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Convergence of Accelerated Brain Volume Decline in Normal Aging and Alzheimer's Disease Pathology

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Abstract.

Background: Age represents the largest risk factor for Alzheimer's disease (AD) but is typically treated as a covariate. Still, there are similarities between brain regions affected in AD and those showing accelerated decline in normal aging, suggesting that the distinction between the two might fall on a spectrum.

Objective: Our goal was to identify regions showing accelerated atrophy across the brain and investigate whether these overlapped with regions involved in AD or where related to amyloid.

Methods: We used a longitudinal sample of 137 healthy older adults from the Alzheimer's Disease Neuroimaging Initiative (ADNI), who underwent magnetic resonance imaging (MRI). In addition, a total of 79 participants also had longitudinal positron emission tomography (PET) data. We computed linear-mixed effects models for brain regions declining faster than the average to investigate variability in the rate of change.

Results: 23 regions displayed a 0.5 standard deviation (SD) above average decline over 2 years. Of these, 52% overlapped with regions showing similar decline in a matched AD sample. Beyond this, the left precuneus, right superior frontal, transverse temporal, and superior temporal sulcus showed accelerated decline. Lastly, atrophy in the precuneus was associated with increased amyloid load.

Conclusions: Accelerated decline in normal aging might contribute to the detection of early signs of AD among healthy individuals.

Keywords: Accelerated atrophy, Alzheimer's disease, amyloid acculumation, gray matter, normal aging

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, with sporadic AD representing 95% of all cases.[1] AD is characterized by worsening cognition, neurodegeneration, and accumulation of amyloid-β (Aβ) plaques and tau neurofibrillary

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[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

tangles. Despite aggressive drug-related research, there is currently no cure but markers that can help identify the disease before irreversible damage has occurred have been widely studied. Most studies follow the A/T/N classification, with Aβ and tau being captured with positron emission tomography (PET) and neurodegeneration with magnetic resonance imaging (MRI). Both of these techniques have been shown to be significant and reliable predictors of AD progression.[2–4]

Potential risk factors for AD include genetics, socioeconomics, lifestyle, and cardiovascular health.[5–7] Despite these, age still represents the largest risk factor for sporadic AD.[1] After the age of 65, the risk of developing the disease doubles every 5 years, reaching 32% of individuals over the age of 85.[8] In particular, many processes associated with normal aging, including neurodegeneration but also neuroinflammation, astrocytic dysfunction, and neurovascular changes, are also involved in AD.[9,10] Of note, research has shown that most brain areas displaying atrophy in AD are also affected in normal aging although to a less extent.[11] However, in most current work, age is typically taken in as a covariate and rarely treated as the variable of interest.[12] Although normal aging and AD show differential functional and structural deficits, it is unlikely that they are in binary opposition. Instead, the distinction between normal and pathological aging falls on a spectrum, and somewhere along this continuum the two may be difficult to tease apart.

An unanswered question is whether signs of accelerated aging are possible early markers for AD. Evidence from more than 1,100 individuals indicates that, although accelerated atrophy is atypical in normal aging, there are several brain regions, including the hippocampus, showing this pattern already in middle age.[13] This is not to say that AD exclusively reflects accelerated aging, but brain regions that show earlier signs of degeneration or more rapid decline in healthy older adults may also be more susceptible to AD. For example, accelerated gray-matter decline can be a sign of increased oxidative DNA damage, which is linked to inflammation and higher susceptibility to neurodegenerative diseases.[14] Similarly, age-related mitochondria dysfunction due to an accumulation of mutations and oxidative stress is detrimental for brain health in normal aging and AD. Finally, other well-known factors associated with aging such as telomere attrition and genomic instability also make the brain more vulnerable to pathology.[14,15]

Table 1
Participants' characteristics

N (Female)	137 (73)
Returning at 1st follow-up	137 (73)
Returning at 2nd follow-up	74* (43)
Age at baseline (Mean ± SD)	74.25 ± 6.12
Age range	56–90
Education (Mean ± SD)	16.64 ± 2.60
Mini Mental State Examination	
Baseline (Mean ± SD)	29.15 ± 1.05
1st follow-up (Mean ± SD)	28.94 ± 1.33
2nd follow-up (Mean ± SD)	29.12 ± 1.13

*Age differences between baseline and follow-up significant at $p < 0.05$.

