



Pathological Aging

Associations among amyloid status, age, and longitudinal regional brain atrophy in cognitively unimpaired older adults



Rachel L. Nosheny^{a,b,*}, Philip S. Insel^c, Niklas Mattsson^c, Duygu Tosun^{a,d}, Shannon Buckley^a, Diana Truran^a, N. Schuff^a, Paul S. Aisen^e, Michael W. Weiner^{a,b,d}, for the Alzheimer's Disease Neuroimaging Initiative¹

^a Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, San Francisco, CA, USA

^b Department of Psychiatry, University of California, CA, USA

^c Department of Clinical Sciences Malmö, Clinical Memory Research Unit, Lund University, Lund, Sweden

^d Department of Radiology and Biomedical Imaging, University of California, CA, USA

^e Alzheimer's Therapeutic Research Institute, Keck School of Medicine of USC, San Diego, CA, USA

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ABSTRACT

The goal of this study was to compare regional brain atrophy patterns in cognitively unimpaired (CU) older adults with and without brain accumulation of amyloid- β ($A\beta$) to elucidate contributions of $A\beta$, age, and other variables to atrophy rates. In 80 CU participants from the Alzheimer's Disease Neuroimaging Initiative, we determined effects of $A\beta$ and age on longitudinal, regional atrophy rates, while accounting for confounding variables including sex, *APOE* $\epsilon 4$ genotype, white matter lesions, and cerebrospinal fluid total and phosphorylated tau levels. We not only found overlapping patterns of atrophy in $A\beta+$ versus $A\beta-$ participants but also identified regions where atrophy pattern differed between the 2 groups. Higher $A\beta$ load was associated with increased longitudinal atrophy in the entorhinal cortex, amygdala, and hippocampus, even when accounting for age and other variables. Age was associated with atrophy in insula, fusiform gyrus, and isthmus cingulate, even when accounting for $A\beta$. We found age by $A\beta$ interactions in the postcentral gyrus and lateral orbitofrontal cortex. These results elucidate the separate and related effects of age, $A\beta$, and other important variables on longitudinal brain atrophy rates in CU older adults.

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1. Introduction

Alzheimer's disease (AD) is characterized by plaques of amyloid- β ($A\beta$) peptides, tangles of phosphorylated tau (pTau) proteins, and neurodegeneration with specific regional distributions. $A\beta$ pathology is believed to begin to accumulate in the neocortex outside the temporal lobe, while tau pathology and neurodegeneration start in the temporal lobe, especially in the entorhinal cortex and

hippocampus (Braak and Braak, 1995; Cardenas et al., 2003; Du et al., 2003; Glenner and Wong, 1984; Jack et al., 2010, 2013; Kosik et al., 1986; Palmqvist et al., 2017; Thal et al., 2002). AD pathology is accompanied by progressive memory dysfunction leading to a continuum of mild cognitive impairment (MCI) and finally dementia (Grundman et al., 2004; Morris et al., 2001; Petersen et al., 1999).

Both aging in older adults and AD are associated with brain atrophy. Brain changes with age occur throughout the lifespan. The results of the present study focus on changes in older adults. The extent to which the regional pattern of atrophy differs between aging and AD has been previously studied with inconsistent results (Fjell et al., 2014a). Past studies have shown that in older adults, age is associated with widespread regional brain volume reductions (Walhovd et al., 2005), with more prominent effects in prefrontal, parietal, and sensorimotor regions than temporal and occipital regions (Allen et al., 2005; Resnick et al., 2003). MCI and AD are associated with accelerated atrophy in the medial temporal lobe, temporoparietal, and medial parietal regions (Dickerson et al., 2009). Some recent studies suggest similar patterns of atrophy in

* Corresponding author at: Department of Veterans Affairs Medical Center, Center for Imaging of Neurodegenerative Diseases, 4150 Clement Street, 114M, San Francisco, CA, USA. Tel.: +1-650 468-0619; fax: +1-415-668-2864.

E-mail address: rachel.nosheny@ucsf.edu (R.L. Nosheny).

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normal aging and AD (Fjell et al., 2014b; Oh et al., 2013), whereas others identify differential patterns with some overlapping regions (Bakkour et al., 2013). The identification of different spatial and temporal patterns of atrophy between aging and AD is likely confounded by many factors. There are methodological inconsistencies, and heterogeneous atrophy patterns are associated with different rates of disease progression and biomarker profiles (Dong et al., 2016; Jack et al., 2017). Recent studies have also highlighted the interacting contributions of multiple factors to brain atrophy, including genetic risk factors, tau, and cerebrovascular factors (Crary et al., 2014; Fletcher et al., 2016; Josephs et al., 2017; Knopman et al., 2015; Mormino, 2014; Mormino et al., 2016; Wilson et al., 2013).

Identification of differential regional atrophy in aging and AD is further complicated by the fact that 20%–40% of older adult cognitively unimpaired (CU) participants have substantial A β deposition (Arriagada et al., 1992; Dickerson et al., 2011; Morris et al., 2009; Rowe et al., 2010). Fibrillar A β deposition, which can be directly assessed in vivo by positron emission tomography (PET) using the radiotracers Pittsburgh Compound B or (18)F-florbetapir (AV45) (Clark et al., 2011; Jack et al., 2008b; Rowe et al., 2007), or reduced cerebrospinal fluid (CSF) A β levels, is associated with brain atrophy in CU participants (Becker et al., 2011; Fagan et al., 2009; Fjell et al., 2010a; Mormino et al., 2009; Schott et al., 2010; Storandt et al., 2009; Tosun et al., 2010). Previous cross-sectional studies have yielded conflicting results regarding associations between regional atrophy and A β in CU older adults, including whether or not differences in regional volumes can discriminate A β + and A β - CU older adults (Whitwell et al., 2013). Some studies have found decreased hippocampal volume associated with A β (Bourgeat et al., 2010; Mormino et al., 2009; Storandt et al., 2009), whereas others have not (Chetelat et al., 2010). Previous studies have also reported decreased cortical thickness and gray matter volume in temporal (Bakkour et al., 2013; Dickerson et al., 2011; Oh et al., 2013), frontal (Becker et al., 2011; Dickerson et al., 2011; Oh et al., 2013), parietal (Becker et al., 2011; Oh et al., 2013), and cingulate cortices (Fjell et al., 2010b; Oh et al., 2013), as well as precuneus (Oh et al., 2013). Interestingly, a few studies also found high brain A β levels to be associated with increased brain volume in older adult CU participants (Chetelat et al., 2010; Johnson et al., 2014).

