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Longitudinal beta-amyloid PET in atypical Alzheimer's disease and frontotemporal lobar degeneration

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Abstract

Background: Rates of beta-amyloid (A β) accumulation have been characterized across the cognitively normal to typical Alzheimer's dementia spectrum, but little is known about A β accumulation in atypical Alzheimer's disease (AD) and other neurodegenerative diseases, such as frontotemporal lobar degeneration (FTLD). We aimed to characterize longitudinal A β accumulation, and determine the influence of age, apolipoprotein E genotype, disease duration, and sex in atypical AD and FTLD.

Methods: 322 patients (138 atypical AD, 184 FTLD) underwent Pittsburgh compound B PET scanning, with 73 having serial PiB-PET scans (42 atypical AD, 31 FTLD). Global A β standard uptake value ratios were calculated for every scan. Mixed effects models were used to assess the effect of age, APOE genotype, disease duration, and sex on baseline and change measures of A β .

Results: Atypical AD showed higher baseline A β than FTLD. Rate of A β accumulation was not associated with baseline A β in either group. Older age was associated with greater baseline A β and faster rates of accumulation in FTLD. In patients under age 70, atypical AD showed faster rates of accumulation than FTLD. APOE ϵ 4 genotype was associated with greater baseline A β in FTLD but did not influence rates of accumulation. Rates of A β accumulation were faster in FTLD patients with time from onset-to-PET $\geq$ 4 years. Female sex was associated with faster rates of accumulation in atypical AD.

Conclusion: Accumulation of A β is observed in atypical AD and FTLN, although different demographic factors influence accumulation in these diseases providing insight into different biological mechanisms of A β deposition.

Keywords

frontotemporal lobar degeneration; Alzheimer's disease; amyloid plaques; positron emission tomography

INTRODUCTION

Deposition of the protein beta-amyloid (A β) is one of the hallmark pathological features defining Alzheimer's disease (AD). Beta-amyloid can be detected during life using positron emission tomography (PET) ligands which provides us with the opportunity to make a biomarker-based diagnosis of AD early in the disease course and to assess accumulation of A β over time in order to model disease progression. Most of what we have learned about A β accumulation in vivo has come from longitudinal studies assessing clinically normal individuals and patients with mild cognitive impairment and typical Alzheimer's dementia. Progressive A β accumulation has been observed in Alzheimer's dementia, mild cognitive impairment and also in clinically normal individuals[1–8], with A β accumulation in normal cohorts greater in people with higher A β burden at baseline[5, 9]. Some studies have also suggested that rate of A β accumulation is greater in apolipoprotein E (APOE) e4 carriers[2, 4–7, 10].

While much has been learnt about A β in typical Alzheimer's dementia, much less is known about A β in atypical clinical presentations of AD, or in other neurodegenerative diseases such as frontotemporal lobar degeneration (FTLD) that can overlap clinically with atypical AD. Two of the most common atypical clinical variants of AD are posterior cortical atrophy[11, 12] and logopenic aphasia[13]; these clinical syndromes are highly associated with underlying AD pathology[14, 15]. Frontotemporal lobar degeneration is the second most common cause of dementia in people under age 65 and is an umbrella term for a number of different pathologies that target the frontal and temporal lobes; these pathologies include primary tauopathies, TDP-43 proteinopathies and fused in sarcoma proteinopathies[16]. Clinical syndromes that are highly associated with FTLD pathology include semantic dementia[17], non-fluent/agrammatic primary progressive aphasia[13], primary progressive apraxia of speech[18] and progressive supranuclear palsy[19]. Although FTLD is typically the underlying pathology in these cases, we and others have shown that A β deposition is still observed on PET scanning during life in FTLD cases[20–23], and A β deposition at autopsy is observed in 37%[24]. However, the rate that A β accumulates over time in atypical AD and FTLD is unclear and it is unknown whether demographic features, such as age, sex, disease duration or APOE genotype play any role in determining rate of A β accumulation. Understanding A β accumulation in these patients will be crucial to help interpret A β -PET findings and in predicting which patients may show the greatest rates of A β accumulation, and hence, potentially, the fastest progression of underlying AD pathology.

