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RESEARCH ARTICLE

Association between structural brain MRI abnormalities and epilepsy in older adults

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Abstract

Objective: To determine the association between brain MRI abnormalities and incident epilepsy in older adults. **Methods**: Men and women (ages 45–64 years) from the Atherosclerosis Risk in Communities study were followed up from 1987 to 2018 with brain MRI performed between 2011 and 2013. We identified cases of incident late-onset epilepsy (LOE) with onset of seizures occurring after the acquisition of brain MRI. We evaluated the relative pattern of cortical thickness, subcortical volume, and white matter integrity among participants with incident LOE after MRI in comparison with participants without seizures. We examined the association between MRI abnormalities and incident LOE using Cox proportional hazards regression. Models were adjusted for demographics, hypertension, diabetes, smoking, stroke, and dementia status. **Results**: Among 1251 participants with brain MRI data, 27 (2.2%) developed LOE after MRI over a median of 6.4 years (25–75 percentile 5.8–6.9) of follow-up. Participants with incident LOE after MRI had higher levels of cortical thinning and white matter microstructural abnormalities before seizure onset compared to those without seizures. In longitudinal analyses, greater number of abnormalities was associated with incident LOE after controlling for demographic factors, risk factors for cardiovascular disease, stroke, and dementia (gray matter: hazard ratio [HR]: 2.3, 95% confidence interval [CI]: 1.0–4.9; white matter diffusivity: HR: 3.0, 95% CI: 1.2–7.3). **Interpretation**: This study demonstrates considerable gray and white matter pathology among individuals with LOE, which is present prior to the onset of seizures and provides important insights into the role of neurodegeneration, both of gray and white matter, and the risk of LOE.

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Introduction

The incidence of epilepsy among persons over the age of 65 years is roughly double that among those under 65[1] and the burden of epilepsy in older adults is likely to grow, as the 65-and-older population is one of the fastest growing cohorts worldwide.[2] Despite this, there remains a misperception that seizures are uncommon in older adults.[1] Late-onset epilepsy (LOE) is commonly associated with both cerebrovascular and neurodegenerative diseases, and in the case of dementia, the relationship is thought to be bidirectional.[2,3] Although the clinical scenario of seizures as a late complication of dementia is well known, more recent evidence points to an epileptic prodromal variant of dementia where seizures represent the initial manifestation of a neurodegenerative process.[4,5]

There is mounting evidence linking epilepsy with neurodegeneration, even among younger people. In a large scale effort at quantifying structural brain abnormalities in over 2000 individuals with epilepsy using structural MRI, the ENIGMA-Epilepsy working group found widespread patterns of cortical and subcortical gray matter atrophy in both focal and generalized epilepsies.[6] Unfortunately, patients over the age of 55 were not included in this study and the cross-sectional design limits inferences about the directionality of the association between brain atrophy and epilepsy. In a longitudinal study by Galovic et al.,[7] the yearly rate of cortical thinning was greater in people with focal epilepsy than controls, with faster rates of decline by age: epilepsy patients <55 years old had double the rate of thinning of controls, and those 55–75 years old had a fourfold greater rate of thinning relative to controls.

Gray matter lesions are classically implicated in epilepsy. However, emerging evidence indicates that epilepsy is also a disorder of abnormally distributed brain networks.[8–10] White matter fiber tracts constitute the structural connections required for optimal function of brain networks and the integrity of these tracts can be inferred from diffusion MRI. Several studies utilizing diffusion MRI reveal widespread white matter abnormalities in both focal and generalized epilepsies.[11] Recent work by the ENIGMA-Epilepsy working group utilizing diffusion tensor imaging to characterize white matter microstructure in 1249 individuals with epilepsy under the age of 55 showed widespread abnormalities in white matter tracts across all forms of epilepsy, with the largest effect sizes in the corpus callosum, cingulum, and external capsule.[12] This was also a cross-sectional study, which limits any inferences as to whether these widespread white matter abnormalities represent a fundamental pathologic element underlying epileptogenesis or a consequence of epileptic seizures.