In the present study, we used a longitudinal sample of 137 healthy older adults obtained from ADNI to investigate possible links between accelerated brain atrophy in healthy aging and AD. Specifically, we hypothesized that (i) brain regions showing accelerated atrophy in normal aging over a 2 year period overlapped with those known to be involved in AD based on previous work and (ii) accelerated decline in these regions was also linked to Aβ burden, which starts accumulating in the brain decades before disease onset.

MATERIALS AND METHODS

Sample characteristics

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). ADNI was launched in 2003 and led by Michael W. Weiner. The main goal was to develop and validate biomarkers for early detection and treatment of AD (for details see http://adni.loni.usc.edu). We included a sample of 137 cognitively normal (CN) participants, who had longitudinal volumetric data over a 2-year period. For additional details on subjects' characteristics see Table 1.

Specifics on the overall inclusion and exclusion criteria can be found elsewhere.[16] Informed consent was obtained from all participants or their authorized representatives. In our study, we included participants who had preprocessed longitudinal volumetric data. From the initial ADNI sample ($N = 2,261$), we excluded those without complete structural MRI status (i.e., failed or only partial preprocessing), leaving a sample of 938 at baseline. Of these, 130 had AD according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associ-

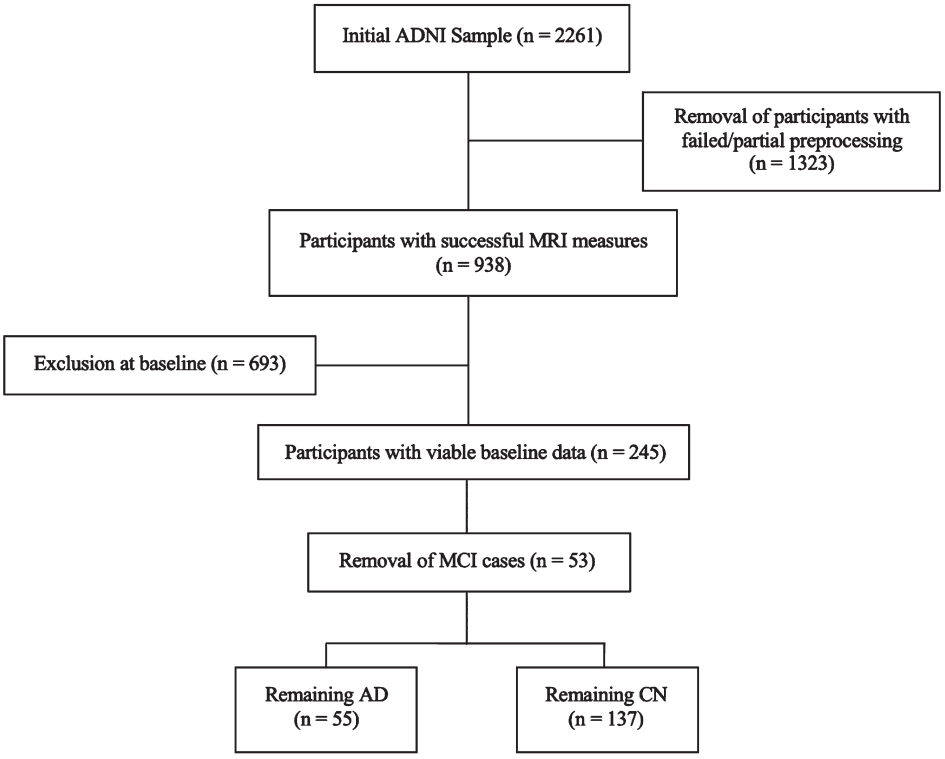

Fig. 1. Flowchart of participants included in the study.

ation (NINCDS/ADRDA) criteria and 808 were CN or had mild cognitive impairment (MCI). We only analyzed subjects who had viable baseline and follow up data, thus excluding 693 participants. From the remaining 245 subjects, we removed subjects with MCI ($N = 53$) leaving 137 CN individuals who remained healthy throughout the study interval. In order to compare the degree of overlap between CN and AD, we also included 55 AD cases who were already diagnosed at baseline. From our CN sample, 17 developed MCI and 2 developed AD within 6 years past the study timeframe. For an overview of the sample included, see Fig. 1.