The aim of this study was to assess rates of A β accumulation and determine how demographic features influence both cross-sectional and longitudinal A β PET measures in atypical AD and FTLN

METHODS

Patients

A total of 322 patients with either an atypical AD or FTLN clinical diagnosis underwent at least one Pittsburgh Compound B (PiB) PET scan between 7/7/2010 and 4/11/2019 as part of a number of NIH-funded grants led by JLW and KAJ (R01-AG50603, R01-DC12519, R01-DC010367, R01-NS89757, R21-NS94684 and R01-DC14942). All patients were recruited from the Department of Neurology, Mayo Clinic Rochester, MN. The 322 patients consisted of 138 with atypical AD and 184 with FTLN, and of these 322 patients, 73 had undergone at least two serial PiB-PET scans (42 atypical AD and 31 FTLN) (Figure 1). The atypical AD cohort consisted of patients that showed evidence for A β deposition on PET and met clinical criteria for posterior cortical atrophy[11] or logopenic progressive aphasia[13] (Figure 1). The FTLN cohort consisted of patients with primary progressive apraxia of speech[18], non-fluent/agrammatic primary progressive aphasia[13], semantic dementia[25], progressive supranuclear palsy[19], and patients with primary progressive aphasia[26] that could not be classified into one of the three variants[13] but were strongly suspected to have FTLN pathology (Figure 1). We also included three patients in the FTLN group that had a clinical diagnosis of logopenic aphasia but were A β - and were found to carry progranulin gene mutations, as we have previously described[27].

All patients underwent a standardized neurological evaluation by a behavioral neurologist (KAJ, JGR, HB) which included testing for cognitive impairment using the Montreal Cognitive Assessment Battery (MoCA)[28], functional severity using the Clinical Dementia Rating-FTLN Scale[29], parkinsonism severity using the Movement Disorder Sponsored revision of the Unified Parkinson's Disease Rating Scale part III (MDS-UPDRS III)[30], and ideomotor apraxia severity using the Western Aphasia Battery-Revised limb apraxia scale[31]. The FTLN patients also all underwent a detailed speech and language assessment by a speech-language pathologist (JRD, HMC, RLU, EAS), as previously described in detail[18], and diagnosis was rendered by consensus of at least two of the speech/language pathologists. Apolipoprotein E genotyping was performed for 301 of the 322 patients (69 of the 73 patients with longitudinal A β PET).

This study was approved by the Mayo IRB and all patients consented to participate in the study.

Neuroimaging analysis

All PET scans were acquired with a PET/CT scanner (GE Healthcare) while operating in 3D mode. Patients were injected with PiB of approximately 628 MBq (range, 385–723 MBq) and after a 40-to-60-minute uptake period a 20-minute PiB scan was obtained. Emission data was reconstructed into a 256 $\times$ 256 matrix with a 30-cm FOV. All patients also underwent a 3T volumetric head MRI within two days of the PiB-PET scan, which included a 3D

magnetization prepared rapid acquisition gradient echo sequence (MPRAGE). All MPRAGE scans underwent corrections for intensity inhomogeneity[32] and gradient unwarping[33] before analysis.

The PiB-PET scans were registered to the corresponding MPRAGE scan using a 6 degrees-of-freedom registration in SPM12. The Mayo Clinic Adult Lifespan Template (MCALT) (<https://www.nitrc.org/projects/mcalt/>) was then transformed into the native space of each MPRAGE using ANTs software[34]. Median A β uptake was calculated for the following regions-of-interest defined using MCALT: inferior parietal, superior parietal, supramarginal gyrus, angular gyrus, cingulate [anterior, mid, posterior and retrosplenial], precuneus, superior frontal, middle frontal, orbitofrontal, inferior frontal [operculum+triangularis], medial frontal, fusiform, lateral temporal [inferior, middle and superior temporal gyri + Heschl], and temporal pole. Uptake was calculated from the grey matter in each region and divided by uptake in the cerebellar crus grey matter to calculate standard uptake value ratios (SUVRs). A global A β SUVR was calculated as the weighted average from the regions-of-interest. A β positivity was defined as a global A β SUVR>1.48. For patients with serial PiB-PET, all global PiB SUVRs were calculated for each time-point separately without reference to the other time-points.