Recent longitudinal studies have consistently found associations between A β and brain atrophy, with variability in the regions of atrophy identified, for example: significant increase in atrophy rate in A β and correlation between baseline A β and atrophy rate, especially in the temporal neocortex and the posterior cingulate cortex (Chetelat et al., 2012); greater atrophy rate in the entorhinal cortex associated with A β positivity but only in pTau-positive participants (Desikan et al., 2011); A β positivity associated with greater atrophy rate in the temporal lobe (Dore et al., 2013; Fletcher et al., 2018; Nosheny et al., 2015), insula and posterior cingulate (Dore et al., 2013; Fletcher et al., 2018; Nosheny et al., 2015), or thalamus (Fletcher et al., 2018); volumetric reductions over one year in multiple brain areas regardless of AD risk factors (Fjell et al., 2013); and increased frontoparietal atrophy rates associated with emerging A β pathology (Mattsson et al., 2014). Elucidating the contribution of A β to atrophy has important implications for the design of future studies of variables that are associated with brain atrophy, as well as clinical trials of AD therapeutics in which A β reduction and brain atrophy are outcome measures.

The goal of this study was to compare the pattern of brain atrophy in A β + and A β - CU older adults, taking into account the contributions of age and other important variables. The novelty of our work compared to past studies is (1) our results include analysis of longitudinal atrophy over 4 years with multiple data points; (2)

our multivariable analyses account for important covariates that have previously been found to have independent associations with brain atrophy (Crivello et al., 2010) (Schott et al., 2010) (Carmichael et al., 2010; Constans et al., 1995; Cowell et al., 1994; Farias et al., 2012; Jagust et al., 2008; Sowell et al., 2007); (3) We considered interactions between A β and age when determining their contributions to regional atrophy. We tested the a priori hypothesis that A β -driven brain atrophy is an accelerated version of atrophy associated with aging, affecting the same regions, but with an increased rate of atrophy. As an exploratory aspect of the study, we determined whether additional variables including sex, APOE ϵ 4 genotype, white matter lesions (WMLs), CSF total tau and pTau, and intracranial volume (ICV) are significantly associated with regional brain atrophy in this population, and if so, which variables are associated with atrophy in which regions.

2. Methods

2.1. Participants

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org.

All ADNI data were downloaded from the ADNI database (www.loni.ucla.edu/ADNI). We included CU ADNI participants with successful longitudinal FreeSurfer processing of MRI images (average number of images per participant = 4.6, minimum number of images per participant = 2, maximum number of images per participant = 6), as well as a valid test result for AV45 imaging. Participants were aged 55–91 years at baseline, English or Spanish speaking, and had an available study partner. All participants met ADNI inclusion criteria for CU at their baseline visit: Mini-Mental State Examination scores of 24–30 (Folstein et al., 1975), Clinical Dementia Rating of 0 and memory box score of 0 (Morris, 1993); absence of major depressive disorder, memory dysfunction (Wechsler, 1987), impairment in activities of daily living, MCI, or

Table 1
Demographics of participants included in this study

	Total	A β +	A β -
Number of participants (%)	80	27 (33.8%)	53 (66.2%)
Age (mean \pm SD, range)	75.6 \pm 4.6, 65.1–89.6	76.1 \pm 3.4, 71.3–84.8	75.4 \pm 5.2, 65.1–89.6
Number female (%)	41 (51.3%)	14 (51.9%)	27 (51.0%)
Years of education (mean \pm SD, range)	16.1 \pm 3.0, 6–20	15.6 \pm 3.1, 6–20	16.4 \pm 2.9, 8–20
APOE ϵ 4+ (% of total)	19 (23.8%)	11 (40.7%)	8 (15.1%) ^a
White matter lesions $\times 10^{-3}$ (mean \pm SD, range)	3.9 \pm 2.2, 1.2–11.1	3.8 \pm 2.2, 1.2–10.0	3.9 \pm 2.2, 1.2–11.0
Intracranial volume $\times 10^{-6}$ (mean \pm SD, range)	1.5 \pm 0.15, 1.2–1.8	1.5 \pm 0.17, 1.3–1.8	1.5 \pm 0.15, 1.2–1.9
Total tau (mean \pm SD, range)	72.4 \pm 32.2, 32–184	92.3 \pm 39.6, 37–184	62.7 \pm 22.9, ^a 32–120
pTau (mean \pm SD, range)	24.4 \pm 10.8, 12–59	31.7 \pm 12.6, 15–49	20.9 \pm 8.0, ^a 12–52

Key: A β , amyloid- β ; pTau, phosphorylated tau.

^a $p < 0.05$ versus A β +

dementia; no memory complaints aside from those common to other normal subjects of that age range. Further details regarding ADNI inclusion and exclusion criteria can be found at <http://adni.loni.usc.edu/methods/documents/>. All ADNI data were downloaded from the ADNI database (www.loni.ucla.edu/ADNI). The demographics of participants included in this study are shown in Table 1.

2.2. T1-weighted magnetic resonance imaging

Participants underwent a standardized 1.5 or 3 Tesla MRI protocol (<http://www.loni.ucla.edu/ADNI/Research/Cores/index.shtml>) that was previously validated across sites by individualized protocols for each scanner (Jack et al., 2008a), adni.loni.ucla.edu/methods/documents/mri-protocols/. The ADNI MRI quality control center at the Mayo Clinic selected the MP-RAGE image with higher quality and corrected for system-specific image artifacts, as described in the study by Jack et al., 2008a.

