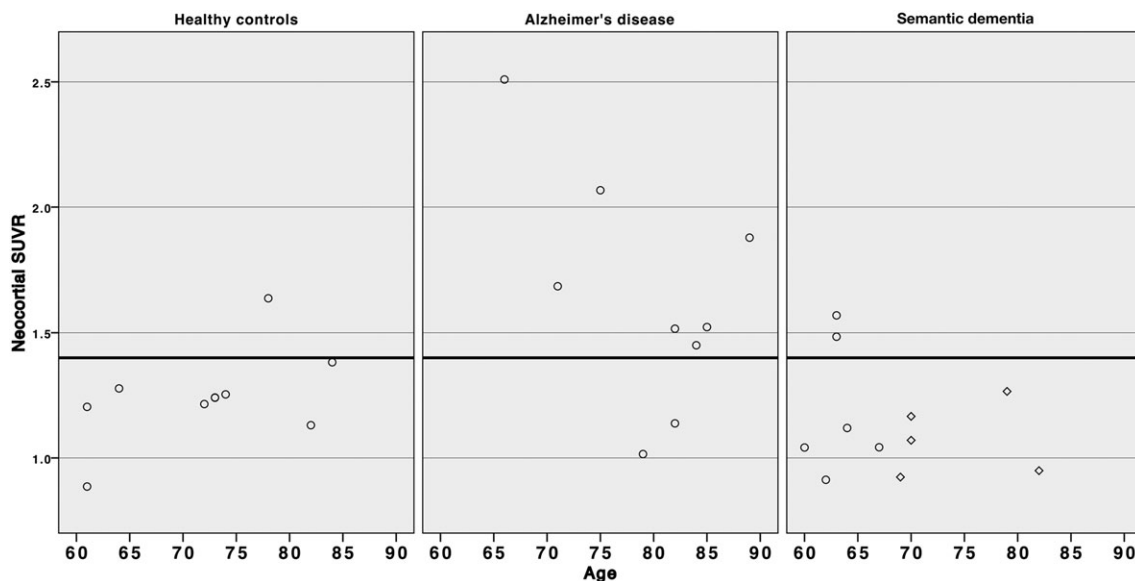
Figure 2 Participants plotted based on age and neocortical standardized uptake value ratio (SUVR). Diamond markers represent late-onset semantic dementia and circle markers represent all other participants. Markers that represent PIB-positive participants are above the cutoff of 1.4 indicated by the thick horizontal line.

Table 2 [11C]-PIB uptake results

	HC	SD			AD	
	n = 10	EO *n* = 6	LO *n* = 5	Pooled *n* = 11	*n* = 9	*p*-value
Frontal lobe SUVR90	1.27 (0.20)	1.23 (0.30)	1.11 (0.15)	1.18 (0.24)	1.68 (0.49)	Among four groups: 0.012[a] AD versus HC: 0.025[b] EO SD versus HC: 0.764[b] LO SD versus HC: 0.144[b] EO SD versus LO SD: 0.430[b] SD (pooled) versus HC: 0.349[b] SD (pooled) versus AD: 0.007[b]
Temporal lobe SUVR90	1.05 (0.18)	0.86 (0.18)	0.75 (0.30)	0.81 (0.24)	1.23 (0.34)	Among four groups: 0.010[a] AD versus HC: 0.143[b] EO SD versus HC: 0.074[b] LO SD versus HC: 0.034[b] EO SD versus LO SD: 0.460[b] SD (pooled) versus HC: 0.022[b] SD (pooled) versus AD: 0.004[b]
Parietal lobe SUVR90	1.21 (0.17)	1.36 (0.46)	1.11 (0.16)	1.24 (0.36)	1.65 (0.44)	Among four groups: 0.023[a] AD versus HC: 0.010[b] EO SD versus HC: 0.380[b] LO SD versus HC: 0.267[b] EO SD versus LO SD: 0.281[b] SD (pooled) versus HC: 0.814[b] SD (pooled) versus AD: 0.036[b]
Frontal, temporal, and parietal lobe (total neocortical) SUVR90	1.25 (0.19)	1.20 (0.27)	1.08 (0.14)	1.14 (0.22)	1.64 (0.46)	Among four groups: 0.008[a] AD versus HC: 0.037[b] EO SD versus HC: 0.655[b] LO SD versus HC: 0.078[b] EO SD versus LO SD: 0.393[b] SD (pooled) versus HC: 0.249[b] SD (pooled) versus AD: 0.005[b]
PIB+	1 (10%)	2 (33%)	0 (0%)	2 (18%)	7 (78%)	Among three groups: X^2 = 11.586, d.f. = 2, *p* = 0.003[c] Between EO SD and LO SD: X^2 = 2.037, d.f. = 1, *p* = 0.154[c]

AD, Alzheimer's disease; EO, early-onset; HC, healthy controls; LO, late-onset; SD, semantic dementia; SUVR, standardized uptake value ratio.
[a]One way analysis of variance, comparing HC, EOSD, LOSD, and AD.
[b]Independent samples *t*-test, two-tailed, equal variances assumed.
[c]Pearson chi-square.