Statistical analysis

Participant characteristics and clinical variables were compared between atypical AD and FTLN groups using Wilcoxon rank sum tests or Fisher's exact tests as appropriate. $P < 0.05$ was considered statistically significant. Within-subject regression models were used to calculate rates of change in global A β SUVR (expressed as SUVR points change per year). We also used log SUVR values to estimate change on an annual percentage scale. We used cut-offs to determine whether a patient is increasing (>2% per year) or declining (<-2% per year) over time. The 2% cut-off is based on a previous publication that reported within-subject measurement error of 2-4%[35].

We used longitudinal linear mixed effects models to separately evaluate the effects of age, APOE ϵ 4, disease duration, and sex on rate of A β change in both diagnosis groups. Age at first A β PET and disease duration were classified into age ≤ 70 , or >70 years old, disease duration ≤ 4 , or > 4 years. The time variable for the models was defined as years from first A β PET. We fit longitudinal models including data from all individuals with one or more A β PET, including all serial A β PET available in each patient (249 with only one PiB and 73 with serial PiB [59 with two A β PET, 12 with three A β PET and two with four A β PET], total n=322 patients). A longitudinal linear mixed effects model can be considered as simultaneously estimating both cross-sectional parameters (i.e., mean A β within a group) and longitudinal, or within-subject change, parameters (i.e., annual change in A β within a group)[32]. Individuals with one A β PET contributed information to the cross-sectional parameters whereas individuals with multiple A β PETs contributed to both cross-sectional and longitudinal parameters.

Estimated A β rates of accumulation for different groups were obtained via interactions in the linear mixed effects models. Each model included all subjects and a three-way interaction between the predictor of interest, diagnosis group (atypical AD vs. FTLN), and

time. This resulted in a separate A β rate estimate for both levels of a covariate within each diagnosis group and allowed us to compare rates for different levels of a covariate within a diagnosis or to compare diagnosis group rates within a level of a covariate. For purposes of comparison, we also fit linear mixed effects models but with the log of A β SUVRs as the response, so that estimated annual change can be interpreted on an annual percentage scale. All of our linear mixed effects models included subject-specific random intercepts. We included continuous age at A β PET as an adjustment variable in all models except the ones in which age group was analyzed.

We also performed correlation analysis between baseline A β SUVRs and subject specific slopes of A β SUVRs stratified by diagnosis within subjects with serial A β -PET scans. Correlation coefficients were compared using Fisher's Z transformation which transforms correlation coefficients (r) into z-scores. The significance of the difference between two correlation coefficients was assessed through the observed Z test statistic.

Analyses were performed with R statistical software (version 3.4.4; R Foundation for Statistical Computing, Vienna, Austria) and models were fit with the lmerTest package (version 3.0.1), which extends R's generalized linear mixed model package "lme4" with p-values for fixed effects.

RESULTS

The atypical AD and FTLN groups did not differ for sex, education and disease duration (Table 1). Atypical AD was younger at onset and scan than FTLN in the cross-sectional cohort, but age did not differ across groups in the longitudinal cohort. Atypical AD had a higher proportion of APOE e4 carriers, and performed worse on the MoCA and CDR-FTLN than the FTLN group. Conversely, FTLN performed worse on the MDS-UPDRS III than atypical AD.

Global A β SUVR was higher in atypical AD compared to FTLN (Table 1). Approximately 50% of both cohorts showed stable A β over time, with 43% of atypical AD and 35% of FTLN showing A β accumulation over time of greater than 2% per year. Very few patients showed declining A β over time. There was no significant difference in rate of A β accumulation between groups, either when expressed as annualized SUVR change or annualized percentage change, although rates were slightly higher in atypical AD. Rate of A β accumulation was not associated with baseline A β SUVR in atypical AD (rank correlation [rho] = -0.05, p=0.77), FTLN (rho=-0.27, p=0.15), or in the cohort as a whole (rho=0.21, p=0.08) (Figure 2).

The results of the mixed models showing the association of demographic factors to baseline A β SUVR are shown in Table 2 and Figure 3. The results showing associations to rate of A β accumulation are shown in Table 3 and Figure 3. When the cohorts were dichotomized by age, older age (>70 years) was associated with higher baseline A β SUVR and faster rates of A β accumulation in FTLN (Figure 4). The effect of age was significantly different in atypical AD compared to FTLN. The two atypical AD age groups had more comparable baseline SUVRs but, if anything, the younger atypical AD group had faster accumulation.