2.3. FreeSurfer longitudinal processing

Automated volume measures from all regions of interest were downloaded from the ADNI LONI website. Automated volume

measures were performed by ADNI staff with FreeSurfer software package, version 5.1. Volume measurements for each of 41 FreeSurfer regions shown in Table 2 were calculated by averaging the volume measurement at each time point from the right and left sides of the region of interest. To reduce confounding effects of intraparticipant morphological variability, each participant's data series was processed by FreeSurfer longitudinal workflow (Fischl et al., 2002, 2004); see <http://surfer.nmr.mgh.harvard.edu/fswiki/LongitudinalProcessing>. Details of quality control procedures are at <http://www.loni.ucla.edu/twiki/pub/ADNI/ADNIPostProc/UCSFFreeSurferMethodsSummary.pdf>."

2.4. PET imaging

18F-AV45 (Florbetapir) images were collected at multiple sites. Participants were injected with 10 mCi AV45, 4 dynamic acquisition frames were obtained 50–70 minutes after injection and coregistered to one another, averaged, interpolated to a uniform image and voxel size ($160 \times 106 \times 96, 1.5 \text{ mm}^3$), and smoothed to a uniform resolution (8 mm FWHM). See also adni.loni.ucla.edu/about-data-samples/image-data. A mean cortical standardized uptake value ratio (SUVr) measure was derived by normalizing average retention values of cortical regions (anterior cingulate, frontal, lateral

Table 2
Regional atrophy rates from 41 FreeSurfer regions of interest in A β + and A β - participants

A β +				A β -				
	Region	Rate	Effect size		Region	Rate	Effect size	p value
1	Hippocampus	-46.87	-2.321	0	Inferior temporal	-96.81	-1.701	0
2	Entorhinal	-38.04	-1.669	0	Lateral occipital	-76.11	-1.356	0
3	Medial orbitofrontal	-41.40	-1.404	0	Hippocampus	-30.70	-1.237	0
4	Superior frontal	-153.20	-1.366	0	Parahippocampus	-17.57	-1.216	0
5	Pars orbitalis	-22.43	-1.355	0	Fusiform	-71.05	-1.209	0
6	Superior temporal	-78.02	-1.331	0	Inferior parietal	-96.13	-1.167	0
7	Lateral orbitofrontal	-55.53	-1.296	0	Superior temporal	-75.81	-1.154	0
8	Lingual	-38.62	-1.289	0	Pars orbitalis	-14.83	-1.115	0
9	Parahippocampus	-25.78	-1.228	0	Middle temporal	-92.20	-1.101	0
10	Middle temporal	-103.79	-1.158	0	Medial orbitofrontal	-26.81	-1.077	0
11	Isthmus cingulate	-13.51	-1.089	0	Entorhinal	-19.72	-1.048	0
12	Rostral middle frontal	-92.23	-1.053	0	Caudal middle frontal	-46.69	-1.009	0
13	Temporal pole	-19.21	-1.030	0	Superior frontal	-118.93	-0.998	0
14	Pars opercularis	-27.61	-1.026	0	Supramarginal	-66.88	-0.997	0
15	Amygdala	-17.61	-0.982	0	Precentral	-93.76	-0.975	0
16	Bankssts	-17.82	-0.979	0	Isthmus cingulate	-14.71	-0.947	0
17	Insula	-30.66	-0.971	0	Insula	-24.62	-0.937	0
18	Inferior temporal	-94.47	-0.968	0	Lingual	-32.64	-0.921	0
19	Superior parietal	-94.78	-0.927	0	Rostral middle frontal	-85.22	-0.908	0
20	Posterior cingulate	-19.04	-0.897	0.0026	Superior parietal	-86.26	-0.868	0
21	Inferior parietal	-100.88	-0.886	0	Transverse temporal	-6.95	-0.861	0
22	Pars triangularis	-21.66	-0.847	0.0024	Lateral orbitofrontal	-46.43	-0.822	0
23	Precuneus	-68.78	-0.791	0.0013	Thalamus	-49.96	-0.809	0
24	Fusiform	-78.83	-0.761	0.0012	Precuneus	-51.10	-0.788	0
25	Paracentral	-19.90	-0.760	0.0104	Pars triangularis	-20.85	-0.783	0
26	Thalamus	-38.93	-0.759	0.007	Bankssts	-13.91	-0.772	0
27	Putamen	-27.70	-0.740	0.0117	Postcentral	-39.00	-0.762	0
28	Accumbens area	-7.27	-0.701	0.0178	Pars opercularis	-24.25	-0.753	0
29	Postcentral	-53.92	-0.689	0.0091	Paracentral	-24.03	-0.749	0
30	Caudal middle frontal	-37.39	-0.685	0.0136	Cuneus	-16.39	-0.714	0
31	Cuneus	-15.40	-0.684	0.0147	Putamen	-38.65	-0.687	0
32	Frontal pole	-6.99	-0.646	0.014	Temporal pole	-14.60	-0.628	0
33	Lateral occipital	-54.11	-0.635	0.0211	Posterior cingulate	-13.94	-0.613	0
34	Rostral anterior cingulate	-11.18	-0.605	0.0201	Caudal anterior cingulate	-7.03	-0.608	0.0024
35	Supramarginal	-48.55	-0.565	0.0342	Rostral anterior cingulate	-10.23	-0.564	0.0012
36	Caudate	-27.98	-0.565	0.0219	Caudate	-20.13	-0.472	0.0164
37	Caudal anterior cingulate	-8.96	-0.564	0.0305	Frontal pole	-3.02	-0.449	0.0588
38	Transverse temporal	-4.69	-0.544	0.0533	Accumbens area	-7.80	-0.389	0
39	Precentral	-52.41	-0.389	0.1406	Amygdala	-5.23	-0.335	0.0688
40	Pericalcarine	-1.81	-0.134	0.6858	Pericalcarine	-6.74	-0.329	0.0812
41	Pallidum	5.04	0.274	0.2517	Pallidum	-0.45	-0.022	0.9043

Regions are listed in order of the effect size for each subgroup (A β + and A β -).
Key: A β , amyloid- β .

temporal, parietal cortex, and precuneus), to retention value of the whole cerebellum. We used previously established thresholds for florbetapir-PET (SUVr >1.11) to identify the presence of A β pathology (Joshi et al., 2012; Landau et al., 2012).