Table 3 Gray matter volumes (ml) compared using independent samples *t*-test, two-tailed, equal variances assumed

		Volume in ml (standard deviation)			Relative volume		
Lobe	Hemisphere	HC	SD	AD	AD versus HC	SD versus HC	AD versus SD
Frontal	R	53.30 (7.17)	46.53 (10.25)	44.15 (9.62)	−17.2%*	−12.7%	−5.1%
	L	58.70 (8.09)	50.24 (11.19)	46.84 (9.13)	−20.2%**	−14.4%	−6.8%
Parietal	R	23.95 (3.32)	22.52 (4.47)	19.97 (3.90)	−16.6%*	−6.0%	−11.3%
	L	28.17 (4.16)	26.41 (5.68)	23.38 (4.64)	−17.0%*	−6.3%	−11.5%
Temporal	R	61.4 (7.65)	51.61 (8.28)	50.51 (10.79)	−17.7%*	−15.9%*	−2.1%
	L	58.33 (6.04)	50.04 (6.59)	49.16 (7.93)	−15.7*	−14.2%**	−1.8%

AD, Alzheimer's disease; HC, healthy controls; SD, semantic dementia.
*$p < .05$.
**$p < .01$.

p = 0.011) less gray matter volume in the right temporal lobes and 14.2% (*t* = 2.992, d.f. = 19, *p* = 0.007) less in the left in comparison with HC (Table 3).

Participants with AD showed statistically significant atrophy in all ROIs, but AD lobar volumes did not differ from those participants with SD.

If low [11C]-PIB retention were due to atrophic changes, temporal lobe volume would be expected to correlate with temporal lobe SUVR. However, this was not the case among PIB- SD participants ($r = 0.314$, $p = 0.410$) or among all participants ($r = 0.187$, $p = 0.322$). Temporal SUVR remained significantly lower in [11C]-PIB-negative (PIB-) SD than in [11C]-PIB- HC, when temporal gray matter volume was included as a covariate ($f = 4.023$, d.f. = 2, $p = 0.040$).

Group comparisons of distribution volume ratios

Compared with controls, participants with AD had significantly higher mean DVR in the frontal lobe (equal variances not assumed, $t = 3.693$, d.f. = 10.342, $p = 0.004$) and parietal lobe (equal variances not assumed, $t = 2.943$, d.f. = 10.091, $p = 0.015$), but not in the temporal lobe.

The mean DVRs in each lobe were not different in participants with early-onset SD compared with controls, but in late-onset SD, the mean frontal ($t = 2.402$, d.f. = 13, $p = 0.032$) and temporal ($t = 3.102$, d.f. = 13, $p = 0.008$) lobe DVRs were lower than those of the controls.

When comparing the early-onset with the late-onset SD, no significant difference in mean DVR was found.

The mean temporal lobe DVR was lower in the group of all SD participants compared with controls ($t = 2.686$, d.f. = 19, $p = 0.015$).

Discussion

[11C]-PIB uptake in semantic dementia

Contrary to our hypothesis, participants with late-onset SD showed similar [11C]-PIB retention to those with early-onset SD and HC, and none of the participants with late-onset SD had high [11C]-PIB retention. However, two of six participants with early-onset SD had high [11C]-PIB retention, even though they did not meet criteria for possible AD (McKhann et al., 2011). These two PIB+ participants had a similar pattern of [11C]-PIB uptake group as the PIB+ AD participants: highest uptake in the frontal and parietal lobes, not the temporal lobes. The proportion of early-onset SD participants that were PIB+ is within the range of that seen in the healthy older population (Price and Morris, 1999; Pike et al., 2007; Rowe et al., 2007; Sojkova et al., 2008). Further imaging studies are needed to reveal whether early-onset FTD cases do harbor significant amyloid deposition. However, co-occurrence of FTLD and AD neuropathology has

been reported infrequently (Barker et al., 2002). In one neuropathological study, FTLD cases had no more Aβ than controls (Arnold et al., 2000).

Without neuropathological diagnostic confirmation, we have not validated our [11C]-PIB SUVR critical value. We found 2 of 11 SD participants to be PIB + similar to AD, and neither participant was an APOE E4 carrier. The diagnostic utility of a [11C]-PIB uptake ratio threshold in a clinical setting would require a long-term prospective study with pathologic confirmation (Drzezga et al., 2007).