Rates of accumulation in the younger atypical AD group were significantly greater than in the younger FTLT group.

All of the following results were corrected for age. APOE e4 carriers had greater baseline A β SUVR than non-carriers in FTLT, but not in atypical AD. APOE genotype did not influence rate of A β accumulation in either group. Disease duration was associated with baseline A β SUVR, with greater A β SUVR in patients with disease duration >4 years, but not with rate of A β accumulation, in atypical AD. However, in FTLT, faster rates were observed in patients with disease duration <4 years compared to patients with disease duration >4 years. The effect of disease duration on rate of A β accumulation was significantly different in atypical AD compared to FTLT. Sex was not associated with baseline A β SUVR in either group, although women showed faster rates of A β accumulation compared to males in atypical AD.

DISCUSSION

Despite the fact that atypical AD and FTLT showed very different baseline levels of A β SUVR, rates of A β accumulation were similar in the two cohorts overall. However, demographic factors had different relationships to A β burden and rate of accumulation in the two diseases, and differences between atypical AD and FTLT emerged in rates of A β accumulation when stratifying by age and disease duration.

As would be expected, and by design, baseline A β SUVR was higher in atypical AD than in FTLT, reflecting the fact that the atypical AD patients all had biomarker evidence for AD. However, we observed more similar results across the two groups regarding rate of A β accumulation. There was a tendency for atypical AD to show higher rates of accumulation than FTLT, although a large degree of variability was observed in both cohorts and the rate measures were not significantly different overall. In fact, a large proportion of patients in both groups showed stable A β SUVR over time. We did not find any relationship between rate of A β accumulation and baseline A β SUVR in either group or across the entire cohort, suggesting that patients' A β SUVR will not help to predict the rate that they will subsequently accumulate A β over time. Studies assessing the normal-to-typical Alzheimer's dementia spectrum have found that rate of A β accumulation increases with baseline A β SUVR up until an SUVR of approximately 2.0 and then starts to plateau as rates decrease again[4, 6]. Our FTLT cohort resembles the cognitively normal patients in these models, showing low A β SUVR and low rate of change. Our atypical AD group nearly all had baseline A β SUVR over 2.0, and hence A β may already be saturated and rates may have plateaued in this cohort. We did, however, have a couple of patients with very high A β SUVR up to 3.0 that were still showing high rates of accumulation.

A number of demographic features influenced baseline A β SUVR and rate of A β accumulation in our analysis, although we typically observed different effects in atypical AD and FTLT. One striking difference was that age was only related to A β in FTLT and not in atypical AD. Within the FTLT cohort, older age was associated with greater baseline A β SUVR, as we and others have noted[20–22], but also greater rates of A β accumulation. Hence, A β deposition is strongly age-related in FTLT, concurring with findings from an

autopsy study of A β in FTLN[24]. This suggests that the development and progression of Alzheimer's continuum pathology is more common in older patients. Of four FTLN patients that showed A β uptake on PiB-PET in one study, 100% showed A β deposition on autopsy and three had sufficient tau pathology to meet pathological criteria for AD[24]. Similarly, age has been shown to be related to A β SUVR[36] and rate of A β accumulation[5] in clinically normal people. The fact that age was not associated with baseline or accumulation of A β in atypical AD concurs with previous cross-sectional studies in atypical AD syndromes [22] and longitudinal studies in typical Alzheimer's dementia [2]. In fact, although not significant, the rate of A β accumulation actually appears a little higher in younger versus older atypical AD patients, and in patients under age 70 atypical AD had significantly faster rates of A β accumulation than FTLN. This difference between diagnostic groups was hidden when all ages were merged in the main analysis. Interestingly, we have also recently shown that younger atypical AD patients have faster rates of accumulation of tau measured by [18 F]flortaucipir PET[37], suggesting a more aggressive disease course in young atypical AD.