The vast majority of studies linking epilepsy and neurodegeneration are cross-sectional. Hence, we sought to determine the directionality of the association between structural brain MRI based measures of gray and white matter pathology and epilepsy in older adults, among participants from the population-based Atherosclerosis Risk in Communities (ARIC) Study. Subjects enrolled in ARIC are followed longitudinally over time and are extensively phenotyped for two factors known to influence epilepsy risk as well as gray and white matter integrity: cerebrovascular disease and neurodegenerative diseases. This study focuses on the subset of ARIC participants who underwent a structural brain MRI between 2011 and 2013. Thus, ARIC offers a unique opportunity to understand the directionality of the association between gray and white matter abnormalities and epilepsy among older adults.

Methods

Study population

Men and women between the ages of 45 and 64 years were recruited to ARIC from 1987 to 1989 from four communities in the United States (Forsyth County, North Carolina; suburbs of Minneapolis, Minnesota; Jackson, Mississippi; and Washington County, Maryland) using probability sampling.[13] Participants underwent an in-person examination at seven visits between 1987 and 2019, with additional visits ongoing, and were contacted yearly via telephone (with semiannual calls beginning in 2012) with continuous surveillance for hospitalizations. In the fifth in-person ARIC visit was the first ARIC Neurocognitive Study (ARIC-NCS) visit, taking place in 2011–2013; brain MRI was performed in a subset of participants (those having had prior MRI, low cognitive scores, or chosen as part of an age-stratified random sample cut at <80 vs. >=80).[14] Due to small numbers and race/center aliasing in ARIC (i.e., only Blacks enrolled at Mississippi and mainly Whites enrolled at Maryland/Minnesota), we excluded participants

of races other than Black or White (n = 6), and Black participants from Minnesota and Maryland (n = 3). The ARIC-NCS Visit 5 MRI was performed between 2011 and 2013, with a 3T MRI obtained at an imaging facility associated with each field center on 1978 participants.[15] MRI was of sufficient quality for analysis in 1960 participants for structural MRI and 1940 participants for diffusion MRI. 640 participants did not have sufficient follow-up information after Visit 5 and were excluded from further analysis. Participants with missing variables (n = 24) at analysis baseline (Visit 5) were also excluded.

Standard protocol approvals, registrations, and patient consents

The institutional review boards at all participating institutions approved the study, and all participants or legally authorized proxies provided written informed consent at each study visit.

Outcome ascertainment

Late-onset epilepsy was defined using ICD-9/10 codes from any setting for epilepsy, seizures, or convulsions (ICD-9: 345.* or 780.39, ICD-10: R56.8, G40) in ARIC hospitalization records or in Medicare claims data (outpatient, inpatient, and carrier claims files). We used diagnosis code data from Centers for Medicare & Medicaid Services (CMS) Medicare fee-for-service (FFS) data from 1991 to 2018. ARIC participant data were linked to CMS data using birthdate, sex, and social security number.[16] We included participants with two or more ICD-9 codes from separate visits (1 outpatient and 1 inpatient claim, 2 separate inpatient claims, or 2 claims for separate outpatient visits from the Carrier and outpatient claims) with the first seizure-related code occurring after at least 2 years of data without a seizure-related code. There was no minimum time period between codes. Hence, age 67 was the earliest age at which a participant could meet the definition for LOE. We included only participants with at least 2 years of Medicare FFS enrollment. We excluded participants with a single seizure-related code (n = 12) and those with a first seizure-related code prior to the date of the visit five MRI (n = 24). To focus on the two main etiologies of LOE (i.e., cerebrovascular disease and dementia) we excluded individuals with the following preexisting neurological conditions: history of brain tumor, brain surgery, brain radiation, and multiple sclerosis.

Covariates

For this analysis, we used covariates ascertained from information collected at Visits 1 and 5. Visit 1 variables include date of birth, sex, race, and education and were self-reported. Blood pressure (BP) at Visit 5 was measured three times, and the second and third values averaged; hypertension was defined as mean systolic BP $\geq$ 140 mm Hg, mean diastolic BP $\geq$ 90 mm Hg, or use of antihypertensive medication. Diabetes was defined as fasting blood glucose $\geq$126 mg/dL, non-fasting blood glucose $\geq$200 mg/dL, HbA1c >= 6.5%, use of insulin or antidiabetic medication, or self-report of physician-diagnosed diabetes. Participants self-identified as never, former, or current smokers. Prevalent stroke information on all ARIC participants was collected at Visit 1 by participant report, and incident stroke information was collected from hospitalization records and adjudicated by expert physician reviewers and computer algorithm during study follow-up.[17] Dementia diagnosis was made at Visit 5 by expert review, using neurocognitive assessments and informant interviews, and also incorporated surveillance data and telephone interviews.[18]

Cerebrovascular disease assessment

A trained image analyst evaluated each MRI for presence, size, and location of cerebral infarctions as well as microbleeds and areas of superficial siderosis. Findings were confirmed by a neuroradiologist.