2.5. Statistical analysis

Baseline values of demographic variables were compared using the Wilcoxon-Mann-Whitney test and Fisher's exact test. Volume was regressed on time since initial scan (baseline time) using linear mixed effect (LME) models, with both a random intercept and slope to estimate individual regional atrophy rates, assuming a compound symmetry correlation structure. The LME model included A β (either AV45 SUVr as a continuous variable, or A β status, as indicated in Section 3), baseline time, and the interaction of A β and baseline time. For results, Section 3.2, an interaction between A β status and pTau was also considered. For multivariable models, APOE ϵ 4 genotype, gender, education, WML, ICV, CSF total, and pTau were included in the model. APOE ϵ 4 genotype was dichotomized as positive (having at least one APOE ϵ 4 allele) or negative. Each predictor was evaluated both separately and in a full model, adjusting for all other predictors. To test the ability of the multivariable models to reduce residual error, R² values were compared after adding groups of predictive variables in a forward, stepwise set of models. For the analyses described in Section 3.4, we also considered an interaction between A β and age in the multivariable model.

For the analysis of effect size in A β ⁺ and A β ⁻ participants (Table 2), volume was regressed on time since initial scan, separately in the A β ⁺ and A β ⁻ subgroups. Effect sizes were calculated as the estimate (β) divided by the standard deviation (SD) of the effect. The SD used to calculate effect size was a function of the slope and the error variance components and follow-up time:

$$f_x = \frac{\beta}{\sqrt{\frac{\sigma_s + \sigma_e}{\sum (t - t_\mu)^2}}}$$

Where f_x = effect size, β = effect estimate, σ_s = slope variance, σ_e = error variance, t = time in years, and t_μ = mean time in years. Model fits were inspected by an analysis of the residuals. All statistics were performed using R (v. 2.8.1, The R Foundation for Statistical Computing).

Although we examined many brain regions, we report nominal *p*-values, without adjustment for multiple testing. We do so because the clear functional and anatomical relationships among the regions examined permit coherent sets of findings to reinforce each other rather than detract from one another. For example, for the examination of the associations between A β status and regional atrophy rate, the significant association found between multiple temporal lobe structures is supported by the functional and biological relatedness of the regions. Multiple comparison adjustment would require that each result detract from the others. We therefore rely on scientific judgment rather than formal adjustment

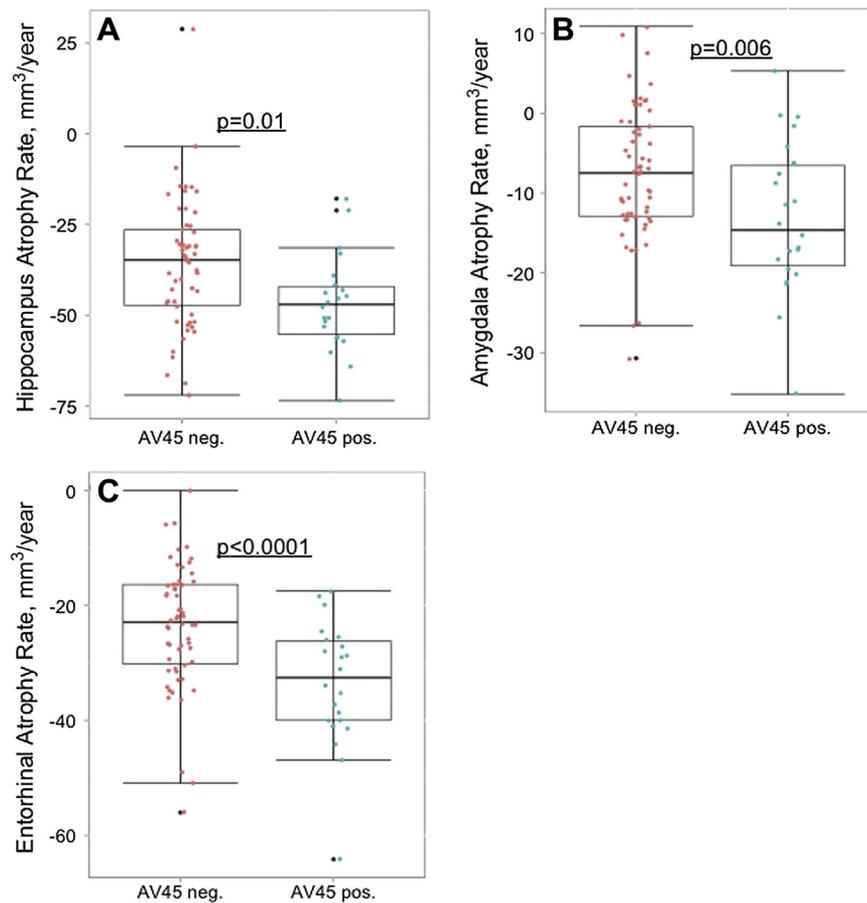


Fig. 1. Effect of amyloid status on regional atrophy rate. Box and whisker plots showing atrophy rates in hippocampus (A), amygdala (B), and entorhinal cortex (C), 3 regions in which amyloid status is significantly associated with longitudinal atrophy rate. Top and bottom limits of the boxes represent the 25th and 75th percentile, box centerlines represent the median value, and whiskers extend to the most extreme data point which is no more than 1.5 times the length of the box away from the box. Atrophy rates of individual participants are indicated by red (A β ⁻) or cyan (A β ⁺) dots. In this and all subsequent figures, higher atrophy rates are indicated by lower values on the y-axis. Abbreviation: A β , amyloid- β .

methods to indicate where caution is warranted despite findings with $p < 0.05$. We also report both nominal and adjusted p -values in the [Supplemental Materials](#) (Table S1).