Structural MRI

Structural images were acquired from all participants using a standardized 3T protocol in a GE, Siemens, or Phillips scanner with a 32-channel coil. Cortical reconstruction and volumetric segmentation were performed with FreeSurfer (version 5.1) by the UCSF Medical Center team and are available on the ADNI website.[17] For further details regarding MRI acquisition, preprocessing pipeline, and quality control procedures, please see the UCSF FreeSurfer Methods (https://adni.bitbucket.io/reference/docs/UCSFFSX51/UCSF%20FreeSurfer%20Methods%20and%20QC_OFFICIAL.pdf). Gray matter volumes of 86 cortical and subcortical regions from the FreeSurfer parcellation were used for subsequent analyses.

Aβ PET

Aβ PET imaging analysis was performed at the University of California, Berkeley using 18F-AV-45 (florbetapir). Details on PET acquisition protocols are also freely accessible on the ADNI website (http://adni.loni.usc.edu/methods/pet-acquisition/). The images were preprocessed and normalized by the whole cerebellum using standard Freesurfer-based processing methods (http://adni.loni.usc.edu/methods/pet-analysis-method/).[18,19]

Statistical analyses

Annual percent change in gray-matter volume was computed for each region using one or two year(s) according to data availability by calculating $PC_{x-y} = \left(\frac{(\text{End volume} - \text{Initial volume})}{\text{Initial volume}}\right) \times 100$.

Table 2
Annual percent change in regions showing decline above 0.5 SD in CN individuals

Brain region	CN	
	Left	Right
Accumbens area	–1.774	–1.385
Amygdala	–2.063*	
Caudal anterior cingulate	–1.295	
Fusiform	–1.144*	
Hippocampus	–1.435*	–1.298*
Inferior parietal	–1.297*	–1.368*
Inferior temporal	–1.058*	–1.219*
Lingual	–1.191	
Middle temporal	–1.188*	
Pallidum	–1.236	
Parahippocampal		–1.414*
Precentral	–1.199	
Precuneus	–1.132^†	–1.238
Superior frontal		–1.059^
Superior parietal	–1.413	–1.518*
Superior temporal sulcus		–1.415*^
Transverse temporal		–1.043^

Above 0.5 SD of whole brain average in controls = –1.043%. *Overlapped with AD (>0.5 SD). ^Showed accelerated brain volume decline. †Linked to amyloid accumulation.

Brain regions were then ranked from those showing the highest annual brain decline to those showing the lowest. In addition to measuring volumetric decline in CN individuals, we carried out the same calculations in a group of AD participants so that we could compare the percentage of brain regions with faster than average decline that overlapped between the two samples. For CN individuals, there was a tight range in annual change for different regions (between –0.020628 and 0.013484%) and, as such, we focused on those whose decline was greater than 0.5 standard deviation (SD) from the whole brain average.

Annual percent change in CN individuals indicated which parts of the brain showed consistently faster than average decline. However, our main aim was to examine whether this decline accelerated over time. To investigate this question, we analyzed the 23 regions showing > 0.5 SD using linear mixed-effects (LME) models in R (version 1.3.1056). This method allows us to account for a different number of observations across subjects. A separate model was computed for each of the brain regions in order to characterize individual trajectories of change in CN participants. Mean-centered baseline age was used as the fixed effect, while time, sex, and intracranial volume (ICV) were added as covariates. We included an interaction term (age x time) which could capture differences in longitudinal change between individuals of different ages. Random effects were used to extract the corresponding slopes and intercepts of each model, allowing for participant-to-participant variability. The intercepts were taken to reflect the baseline relationship between the variable of interest (i.e., volume) and age, whereas slopes were used to indicate change in the same variable over time. Our main outcome of interest were regions showing negative age by time interactions. To further explore the trajectory of age-related changes, we applied generalized additive mixed models (GAMM) using the gamm4 package in R.[20,21] This fits the association between volume and age semi-parametrically and allowed us to illustrate each participant's trajectory.

After this, we focused on whether there were associations between change in accelerated volume decline (e.g., negative age by time interactions) and increased Aβ accumulation. A total of 79 participants had longitudinal PET data. We computed LME models for these subjects in brain regions showing negative interactions for volume. We extracted intercept and slope for volume and Aβ models and ran pairwise association tests.