Imaging processing and analysis

For structural MRI, cortical reconstruction and volumetric segmentation were performed on each participant's MPRAGE with FreeSurfer (version 5.1.0).[19] All results were visually inspected by a trained MR image analyst. We extracted mean values from the following regions in the Desikan-Killiany atlas: volumetric measures for 12 subcortical regions (left and right amygdala, caudate, nucleus accumbens, pallidum, putamen, thalamus, hippocampus, lateral ventricle) and cortical thickness for 34 left-hemispheric and 34 right-hemispheric regions.[20] Subcortical volumes were scaled by estimated total intracranial volume using the residual approach as described by Voevodskaya et al.[21]

For diffusion MRI, processing was performed on an axial DTI sequence with 2.7 mm isotropic voxel size and 64 directions at b = 1000 s/mm^2. Mean diffusivity (MD) and fractional anisotropy (FA) maps were created from a tensor fit using a weighted least squares algorithm.[22] Median MD and FA values were next extracted from regions of interest from the 2009 Johns Hopkins University single subject ("Eve") atlas.[23] Brainstem and gray matter regions were excluded from analysis. Twelve cerebral white matter regions of interest were not analyzed due to missing data in more than 3% of the cohort.

Cortical thickness, subcortical volume, and cerebral white matter FA and MD were then separately harmonized using ComBat, a batch effect removal technique that removes acquisition and processing differences while retaining the effects of biology (e.g., age, sex, and group).[24] We set ARIC center as the batch effect and age, sex, and diagnosis of seizure, stroke, and dementia were used as biological phenotypes of interest.

We utilized a spatial normative modeling framework to delineate participant-level variability in gray and white matter regions.[25–27] This process is summarized in Figure 1. Principally, this involves estimating the degree of deviation from a normative cohort. To do this, we constructed a normative cohort from Visit 5 MRI data from ARIC participants without LOE. We included all participants without seizures, including those with stroke and dementia, to account for the effects of demographics and neurological disorders on brain structure in the normative cohort. For this normative cohort, we constructed a reference distribution for each of the 68 cortical and 16 subcortical regions in the Desikan-Killiany atlas. Similarly, we constructed a reference distribution for each of the 70 white matter regions in the Johns Hopkins University atlas. For each region, we fit a linear regression model predicting the neuroimaging variable (i.e., mean cortical thickness or subcortical volume for structural regions, median FA or MD for white matter regions) using age and sex as predictors. For each region in each participant, we determined the distance between the mean of the participant's neuroimaging variable from the least square line from the above normative model. The distance was expressed as a z-score by subtracting the mean of the normative cohort and dividing by the standard deviation of the normative cohort. The region was considered an outlier if the z-score exceeded 1.96 (−1.96 for cortical thickness, subcortical volume, and FA; +1.96 for lateral ventricle volume and MD). For cortical thickness, gray matter volume, and FA only *z*-scores below −1.96 were considered abnormal. Lower *z*-scores are considered abnormal and reflect cortical thinning, subcortical gray matter atrophy, and abnormal white matter microstructure, respectively. For lateral ventricle volume and MD, only *z*-scores above +1.96 were considered abnormal, reflective of ventriculomegaly, and abnormal white matter diffusivity, respectively.