Lower temporal and frontal lobe standardized uptake value ratio in semantic dementia

Although no significant group difference in mean [11C]-PIB retention between early-onset and late-onset SD was found, we unexpectedly found lower temporal lobe SUVR in the SD group than the HC. When the PIB+ participants were removed from both groups, the mean temporal and frontal lobe SUVRs were still lower in the SD group. This has not been explicitly reported and is of unknown significance.

Rabinovici et al. (2008) compared [11C]-PIB in SD and HCs. They reported the means and standard deviations of [11C]-PIB DVRs for each of the ROIs analyzed, for both PIB+ and PIB− participants with SD and HC. Performing t-tests with their data, the PIB− SD group had significantly lower DVR than HC in the frontal lobes (left $p < 0.001$, right $p < 0.01$), anterior temporal lobes ($p < 0.001$), and overall (left $p < 0.001$, right $p < 0.01$), but not in the temporoparietal ROI. This is entirely consistent with our data.

There are several possible explanations for the lower Aβ deposition in our participants with SD than in HC. First, the SD participants had more atrophy in the temporal and frontal lobes than HC, and lower [11C]-PIB retention could be accounted for by partial volume effect. Partial volume correction increases SUVR more in AD participants than in HC when employing a clinical PET camera with lower spatial resolution than our HRRT (Villemagne et al., 2011). By contrast, using this HRRT, we have reported similar uptake results regardless of whether or not partial volume correction is performed in HC across the life span (Uchida et al., 2011). Another possibility is that the pathophysiology of SD, whether tauopathy or TDP-43-opathy, may be somehow protective against Aβ deposition, although no difference in Aβ was seen between FTD and HC in a small neuropathological study that was not restricted to SD (Arnold et al.,

2000). There is evidence for altered Aβ metabolism in FTD. FTLD was associated with lower CSF Aβ40 levels compared with AD or HC (Bibl *et al.*, 2012). CSF levels of Aβ40 have also been shown to correlate with frontal atrophy in FTD (Bibl *et al.*, 2012). These alterations have been replicated, and CSF Aβ has been proposed as a potential diagnostic biomarker for AD, FTD, and dementia with Lewy bodies (Bibl *et al.*, 2012).

Limitations

The dementia group sample sizes were small and limit the statistical power of the multiple comparisons. The lack of neuropathologically confirmed diagnoses is also a limitation. While [11C]-PIB is a good surrogate for amyloid pathology on autopsy (Wang *et al.*, 2002; Ikonomovic *et al.*, 2008; Leinonen *et al.*, 2008), we do not know whether the participants have other underlying pathologies. Identifying the pathology or pathologies in the PIB+ SD participants and the PIB− AD patients would be particularly informative.

Conflict of interest

E. E. Brown is married to an employee of Teva Canada Limited.

A. Graff-Guerrero receives grant support from NIH, CIHR, Ontario Mental Health Foundation, CONACyT, ICyTDF, Ontario AFP Innovation Fund, NARSAD, and Janssen. He has served as consultant for Abbott Laboratories, Gedeon Richter Plc, and Eli Lilly.

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> ### Key points
> - This study compared amyloid-β deposition in early-onset semantic dementia (SD), late-onset SD, Alzheimer's dementia, and HCs.
> - Amyloid-β deposition does not appear to be associated with late-onset SD.

Ethics statement

This study received Research Ethics Board approval at Baycrest Health Sciences and the CAMH.

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Author contributions

E. E. Brown participated in the analysis and interpretation of data, and helped to draft, revise, and finalize the manuscript.

A. Graff-Guerrero participated in the conception and design of the study; acquisition, analysis and interpretation of data; draft of manuscript, critical revision of the manuscript for important intellectual content; statistical analysis, obtaining funding, technical support, and can take responsibility for the whole content.

S. Houle participated in the conception and design of the study, obtaining funding as well as administrative, technical, or material support: and study supervision. He also participated in the analysis and interpretation of data as well as critical revision of the manuscript for important intellectual content.

R. Mizrahi participated in the acquisition of data, and helped to draft, revise, and finalize the manuscript.

A. Wilson participated in the conception and design of the study, obtaining funding as well as administrative, technical, or material support: and study supervision. He also participated in the analysis and interpretation of data as well as critical revision of the manuscript for important intellectual content.

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D. Felsky participated in the design of the study, in the acquisition of data, and helped to draft, revise, and finalize the manuscript.

A. N. Voineskos participated in the design of the study, in the acquisition of data, and helped to draft, revise, and finalize the manuscript.

D. F. Tang-Wai participated in the acquisition of data, and helped to draft, revise, and finalize the manuscript.

N. P. L. G. Verhoeff participated in the acquisition of data, and helped to draft, revise, and finalize the manuscript.

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Z. Ismail participated in obtaining funding, and manuscript revision, and finalization.

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