RESULTS

Annual brain volume decline in CN individuals

We first investigated the degree of overlap between regions showing faster than average decline in CN individuals and AD patients. Ranking the brain regions based on decline alone, two brain regions showed the strongest atrophy in both groups; the left amygdala (1st in CN and 2nd in AD) and left hippocampus (4th in CN and 3rd in AD). Our findings further indicated that, in CN individuals, 23 regions showed a decline 0.5 SD (–1.0429%) above the whole brain average. The same strategy was followed for AD cases, which resulted in 27 regions declining 0.5 SD above the whole brain average (Supplementary Material). Of those brain regions, 12 were common between CN and AD participants, corresponding to a 52% overlap. For details on annual percent change estimates in the CN group, see Table 2.

Accelerated brain volume decline in CN individuals

We further examined whether the 23 regions identified above not only showed consistently fast

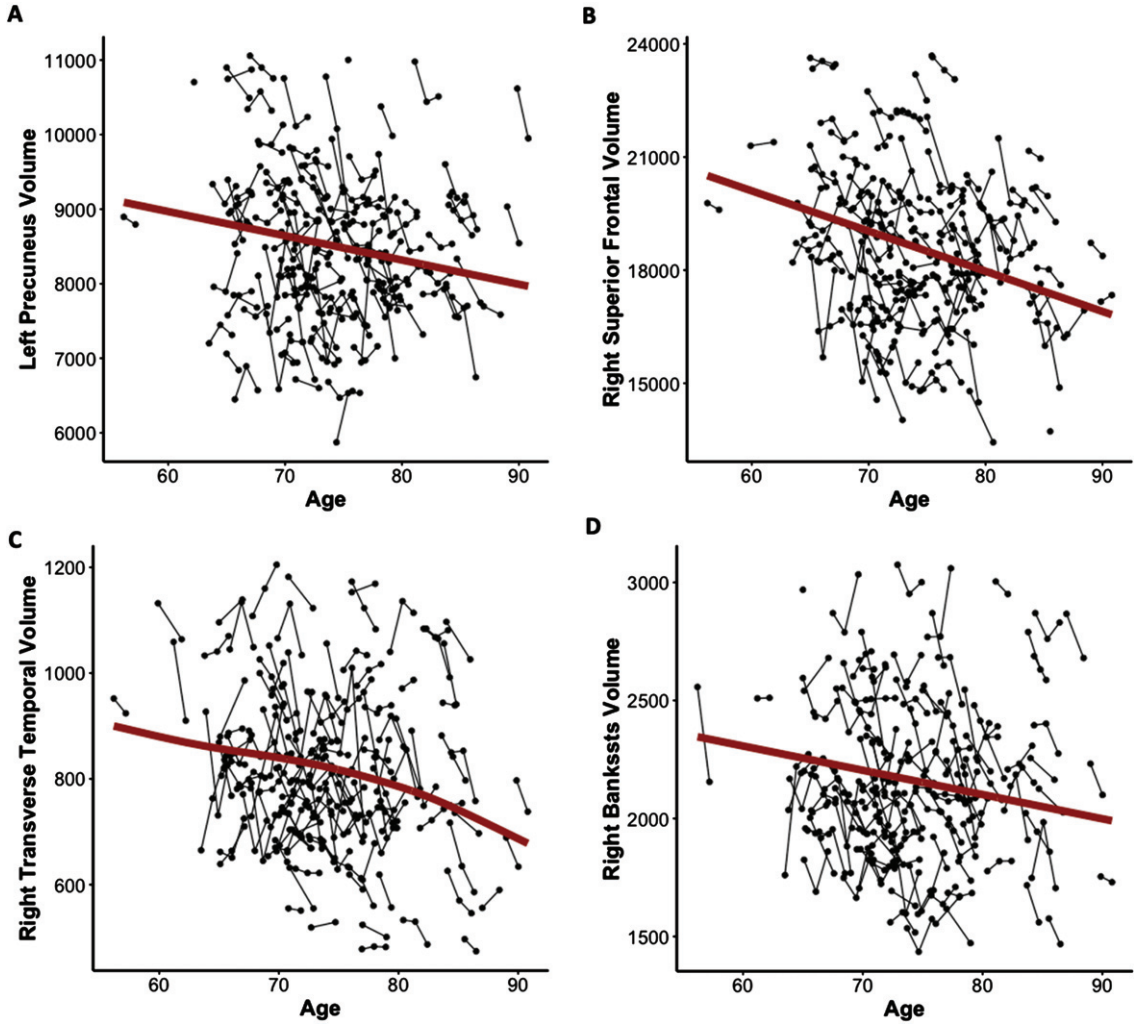

Fig. 2. Individual trajectories for decline in gray matter in the (A) left precuneus, (B) right superior frontal gyrus, (C) right transverse temporal gyrus, and (D) right superior temporal sulcus. The bold line indicates mean change.

decline, but also whether this decline accelerated over time, as indicated by significant age by time interactions with negative coefficients in our LME models. The majority of brain regions displayed steady degeneration over the 2-year follow-up period (Supplementary Table 1), suggesting that the level of atrophy was identical throughout the investigated time period. However, there were four regions for which decline became significantly steeper over time (Fig. 2).

These regions were the left precuneus ($\beta = -8.750$, $p = 0.028$), right superior frontal gyrus ($\beta = -16.353$, $p = 0.0184$), right transverse temporal gyrus ($\beta = -0.201$, $p = 0.001$), and right temporal sulcus ($\beta = -2.656$, $p = 0.0469$). For additional details, see Table 3. In these regions, decline became steeper over time and it was also more pronounced in older individuals.

Links to Aβ accumulation