3. Results

3.1. Associations between A β and atrophy rate

We classified participants as A β + or A β - and calculated atrophy rates for 41 FreeSurfer regions in each subgroup (Table 2). Using LME models, we identified 3 regions in which atrophy rate was significantly higher in A β + versus A β -: the hippocampus, entorhinal cortex, and amygdala (Fig. 1). Using AV45 as a continuous measure rather than classifying participants as A β + or A β - gave similar results (Supplemental Fig. 1).

We also measured the association between A β status and atrophy rate in models accounting for multiple confounding variables that have independent associations with regional atrophy rate: age, ApoE ϵ 4 genotype, ICV, WMLs, and gender. The association between positive A β status and higher atrophy rate remained significant when accounting for confounding variables. Including WMLs in the model resulted in a significant ($p = 0.04$) association between A β + and higher frontal pole atrophy rate. In the multivariable model, no significant associations between regional atrophy rates and variables other than A β or age were found for the regions shown in

Fig. 1. However, a number of independent associations between these additional variables and regional atrophy rates were found in a series of univariable models (Supplemental Tables S2–S6).

3.2. Contributions of tau

pTau was significantly associated with atrophy rates in several regions in univariable models (Supplemental Table S6). When we included pTau in the multivariable model, the areas with significant associations between A β + and higher atrophy rate were the amygdala ($p = 0.04$) and entorhinal cortex ($p = 0.0014$). In this model including pTau, there was no significant association between A β and hippocampal atrophy ($p = 0.07$). We also considered A β by pTau interactions in a separate series of multivariable models. We found significant interactions between A β and pTau in their associations with atrophy in the fusiform gyrus ($p = 0.008$); the association between A β and atrophy rate was significantly higher in those with higher pTau levels.

3.3. Regions showing a significant association between age and longitudinal atrophy rate

LME models were used to determine the relationship between age and regional atrophy rate. In a univariable model including only age as the independent variable, significant associations were

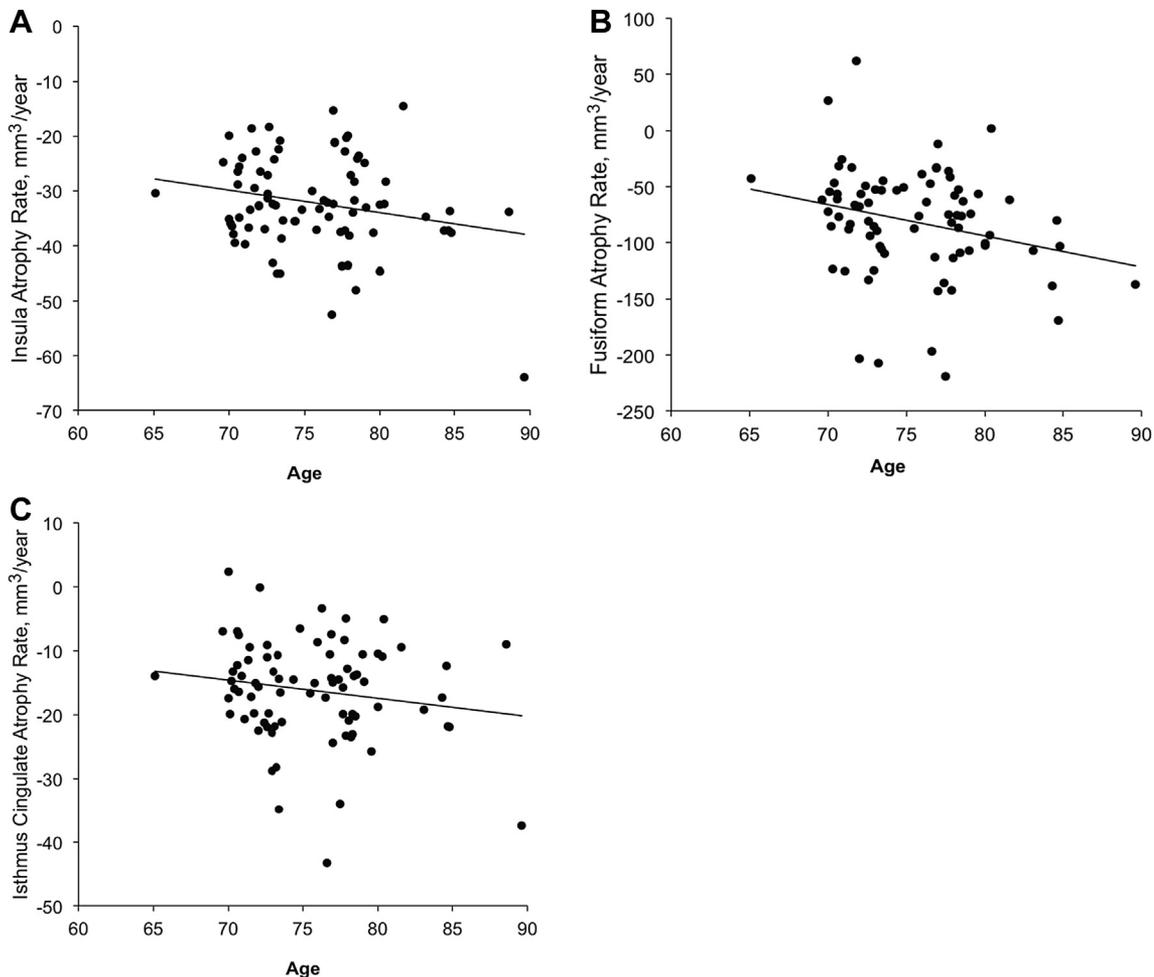


Fig. 2. Effect of age on regional atrophy rate. Scatter plots showing the association between age and longitudinal atrophy rate in 3 regions. Multivariable linear mixed effects analysis (black lines) shows significant associations between age and atrophy rate in the insula (A, $p = 0.05$), fusiform gyrus (B, $p = 0.03$), and isthmus cingulate (C, $p = 0.05$). Atrophy rates of individual participants are indicated by black dots. Higher atrophy rates are indicated by lower values on the y-axis. Abbreviation: A β , amyloid- β .

found between advanced age and higher atrophy rate in the lingual gyrus ($p = 0.03$) and temporal pole ($p = 0.01$). However, when accounting for the effects of A β status and age together in a multivariable model, we found significant associations between advanced age and higher atrophy rate in the insula ($p = 0.05$), fusiform gyrus ($p = 0.03$), and isthmus cingulate ($p = 0.05$) (Fig. 2). The associations retained significance in multivariable models including the covariates described previously. Fig. 3 summarizes the anatomical relationships between regions in which there are significant associations between higher atrophy rate and advanced age in univariable and multivariable models.