The influence of the APOE e4 genotype was also only observed in FTLN, with greater baseline A β burden observed in APOE e4 carriers. This finding that APOE e4 increases the risk of A β deposition has previously been noted in other autopsy and cross-sectional studies that have assessed FTLN phenotypes [20, 22, 38]. We did not, however, find any evidence that APOE e4 influences rate of A β accumulation in FTLN. Hence, APOE e4 appears to increase the risk of developing A β but does not play a role in the rate that the A β spreads through the brain. This concurs with previous longitudinal findings from one study in clinically normal individuals [5], although others did find a relationship between APOE e4 genotype and faster rates of A β accumulation in clinically normal individuals [10, 36]. Of note, the FTLN APOE e4 carriers still had a very low A β SUVR and atypical AD showed higher baseline A β than FTLN both in APOE e4 carriers and non-carriers. APOE e4 genotype did not influence the A β SUVR or rate of accumulation of A β in atypical AD. While APOE e4 may have played a role in the original development of A β in these patients, there may, therefore, be another unknown factor, or factors, which play a role in determining A β burden and rate once A β is present. There has been mixed results concerning whether APOE e4 influences rate of A β accumulation in Alzheimer's dementia, with some finding an association [2] and others not [6].

An unexpected finding was that disease duration was strongly associated with rate of A β accumulation in FTLN, with faster rates in patients with disease duration under four years. This finding does not appear to be driven by the distribution of the specific FTLN syndromes, since disease duration did not differ across the syndromic groups ($p=0.88$). In addition, disease duration was not correlated with age (Spearman correlation= -0.14 , $p=0.47$) or scan interval (Spearman correlation= -0.07 , $p=0.70$) in FTLN, and age was accounted for in the analysis. These results could suggest that patients with shorter disease duration may have more rapidly progressing illnesses, and the spread of AD continuum pathology may be in some way contributing to, or be associated with, worse clinical outcomes that lead the patient to present to a clinician earlier in the disease course; it is possible they may even die sooner than patients with FTLN in the absence of AD. There could also be bias in our cohort, whereby patients with both FTLN and AD continuum pathology are less likely to

return to be assessed at longer disease durations. Given this uncertainty, the finding will need to be confirmed in independent samples. Rate of A β accumulation did not differ by disease duration in atypical AD, although baseline A β SUVR was higher in patients with longer disease duration. This finding makes sense given that we know A β accumulates over time in atypical AD, and hence, the longer a patient has been affected then the higher the A β burden.

The only demographic factor that influenced rates of A β accumulation in atypical AD was sex, with faster rates observed in women, even after correcting for age. We did not observe any sex differences in A β burden at baseline. The reason for this sex difference is unclear. Sex differences have been observed in relation to A β in patients in the clinically-normal-Alzheimer's dementia spectrum, although results are mixed. Consistent with the fact that we did not observe any sex differences in baseline A β , a pathological study found no differences in senile plaque burden by sex in cases with advanced neurofibrillary tangle stage, and a PET study did not identify differences in global A β uptake by sex [39]. One study suggested that women have early neural resistance to A β [40]. However, other studies found that men had greater A β burden than women [41, 42]. One longitudinal PET study found no differences in rate of A β accumulation by sex [5], although another found that rates were greater in men than women, although this effect went away after correcting for baseline A β burden [4]. More work will, therefore, be needed to confirm our finding and to determine how these findings relate to disease progression in atypical AD. Of note, our cohort had a high proportion (67%) of women, as is typical of other posterior cortical atrophy and logopenic aphasia cohorts [12, 23].

An important aspect of our study was that we analyzed relationships separately between atypical AD and FTLD, allowing us to identify different demographic determinants of A β accumulation in the different cohorts. Evaluating them together would have masked these associations and potentially driven other misleading associations. We also analyzed rate of A β accumulation as an annualized change in A β SUVR, as well as annualized percent change in SUVR, and the results were almost identical using the two methods. Our cohorts were large and consisted of a number of different atypical AD and FTLD syndromes which should increase generalizability of the findings. However, we acknowledge that the results may not generalize to other syndromes that were not included or to cohorts with different syndromic breakdowns. We also lacked autopsy findings to confirm pathological diagnosis which is most important in FTLD since we lack neuroimaging biomarkers for the underlying FTLD proteinopathies. However, previous studies have shown good concordance between the syndromes we assessed and underlying FTLD pathology [16, 43], particularly between primary progressive apraxia of speech [44], progressive supranuclear palsy [43, 45] and agrammatic primary progressive aphasia [43, 46] and underlying FTLD tauopathies; and between semantic dementia and underlying TDP-43 deposition [46–48]. We did not include behavioral variant frontotemporal dementia or corticobasal syndrome in our FTLD cohort since the pathology of these syndromes is notoriously heterogeneous and often includes AD [43, 47, 49, 50].