The number of outliers were then summed across the 68 cortical and 16 subcortical regions to give an aggregate burden of gray matter outliers (max number of outliers = 84). Similarly, for both FA and MD, the number of outliers were summed across the 70 white matter regions of interest to give an aggregate burden of white matter outliers for both FA and MD, respectively. We used a similar approach to determine the proportion of participants with cortical thinning in a composite ROI, including bilateral precuneus, parahippocampal gyrus, entorhinal cortex, and inferior parietal lobules, known as the temporal parietal meta-ROI. These regions were selected based on prior studies demonstrating a predilection of these regions to atrophy among those with Alzheimer's pathology.[28,29]

Data analysis

Statistical analysis was performed with Stata 17.0 software (StataCorp, College Station, TX, USA) and MATLAB 2022a (MathWorks, Natick, MA, USA). A two-sided *P*-value of 0.05 was considered statistically significant. For group comparisons, we used a Wilcoxon rank-sum or chi-squared /Fisher's exact test. For comparison of regional outlier proportions, given the large number of regions (i.e., 68 cortical regions, 16 subcortical regions, 70 white matter regions), we present results after false discovery rate correction using the Benjamini–Hochberg method[30] with $P < 0.05$ considered statistically significant. For visualization purposes, regions with statistically significant differences in the proportion of outliers were mapped to the template brain (the ENIGMA toolbox[31] was used for gray matter regions). To analyze the longitudinal association between the aggregate burden of outliers with incident LOE, we used survival analysis with a Cox proportional hazards model to estimate the hazard ratio (HR) for risk of LOE, using the Visit 5 MRI date as the origin time, and the date of the first seizure code as the event time failure. Participants were censored at date of death or last ARIC or CMS contact as of 2018. First-level models were adjusted for age, gender, and race. Although it is typical in ARIC studies to include field center as a covariate, the small number of participants with LOE precluded this. Second level models were additionally adjusted for education level, hypertension, diabetes, and smoking status. Each first- and second-level model was then fit with additional time-varying covariates for stroke and dementia. Therefore, there were four models for each neuroimaging measure: a base model with demographic covariates (Models 1, 2), base model plus additional covariates for educational level, hypertension, diabetes, and smoking status (Models 3, 4). Models 2 and 4 additionally include time-varying covariates for stroke and dementia. We fit one additional model (Model 5), which included covariates from Models 3 and 4 along with additional covariates for prevalent stroke and neurocognitive status at Visit 5 (i.e., normal, mild cognitive impairment, or dementia). We also performed two sensitivity analyses to ensure robustness of findings. First, we fit the above Cox models (Models 1–4) using (1) a more liberal definition of LOE after Visit 5 requiring only one ICD-9/10 code for epilepsy, seizures, or convulsions and (2)