3.4. Regions with differential age-related atrophy rate in A β + and A β - participants

To determine which regions have different age-related atrophy in A β + and A β - participants, we considered an interaction between age and A β status in their association with atrophy rate. We identified 2 regions with significant interactions: postcentral gyrus ($\beta = -19.00$, SE = 6.80, $p = 0.006$), and lateral orbitofrontal cortex ($\beta = 8.12$, SE = 4.19, $p = 0.05$). In the postcentral gyrus, age-related atrophy was greater in A β + than in A β - participants (Fig. 4A). Conversely, in the lateral orbitofrontal cortex, age-related atrophy was greater in A β - participants than in A β + participants (Fig. 4B).

4. Discussion

The major findings of this study are the following: (1) in CU older adults, higher 4-year atrophy rates in several temporal lobe regions are significantly associated with A β + status, with the strongest associations in the entorhinal cortex and amygdala (Section 3.1); (2) significant associations between A β + status and higher atrophy rates in these regions exist even after accounting for several covariates, such as APOE $\epsilon 4$ genotype, gender, WMLs (a marker of cerebrovascular disease), and ICV (Section 3.1); (3) advanced age is significantly associated with higher atrophy rates in the insula, fusiform gyrus, and isthmus cingulate, even when accounting for A β (Section 3.3); and (4) 2 regions show an interaction between A β status and age in the association with atrophy rate. In the postcentral gyrus, there was accelerated age-related atrophy in A β + participants, and in the lateral orbitofrontal cortex, there was accelerated age-related atrophy in A β - participants (Section 3.4).

We found significant associations between A β + and brain atrophy in the entorhinal cortex, hippocampus, and amygdala. Using multivariable models, we demonstrated that the effect is unlikely to be confounded by other variables that have independent association with atrophy rate in some regions, including some related to other types of neurodegeneration (Section 3.1 and Tables S1–S6). Many of the previous cross-sectional and

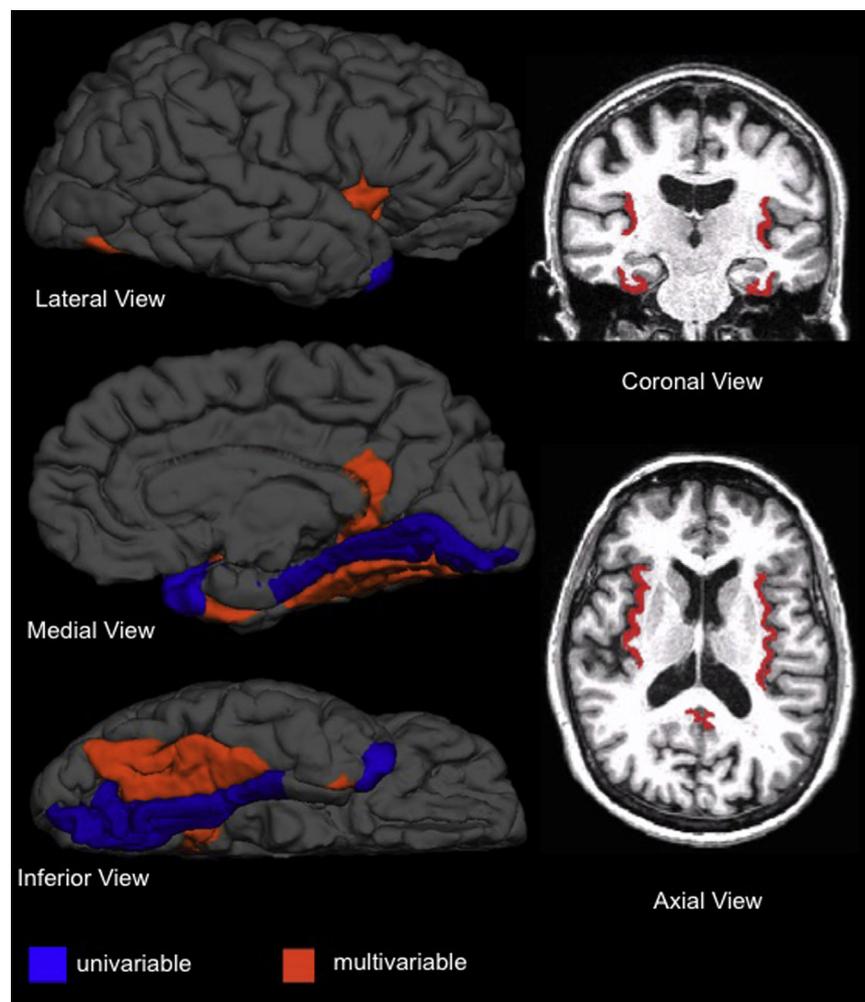


Fig. 3. Regions with significant associations between age and atrophy rates. FreeSurfer ROIs with significant associations between age and atrophy rate are shown in red and blue. Regions with a significant association between age and atrophy rate in the univariable model, shown in blue, include the temporal pole and lingual gyrus. When accounting for A β status, significant associations between age and atrophy rate are present in adjacent but nonoverlapping areas within the temporal lobe and occipital lobe (red) including the insula, fusiform gyrus, and isthmus cingulate. Abbreviations: A β , amyloid- β ; ROIs, regions of interest.