Finally, we set out to investigate if, among the regions showing age by time interactions, there were significant increases in Aβ load. From the sample of CN individuals, 79 had longitudinal PET Aβ data. First, we computed LME models for the four regions of interest (see Table 4). We found a change–change association between decrease in volume and increase in Aβ for the precuneus ($r = -0.207$, $p = 0.04$; Fig. 3). Furthermore, Aβ increase was associated with baseline volume ($r = 0.243$, $p = 0.019$) for this region. No other regions showed significant associations.

Table 3
Volume LME estimates for each of the brain regions showing accelerated brain volume decline

Brain region	Predictor	Coefficient	*SE*	*t*	*p*
Left precuneus	Age	–20.212	14.1005	–1.433	0.154
	Time	578.820	294.560	1.965	0.051
	Age x time	–8.750	3.967	–2.205	0.029*
	ICV	0.003	0.001	6.504	<0.001**
	Sex	206.828	161.5356	1.280	0.203
Right superior frontal	Age	–78.788	25.569	–3.081	0.003*
	Time	1037.040	507.722	2.043	0.042*
	Age x time	–16.253	6.840	–2.376337	0.018*
	ICV	0.006	0.001	6.143	<0.001**
	Sex	719.649	313.182	2.298	0.023*
Right transverse temporal	Age	–2.346	2.190	–1.071	0.286
	Time	140.394	44.731	3.139	0.002*
	Age x time	–2.009	0.603	–3.334	0.001*
	ICV	0.000	0.000	2.614	0.010*
	Sex	51.114	26.656	1.918	0.057
Right superior temporal sulcus	Age	–2.475	5.002	–0.495	0.622
	Time	173.089	98.667	1.754	0.081
	Age x time	–2.656	1.329	–1.999	0.047*
	ICV	0.001	0.000	3.550	0.001**
	Sex	62.520	62.355	1.003	0.318

*$p < 0.05$; **$p < 0.001$.

Table 4
Amyloid LME estimates for each of the brain regions showing accelerated brain volume decline

Brain region	Predictor	Coefficient	*SE*	*T*	*p*
Left precuneus	Age x time	0.009	0.003	2.507	0.014*
	Age	0.006	0.005	1.121	0.266
	Time	–0.602	0.255	–2.358	0.021*
	Sex	–0.026	0.066	–0.392	0.696
	ICV	0.000	0.000	1.047	0.298
Right superior frontal gyrus	Age x time	0.007	0.004	1.805	0.075
	Age	0.003	0.004	0.647	0.520
	Time	–0.491	0.286	–1.718	0.090
	Sex	–0.054	0.046	–1.174	0.244
	ICV	0.000	0.000	1.049	0.297
Right transverse temporal gyrus	Age x time	0.003	0.002	1.469	0.146
	Age	0.009	0.004	2.050	0.044*
	Time	–0.206	0.148	–1.388	0.169
	Sex	–0.058	0.057	–1.030	0.306
	ICV	0.000	0.000	1.158	0.251
Right temporal sulcus	Age x time	0.007	0.004	1.551	0.125
	Age	0.005	0.005	1.144	0.256
	Time	–0.456	0.319	–1.427	0.158
	Sex	–0.079	0.055	–1.437	0.155
	ICV	0.000	0.000	0.894	0.374

*$p < 0.05$.