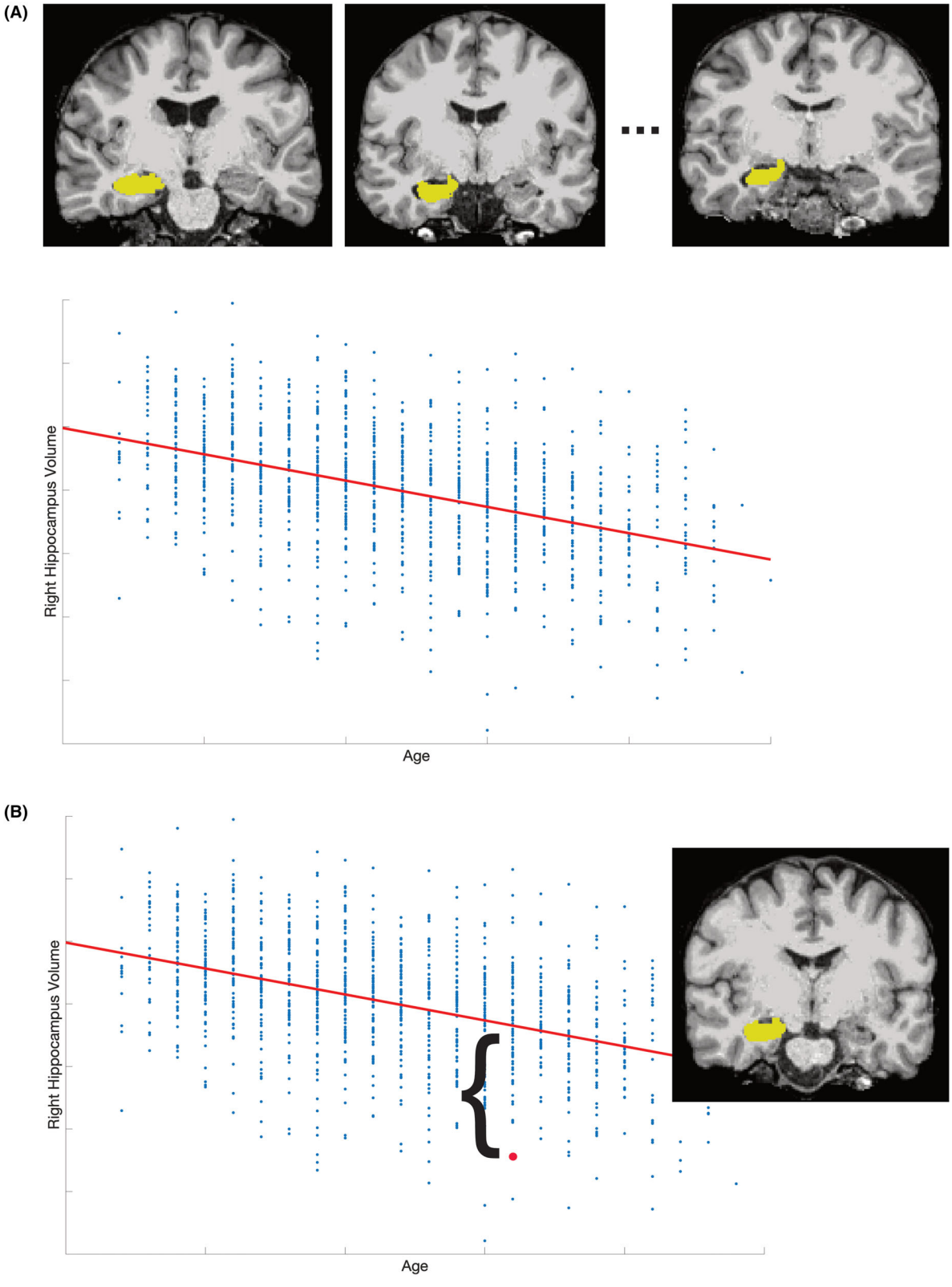

Figure 1. Overview of the spatial normative modeling process. (A) For each neuroimaging feature and region of interest, the mean value is extracted (right hippocampal volume in this case). Utilizing only data from the control cohort (i.e., ARIC participants without seizures), we fit linear regression models predicting the neuroimaging variable of interest (e.g., right hippocampal volume) using participant age and sex as predictors. (B) Next, we determined the distance between the mean of each late-onset epilepsy (LOE) participant's neuroimaging variable from the least square line from the control model. For simplicity, only one LOE participant is shown (red circle). The distance is then converted to a *z*-score by subtracting the mean of the normative cohort and dividing by the standard deviation of the normative cohort. The region is considered an outlier if the *z*-score exceeds 1.96. For gray matter, the process is then repeated for each of the 68 cortical and 15 remaining subcortical regions of the Desikan-Killiany atlas and the number of outliers is totaled to give an aggregate burden of gray matter outliers (max number of outliers = 84). An analogous process is carried out separately for white matter fractional anisotropy and mean diffusivity.

excluding all participants (both with and without LOE) with prevalent stroke or dementia at Visit 5.

Results

The analytic cohort consisted of 1251 individuals (Fig. 2). All 1251 participants had structural MRI of sufficient quality for analysis; however, 20 participants either did not have a diffusion MRI scan or the scan was of insufficient quality. The characteristics of the analytic cohort are shown in Table 1. Twenty-seven participants had incident LOE (at least two seizure-related codes with first code at age 67 or greater) after Visit 5 MRI. Among the 27 participants with LOE, 8 had either clinical or radiologic evidence of a stroke prior to onset of LOE, 18 participants developed mild cognitive impairment or dementia either prior to or after identification of LOE, and 7 participants with LOE had normal neurocognitive status and no evidence of stroke by the end of follow-up (Table S1).