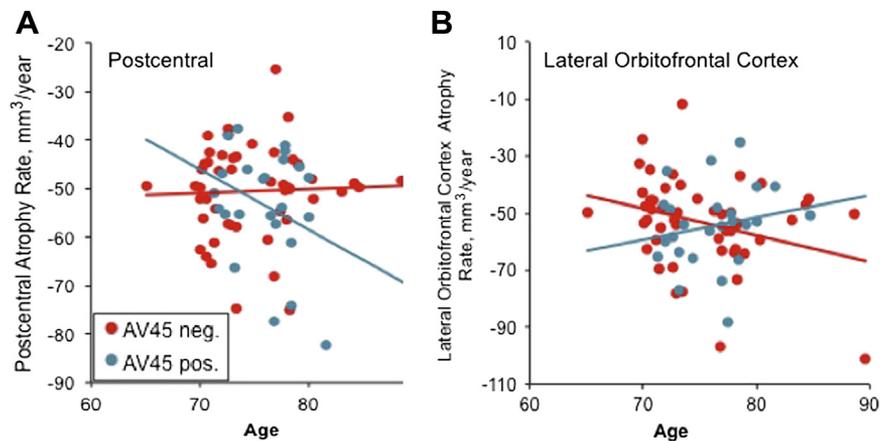


Fig. 4. Effects of age on atrophy rates in Aβ+ and Aβ- participants. Scatter plots showing the effect of age on atrophy rate in a cohort of participants classified as Aβ- (red circles) or Aβ+ (cyan circles). Linear mixed effects models (solid red and cyan lines) show a significant interaction between age and Aβ status in 2 regions. In (A) the postcentral gyrus, age-related atrophy rate is greater in Aβ+ than in Aβ- ($p = 0.006$), whereas in (B) the lateral orbitofrontal cortex, age-related atrophy rate is greater in Aβ- than in Aβ+ ($p = 0.05$). Higher atrophy rates are indicated by lower values on the y-axis. Abbreviation: Aβ, amyloid-β.

longitudinal work measuring associations between brain atrophy and Aβ specifically analyzed changes in the temporal lobe (Becker et al., 2011; Bourgeat et al., 2010; Desikan et al., 2011; Mormino et al., 2009; Nosheny et al., 2015) or focused on cortical thinning (Becker et al., 2011; Dickerson et al., 2009, 2011; Dore et al., 2013). In contrast, we measured associations between Aβ and atrophy rates in multiple regions. This informs us about associations between individual regional atrophy rates and Aβ status but fails to answer the question of whether there are differences in the overall spatial pattern of atrophy across multiple brain regions. Therefore, we also compared effect sizes in the 2 groups (Table 2) to give a more global picture of atrophy pattern. Comparing atrophy rates by effect size separately in Aβ+ and Aβ- participants demonstrated that in both groups, highest rates of brain atrophy are in temporal lobe regions including the hippocampus, parahippocampus, entorhinal cortex, and the superior, middle, and inferior temporal cortices (Table 2).

Our results on the association between regional brain atrophy and Aβ are consistent with some recent longitudinal studies (Fjell et al., 2009, 2014a; Mattsson et al., 2014). Like Chetelat et al., 2012 and Fletcher et al., 2018, we found accelerated atrophy associated with Aβ in the temporal lobe. Unlike Chetelat et al., 2012, we did not find accelerated atrophy in the cingulate cortex, superior and middle frontal gyri, temporo-occipital regions, medial temporal lobe, or precuneus. Unlike Fletcher et al., 2018, we did not find associations between Aβ and atrophy in the parahippocampal gyrus, thalamus, or parieto-temporal regions. The discrepancies may be explained by different cohorts and different methodology. For example, Fletcher et al., 2018 used CSF Aβ as a continuous measure. One important note is that the previous important articles analyzing longitudinal atrophy did so over a period of two years or less. In contrast, our data include analysis of longitudinal atrophy over four years with multiple data points. The longer period of observation time in our analysis allows for greater sensitivity to detect small changes and to detect differences between regions. Furthermore, in contrast, our data analyze atrophy in the entire brain using all the regions parcellated by FreeSurfer. Therefore, our results measuring regional atrophy throughout the brain, across a longer time span with multiple data points, and accounting for important covariates that have previously been found to have independent associations with brain atrophy, are new and add to previous reported findings.

Interestingly, atrophy rates in the entorhinal cortex and amygdala were most strongly associated with Aβ status. The association between Aβ status and hippocampal atrophy rate is weaker and loses significance when accounting for pTau. This is in line with the finding of a significant association between Aβ and longitudinal entorhinal atrophy only in CU participants classified as pTau positive (Desikan et al., 2011). Unlike previous cross-sectional studies (Bakkour et al., 2013; Becker et al., 2011; Bourgeat et al., 2010; Chetelat et al., 2010; Dickerson et al., 2011; Fjell et al., 2010b; Mormino et al., 2009; Oh et al., 2013; Storandt et al., 2009), we did not find areas outside of the temporal lobe with a significant association between Aβ status and atrophy rate. Thus, although Aβ status may be associated with baseline volume in many different regions, we find that Aβ status is only associated with longitudinal atrophy rates in the temporal lobe, with the strongest associations in the entorhinal cortex and amygdala.

In CU older adults, age was significantly associated with atrophy in different brain regions depending on whether or not Aβ was accounted for in the model. In a univariable model using age alone, there was a significant association between age and atrophy rate in the lingual gyrus and temporal pole. When we included Aβ status in the model, we found a significant association between age and atrophy rate in the insula, fusiform gyrus, and isthmus cingulate. There are 2 main conclusions from the age data. First, age-related atrophy involves multiple medial temporal lobe brain regions. Although the regions independently associated with age are adjacent to the regions independently associated with Aβ, there is no overlap in regions. This finding contrasts those of cross-sectional studies in which age was found to be associated with widespread reductions in volume and cortical thickness, independent of Aβ status (Becker et al., 2011; Oh et al., 2013). Thus, the interdependence of age and Aβ in determining brain atrophy differs when using baseline volume versus longitudinal atrophy rate as an outcome measure. Furthermore, regional atrophy associated with age depends on Aβ status in this cohort, and it is therefore crucial to account for Aβ in models of age effects on regional atrophy. It is important to point out that our results focus solely on the effects of aging in older adults and therefore cannot address effects of age observed across the lifespan.