The findings from this study increase our knowledge of A β pathology in neurodegenerative diseases, and provide demographic risk factors for A β accumulation, including age and

disease duration in FTLN and sex in atypical AD. This will be important to help predict the behavior of A β PET in patients with these neurodegenerative diseases and aid in the interpretation of A β PET findings. The results also highlight interesting associations that may lead to a better understanding of the underlying pathophysiological mechanisms in these diseases.

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Figure 1:

Flow chart illustrating the cross-sectional and longitudinal patient cohorts. AD = Alzheimer's disease; FTLD = frontotemporal lobar degeneration; PPA = primary progressive aphasia

Figure 2:
Plots of baseline A β SUVRs versus rate of A β accumulation (SUVR change and percentage change) by diagnosis

Figure 3:

Plots illustrate the association between demographic features (age, APOE genotype, disease duration and gender) and both baseline A β SUVR and rate of A β accumulation (expressed as annualized SUVR change and annualized percentage change). Plots for APOE, disease duration and gender were age corrected.

Figure 4:
Plots of global A β SUVRs by age in atypical AD and FTLD

TABLE 1:

Patient characteristics

	All subjects (n = 322)			Subjects with serial PiB scans (n = 73)		
	Atypical AD (n = 138)	FTLD (n = 184)	P-values	Atypical AD (n = 42)	FTLD (n = 31)	P-values
Demographic and clinical characteristics						
No. Female, n (%)	80 (58%)	94 (51%)	0.26	28 (67%)	16 (52%)	0.23
No. APOE ε4 carrier, n (%)	66 (53%)	43 (24%)	<0.001	20 (51%)	6 (20%)	0.01
Education, yrs.	16 [14, 18]	16 [13, 16]	0.38	16 [14, 16]	16 [14, 16]	0.26
Age at onset, yrs.	62 [56, 67]	66 [59, 71]	0.002	64 [56, 68]	66 [54, 72]	0.71
Age at PiB scan, yrs.	67 [59, 71]	69 [63, 75]	0.003	68 [59, 71]	69 [57, 75]	0.70
Follow-up, yrs.	-	-	-	1.1 [1.0, 2.4]	2.0 [1.0, 4.3]	0.02
Disease duration, yrs.	3.8 [2.7, 5.0]	3.5 [2.5, 4.8]	0.35	3.4 [2.6, 4.4]	3.7 [2.4, 4.6]	0.65
MoCA	18 [12, 21]	24 [21, 27]	<0.001	20 [18, 25]	25 [23, 28]	<0.001
CDR-FTLD	4.0 [2.5, 7.0]	2.5 [1.0, 4.0]	<0.001	3.0 [2.0, 4.0]	1.0 [1.0, 3.0]	0.02
MDS-UPDRS III	3 [1, 6]	10 [4, 25]	<0.001	2 [1, 3]	6 [2, 12]	0.001
WAB apraxia	57 [53, 59]	57 [52, 59]	0.59	58 [56, 60]	58 [55, 59]	0.33
Aβ PET findings						
No. Aβ positive, n (%)	138 (100%)	48 (26%)	<0.001	42 (100%)	8 (26%)	<0.001
Global Aβ SUVRs	2.35 [2.15, 2.58]	1.25 [1.18, 1.34]	<0.001	2.39 [2.17, 2.56]	1.21 [1.17, 1.33]	<0.001
Aβ rate, n (%)			-			0.65
Increased > 2%	-	-	-	18 (43%)	11 (35%)	
Stable	-	-	-	21 (50%)	16 (52%)	
Decreased < -2%	-	-	-	3 (7%)	4 (13%)	
Aβ rate (SUVRs)	-	-	-	0.03 [-0.02, 0.12]	0.01 [-0.01, 0.04]	0.08
Aβ rate (%)	-	-	-	1.30% [-0.71%, 5.33%]	0.55% [-0.76%, 2.95%]	0.16

Data shown are N (%) or median [IQR]. P-values for continuous variables are from Wilcoxon Rank Sum test. P-values for categorical variables are from Fisher Exact test. MoCA = Montreal Cognitive Assessment battery; CDR-FTLD = FTLD modified version of the Clinical Dementia Rating Scale; MDS-UPDRS III = Movement Disorder Society sponsored revision of the Unified Parkinson's Disease Rating Scale part III; WAB = Western Aphasia Battery-Revised