Spatial location of outliers in LOE

The normative distribution for each brain region was modeled using data from participants without LOE (n = 1224 for gray matter regions; n = 1204 for white matter regions). Participant-level deviations at each brain region were next inferred based on distance from the normative data, then the proportion of outliers at each region was compared between those with and without LOE. The proportion of

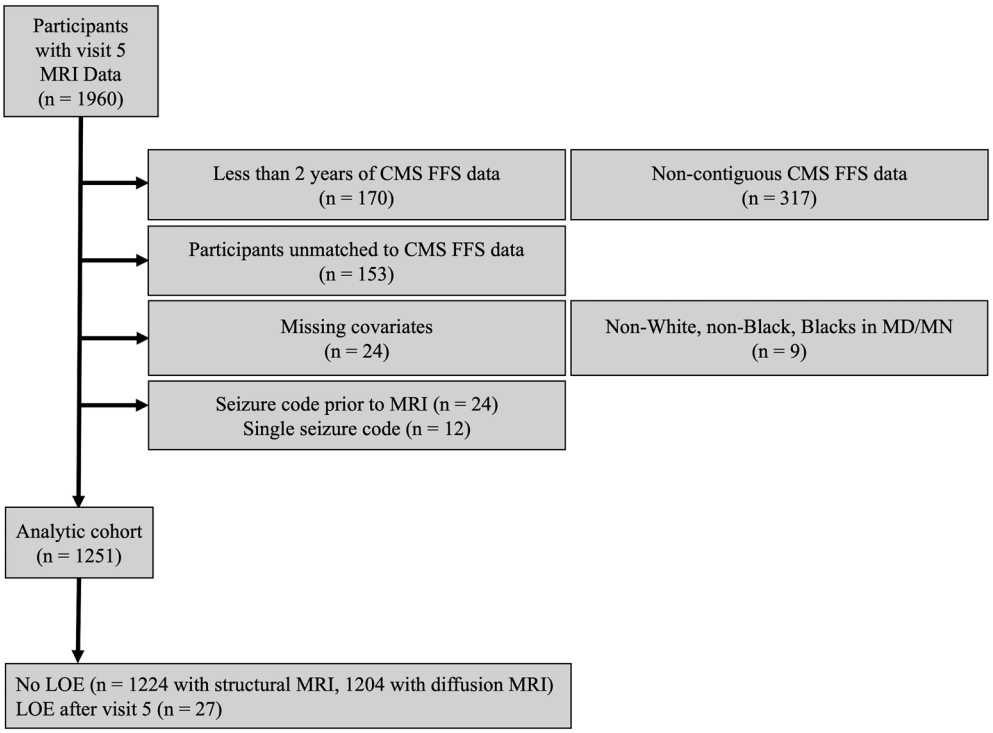

Figure 2. Study flow chart. CMS, Centers for Medicare and Medicaid Services; FFS, fee-for-service; LOE, late-onset epilepsy; MD, Maryland; MN, Minnesota.

Table 1. Demographic information among those with and without LOE after MRI.

	No LOE (n = 1224)	LOE (n = 27)	P-value
Age at Visit 5	76.0 (72.0–81.0)	75.0 (71.0–82.0)	0.9
Sex, female n (%)			
Female	740 (60.5)	13 (48.1)	0.2
Race, n (%)			
Black	291 (23.8)	10 (37.0)	0.1
Field center, n (%)			
Forsyth	271 (22.1)	5 (18.5)	0.5
Jackson	278 (22.7)	9 (33.3)	
Minnesota	287 (23.4)	4 (14.8)	
Washington	388 (31.7)	9 (33.3)	
Education level, n (%)			
<High school	148 (12.1)	4 (14.8)	0.8
High school or equivalent	509 (41.6)	12 (44.4)	
Any college or professional education	567 (46.3)	11 (40.7)	
APOE E4 genotype, n (%)			
1 allele	320 (26.1)	8 (29.6)	0.1
2 alleles	23 (1.9)	2 (7.4)	
Current or former smoker, n (%)	609 (49.8)	11 (40.7)	0.4
Prevalent diabetes, n (%)	388 (31.7)	13 (48.1)	0.07
Prevalent hypertension, n (%)	918 (75.0)	22 (81.5)	0.4
Prevalent head injury, n (%)	367 (30.0)	6 (22.2)	0.4
Prevalent stroke, n (%)	41 (3.3)	2 (7.4)	0.3
Neurocognitive status, n (%)			
Dementia	63 (5.1)	4 (14.8)	0.05
Mild cognitive impairment	414 (33.8)	11 (40.7)	
Normal	747 (61.0)	12 (44.4)	