Although age, independent of Aβ, is associated with atrophy in different brain regions, this effect is likely mediated by a combination of the effects of “normal aging” together with other factors

responsible for neurodegeneration, including tau, cerebrovascular factors, genetic risk factors, and inflammation (Deming et al., 2017; Irwin et al., 2017; Josephs et al., 2017; Mormino et al., 2016; Wilson et al., 2013). Although this work does not address the contribution of each of these pathologies to regional atrophy, we do address contributions of CSF pTau and WML in addition to A β .

To identify regions in which age-related atrophy differs in A β + versus A β - participants, we tested for an interaction between age and A β status in our models and identified only 2 regions with a significant interaction. In the postcentral gyrus, age-related atrophy rate is greater in A β + participants than in A β - participants. Conversely, in the lateral orbitofrontal cortex, age-related atrophy is greater in A β - participants than in A β +. The significance of this novel finding is not entirely clear. Others have previously found increased gray matter and hypermetabolism associated with high levels of brain A β in temporal and parietal regions in CU (Chetelat et al., 2010; Fortea et al., 2011; Iacono et al., 2008; Johnson et al., 2014) A β + participants. Some of these studies suggest that such changes may be due to inflammation or compensation for atrophy or that they may be driven by a subset of A β + CU individuals who are resistant to the neurodegenerative and/or cognitive effects of A β due to some unknown protective factor. Further investigation of cognitive status in this cohort is necessary to investigate this possibility.

Although this study provides important new information about the factors contributing to regional brain atrophy in older adults, it has limitations. First, the ADNI cohort may not accurately reflect the population in terms of atrophy in CU participants (Whitwell et al., 2012), and ADNI exclusion criteria limit the range of values of variables such as WML, so that effects of WML may be underestimated in our model. Second, because we use a single A β measurement to classify participants as A β + or A β -, we cannot fully account for the role of emerging A β pathology in our model (Mattsson et al., 2014). In addition, the vast majority of participants had AV45 PET performed after the final MRI used to calculate atrophy rate (see Section 2). Thus, our A β + group includes both those who were A β + at baseline and those who developed significant A β accumulation over the course of the study, including those who became A β + after the volume measurements were made. To rule out the possibility that using a dichotomous A β measure obscured the role of emerging A β pathology on brain atrophy, we confirmed these results using AV45 SUVR as a continuous measure (Supplemental Fig. 1). Furthermore, 58% of participants in this study also had CSF A β 1–42 measured at baseline, and of these, 93% had agreement between A β status measured using CSF A β 1–42 and AV45, suggesting that our A β + cohort does not include many participants who were A β - at baseline. Another limitation is that we relied on CSF pTau and total tau measurements. Because the associations between CSF tau measures and tau accumulation measured by tau PET imaging is only modest (Mattsson et al., 2017) and CSF tau is an overall measure which does not give any information about local tau pathology, it would be interesting to complement the current analysis with regional tau PET data in future studies.

Although we examined many brain regions, we report nominal *p*-values, without adjustment for multiple testing, throughout the article. We do so because multiple comparison adjustment would require that each result detract from the others, but the clear functional and anatomical relationships among the regions examined permit coherent sets of findings to reinforce each other rather than detract from one another. However, we acknowledge that thresholding for a nominal *p*-value of 0.05 when comparing a large number of brain regions of interest is permissive. Therefore, we report both nominal and adjusted *p*-values (see Supplemental Table S1), and we rely on scientific judgment rather than formal adjustment methods to indicate where caution is warranted despite findings with *p* < 0.05.

5. Conclusions

These findings elucidate the separate and related effects of age, A β , and other factors that may be associated with age on longitudinal brain atrophy rates in CU older adults. We identified the hippocampus, amygdala, and entorhinal cortex as specific brain regions in which A β is associated with atrophy when accounting for age; the insula, fusiform gyrus, and isthmus cingulate as specific regions where atrophy is associated with age, even when accounting for A β ; and the postcentral gyrus and lateral orbitofrontal cortex as regions with differential age-related atrophy in A β + and A β - CU older adults.

Disclosure

N.R.L., I.P.S., M.N., To.D., B.S., Tr.D., and S.N. have nothing to disclose. A.P.S. performed the following activities during the period of work, all outside of the scope of the submitted work, received personal fees from NeuroPhage; Elan Corporation; Wyeth; Eisai Inc; Schering-Plough Corp.; Bristol-Myers Squibb; Eli Lilly and Company; NeuroPhage; Merck & Co; Roche; Amgen; Genentech, Inc; Abbott; Pfizer Inc; Novartis; Bayer; Astellas; Dainippon; BioMarin; Solvay; Otsuka; Daiichi; AstraZeneca; Janssen; Medivation, Inc; Ichor; Toyama; Lundbeck; Biogen Idec; iPierian; Probiobdrug; Somaxon; Biotie; Anavex; and Kyowa Hakko Kirin Pharma, and received grants from Lilly, Baxter, and FNIH. W.M.W. performed the following activities during the period of work, all outside of the scope of the submitted work, received personal fees from Pfizer; Janssen; KLJ Associates; Easton Associates; Harvard University; inThought Research; INC Research, Inc; University of California, Los Angeles (UCLA); Alzheimer's Drug Discovery Foundation (ADDF); Sanofi-Aventis Groupe; Avid RadioPharmaceuticals; Eli Lilly & Co, Paul Sabatier University; Novartis; Tohoku University; MCI Group, France; Travel eDreams, Inc, Neuroscience School of Advanced Studies (NSAS); Danone Trading, BV; CTAD ANT Congres; ADRC; and received grants/contracts from Merck, Avid RadioPharmaceuticals, and Janssen Pharmaceutical.

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of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.neurobiolaging.2019.07.005>.

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