TABLE 2:Effects of age, APOE ϵ 4, disease duration, and sex on baseline A β SUVR

	Atypical AD Est SUVR (95% CI)	FTLD Est SUVR (95% CI)	Between diagnosis P-values	Interaction P- values
Age				
Age 70	2.38 (2.31, 2.46)	1.28 (1.20, 1.35)	<0.001	0.02
Age > 70	2.38 (2.27, 2.48)	1.47 (1.39, 1.54)	<0.001	
P-values between age groups	0.91	<0.001		
APOE ε4				
APOE ε4-	2.46 (2.37, 2.56)	1.32 (1.26, 1.38)	<0.001	<0.001
APOE ε4+	2.42 (2.34, 2.50)	1.60 (1.49, 1.70)	<0.001	
P-values between APOE groups	0.53	<0.001		
Disease duration				
Disease duration 4	2.35 (2.26, 2.43)	1.36 (1.29, 1.42)	<0.001	0.33
Disease duration > 4	2.48 (2.39, 2.57)	1.40 (1.32, 1.49)	<0.001	
P-values between disease duration levels	0.04	0.39		
Sex				
Female	2.43 (2.35, 2.52)	1.40 (1.33, 1.47)	<0.001	0.86
Male	2.37 (2.28, 2.47)	1.35 (1.27, 1.43)	<0.001	
P-values between sex	0.32	0.37		

TABLE 3:
Effects of age, APOE ε4, disease duration, and sex on rates of Aβ accumulation expressed as either percent change or SUVR change

	Percent change					SUVR change				
	Atypical AD Est (95% CI)	P	FTLD Est (95% CI)	P	P-values Between Diagnosis	Atypical AD Est (95% CI)	P	FTLD Est (95% CI)	P	P-values Between Diagnosis
Age										
Age 70	1.28% (0.47%, 2.09%)	0.003	-0.30% (-1.28%, 0.67%)	0.54	0.02	0.03 (0.01, 0.05)	0.001	-0.004 (-0.03, 0.02)	0.70	0.02
Age > 70	0.96% (-0.78%, 2.70%)	0.29	2.04% (1.22%, 2.86%)	<0.001	0.28	0.02 (-0.01, 0.06)	0.23	0.03 (0.01, 0.05)	0.001	0.73
P-values between age groups	0.75		<0.001		0.03	0.76		0.02		0.11
APOE ε4										
APOE ε4-	0.66% (-0.31%, 1.63%)	0.19	0.58% (-0.21%, 1.37%)	0.16	0.90	0.02 (0.00, 0.04)	0.055	0.01 (-0.007, 0.03)	0.25	0.42
APOE ε4+	0.65% (-1.00%, 2.29%)	0.45	0.66% (-2.08%, 3.39%)	0.64	>0.99	0.02 (-0.02, 0.05)	0.28	0.001 (-0.06, 0.06)	0.97	0.60
P-values between APOE groups	0.99		0.96		0.96	0.97		0.78		0.84
Disease duration										
Disease duration 4	0.31% (-0.79%, 1.42%)	0.59	1.73% (0.86%, 2.59%)	<0.001	0.047	0.012 (-0.01, 0.04)	0.34	0.03 (0.01, 0.05)	0.007	0.33
Disease duration > 4	1.18% (0.17%, 2.19%)	0.03	-0.75% (-1.71%, 0.21%)	0.13	0.007	0.03 (0.009, 0.05)	0.007	-0.01 (-0.03, 0.01)	0.29	0.006
P-values between disease duration levels	0.25		<0.001		0.001	0.24		0.008		0.009
Sex										
Female	1.71% (0.67%, 2.76%)	0.002	0.69% (-0.20%, 1.57%)	0.14	0.14	0.04 (0.02, 0.07)	<0.001	0.01 (-0.01, 0.03)	0.29	0.02
Male	-0.41% (-1.57%, 0.76%)	0.50	0.50% (-0.52%, 1.52%)	0.35	0.25	-0.005 (-0.03, 0.02)	0.70	0.01 (-0.01, 0.03)	0.45	0.42
P-values between sex	0.008		0.78		0.07	0.004		0.89		0.03

All models were age adjusted except model with age as predictor.

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