LOE, late-onset epilepsy.

outliers in participants with and without incident LOE was similar across all subcortical gray matter regions. Among participants with incident LOE, there were 13 cortical regions with a greater proportion of thinning compared to those without LOE. Among those without incident LOE, there were no regions with more cortical thinning compared to participants with LOE (Tables S2 and S3). Areas where the proportion of outliers for cortical thickness differed between those with and without LOE are shown in Figure 3. Among participants with LOE, there were 12 white matter regions with a greater proportion of white matter FA abnormalities compared to those without LOE. In participants without LOE, there were no regions with more white matter FA abnormalities (Table S4). Areas where the proportion of outliers for white matter FA abnormalities differed are shown in Figure 4. Among participants with LOE, there were 25 white matter regions with a greater proportion of white matter MD abnormalities compared to those without LOE. In participants without LOE, there were no regions with more white matter MD abnormalities (Table S5). Areas where the proportion of outliers for white matter MD abnormalities differed are shown in Figure 5. The proportion of outliers in each region is shown in Tables S2–S5.

Aggregate burden of outliers and influence of cerebrovascular disease and neurodegeneration

Table 2 shows the total number of outliers in gray and white matter, the proportion of cortical thinning in the temporal–parietal meta-ROI, and the distribution of cerebrovascular lesions among participants with and without LOE. The median total number of outliers in both gray and white matter was higher among participants with LOE compared to those without. The distribution of cerebrovascular lesions and temporoparietal cortical thinning was overall similar among participants with and without LOE, but participants with LOE had a greater proportion of small subcortical stroke lesions as well as lobar cerebral microbleeds.

Longitudinal analyses

We fit Cox proportional hazards models assessing the risk of incident LOE after MRI according to high versus low outlier count (split at the median). The median follow-up time of the cohort was 6.4 years (25th–75th interval 5.8–6.9) post-brain MRI. After adjusting for demographics, high (vs. low) gray matter and white matter MD outlier counts were associated with development of LOE (Table 3). White matter FA outlier count was not associated with the development of LOE. Results were similar after further adjusting for education, hypertension, diabetes, and smoking. The risk was slightly attenuated but remained significant when stroke and dementia were added to the model as time-varying covariates as well with models including covariates for prevalent stroke and neurocognitive status at Visit 5. We performed sensitivity analyses using a more liberal definition of LOE after Visit 5 requiring only one ICD-9/10 code for epilepsy, seizures, or convulsions, which showed similar findings (Table S6). Results were also similar after excluding all participants with prevalent stroke or dementia. Table S7 shows adjusted hazard ratios for incident LOE among 1145 participants without prevalent stroke or dementia (n = 1124 without LOE, n = 21 with incident LOE).

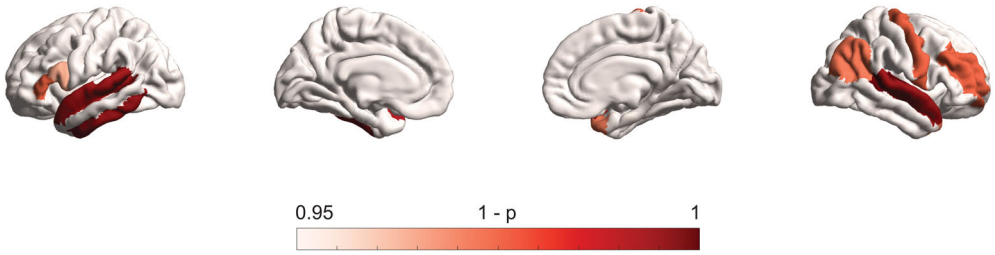

Figure 3. Distinct pattern of cortical thinning in LOE compared to individuals without LOE. Cortical surface map shows group differences in the proportion of outliers between those with and without LOE. Areas with a significantly higher proportion of cortical thinning among those with LOE are shown in color. The color bar highlights statistically significant differences (1−*P*-value) with warmer regions corresponding to lower *P*-values after correction for the false discovery rate. LOE, late-onset epilepsy.