DISCUSSION

In this study, we identified brain regions displaying accelerated decline in gray matter volume over a period of 2 years in healthy older adults. Our goal was to examine if these regions overlap with those known to be traditionally associated with AD and investigate if this decline was further linked to increased Aβ burden over the same time period. Several factors impact the aging brain, including cardiovascular health, myelin loss, astrocytic disfunction, alterations in neurotransmission, neuroinflammation, and gene expression. These changes are part of normal aging but can also lead to increased vulnerability to AD dementia.[11] In fact, brain aging that deviates from one's expected chronological age has been previously linked to AD and cognitive decline.[22,23] In a study by Glorioso et al. (2019),[24] older brain age was associ-

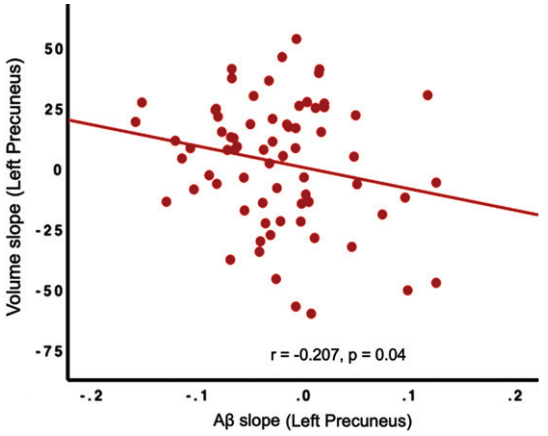

Fig. 3. Scatterplot showing a chang–change association between volume and Aβ in the left precuneus.

ated with an increase in AD cases, whereas younger age was protective even in the presence of APOE ε4. Our findings indicate that the left precuneus, right superior frontal gyrus, right transverse temporal gyrus, and right superior temporal sulcus display significant accelerated decline in healthy aging and might be associated with early signs of AD. These regions are among those known to be hallmarks of the disease, with our study further showing an association between accelerated decline in the left precuneus and increasing Aβ accumulation. Given that previous work has found large early Aβ accumulation in the precuneus, this supports our hypothesis linking gray-matter decline to AD pathology.

The hippocampus and amygdala were among regions showing the strongest overlap between CN and AD patients. These, together with other limbic regions, are well-known early predictors of AD.[25,26] This overlap is promising and suggests that fast (>0.5 SD) volume decline can serve as a benchmark of age-related pathological processes even in healthy individuals. Still, our findings show that a total of 23 regions decline quickly in older adults, but not that this decline accelerates over time. Given that we were interested in identifying interactions between aging and AD, we analyzed these regions using LME models to capture non-linear trajectories of decline.

Four regions were identified as displaying accelerated decline measured using age by time interactions in the LME models. These regions have well-established relevance in the field of AD. Firstly, regional dysfunction in the precuneus is an indicator of future AD pathology, as it displays early accumulation of Aβ and neurofibrillary tangles, but also disproportioned atrophy at relatively younger ages.[27,28] In our study, we also found a change–change association between volumetric decline in the precuneus and Aβ accumulation, suggesting an interaction between accelerated brain aging and AD. In addition, this region is considered one of the main hubs of the default mode network (DMN), which has been widely linked to AD diagnosis and progression[29] and is a prominent location for neuroinflammation.[30] In fact, disconnection of the precuneus precedes and contributes to regional brain atrophy in early AD stages.[31] Similarly, the superior frontal gyrus is part of the DMN, where the first signs of Aβ buildup occur.[27,32] Since it is involved in a myriad of cognitive domains, this region is one of those showing highest age-related decline which predicts risk of cognitive impairment as well as dementia.[33]

Early annual Aβ accumulation has been seen in the transverse temporal gyrus.[27] In a study investigating cortical spreading of tau and Aβ in AD, the authors found that Aβ was most frequently observed in the frontotemporal cortices, including the superior frontal gyrus, spreading through the neocortex afterwards.[32] This region is also the auditory center of the brain and has been linked to memory registration,[34] with AD patients showing reduced activity during short-term memory recognition.[35] Still, the most established theory relating the transverse temporal gyrus to AD is that hearing deprivation leads to social isolation which, therefore, can increase the risk of dementia.[36] Compared to healthy older adults, individuals at risk for AD also exhibit reduced glucose metabolism in the right transverse temporal gyrus as well as in the precuneus, among other areas.[37] This could indicate that this region functions as a possible indicator of future AD.

Lastly, the superior temporal sulcus displays high AD-pathology burden early on the disease stage,[38,39] with evidence further indicating that healthy individuals with high Aβ are at increased risk of cognitive decline.[38] This region appears to be especially successful as an MRI marker of AD,[3,28] but recent work also shows that regional Aβ PET in the superior temporal sulcus may be more sensisitve than global SUVR for detecting early Aβ deposition.[38] Importantly, this region is vulnerable to neurotoxicity and exhibits very early glucose hypometabolism.[40,41] Given that signs of oxidative stress and altered glucose metabolism are also part of the normal aging process, our findings suggest that there may be a direct link between accelerated gray-matter decline in healthy older adults and pathological processes

in AD.[42] Both the precuneus and superior temporal regions, and to a lesser extent the superior frontal gyrus, are known brain network hubs central to cognitive functions, neural integration, and communication.[43] Their highly demanding functional role is linked to increased metabolic demands and, consequently, might result in faster aging or higher vulnerability to early signs of brain aging. There is also work showing interactions between time and Aβ as well as tau in the superior temporal sulcus and precuneus.[41] This research indicates that the link between tau and volumetric measures might be distinct from that of Aβ. Such results could explain why only atrophy in the precuneus was associated with increased Aβ burden. They also indicate that greater atrophy could predict future Aβ or tau PET. This can occur as a consequence of MRI atrophy categorized by neuronal dysfunction and reduced dendritic branching being present before tau tangles mature.[41]

In summary, our results suggest that, across the brain, four regions are most impacted by age-related processes which makes them more susceptible to neuropathology. However, only the precuneus displayed a change–change association with Aβ. One explanation for this is sample heterogeneity. AD is a multifactorial condition, with only 55% of cases displaying signs of typical AD.[44] Trajectories for different AD subtypes may become more noticeable closer to diagnosis. Secondly, it could be that some regions are more sensitive to signs of regional tau accumulation but these data were not available. Given the sample size, we cannot make claims regarding laterality of these four regions. Although evidence is mixed, there is work suggesting that increased AD burden in the right hemisphere may increase the risk of dementia.[45] In our study, there were not considerable differences in the degree of decline between hemispheres. Most of the brain regions reported showed lower decline in the left hemispheric but the difference was smaller than 0.03%. This might be indicative that the same process is expected in both hemispheres but slightly delayed in the left side of the brain. Overall, postponing disease onset by even a year through behavioral or drug-related approaches has benefits for individuals and can reduce economical costs. Our study suggests that identifying regions with accelerated decline in healthy older adults provides important insights regarding early predictors of AD. By focusing on commonalities between AD and normal aging, instead of ignoring them, we were able to pinpoint four regions that can potentially be used to detect at-risk healthy individuals.

AUTHOR CONTRIBUTIONS

Bárbara Avelar Pereira (Conceptualization; Formal analysis; Writing – original draft; Writing – review & editing); Curran Phillips (Data curation; Formal analysis; Methodology; Validation; Visualization; Writing – review & editing); S. M. Hadi Hosseini (Conceptualization; Funding acquisition; Investigation; Methodology; Validation; Writing – review & editing).

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CONFLICT OF INTEREST

Hadi Hosseini is an Editorial Board Member of this journal but was not involved in the peer-review process nor had access to any information regarding its peer-review. All other authors have no conflict of interest to report.

DATA AVAILABILITY

Data used in the preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu) and are available upon request. All code related to analyses of the manuscript will also be available upon request.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-231458.

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