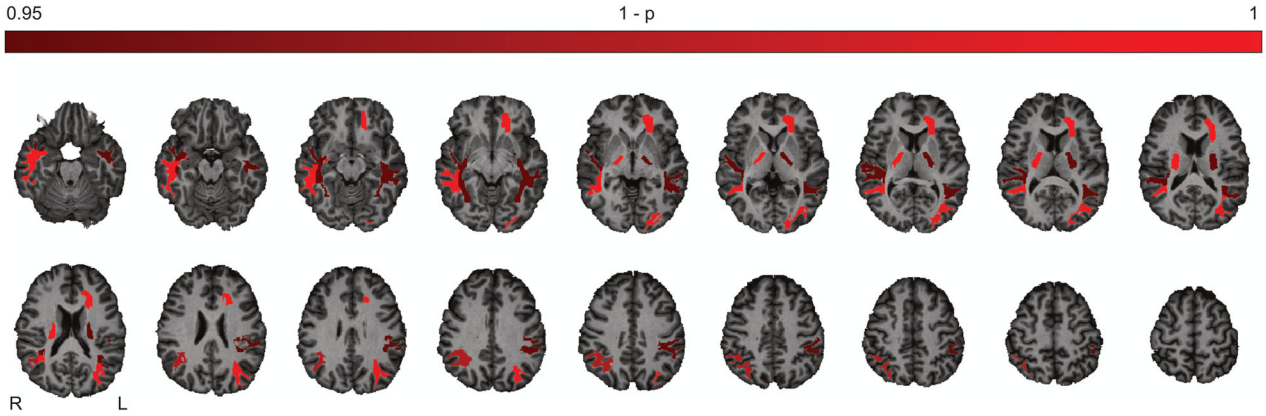

Figure 4. Distinct pattern of white matter FA abnormalities in LOE compared to individuals without LOE. Volumetric map in template space shows group differences in the proportion of outliers between those with and without LOE. Areas with a significantly higher proportion of white matter FA abnormalities among those with LOE are shown in color. The color bar highlights statistically significant differences (1−*P*-value) with warmer regions corresponding to lower *P*-values after correction for the false discovery rate. FA, fractional anisotropy; LOE, late-onset epilepsy.

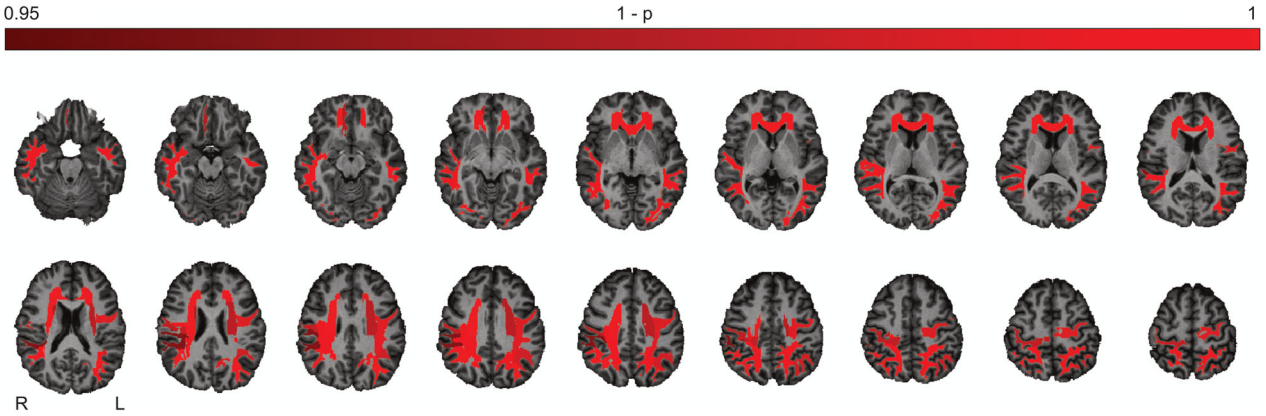

Figure 5. Distinct pattern of white matter MD abnormalities in LOE compared to individuals without LOE. Volumetric map in template space shows group differences in the proportion of outliers between those with and without LOE. Areas with a significantly higher proportion of white matter MD abnormalities among those with LOE are shown in color. The color bar highlights statistically significant differences (1−*P*-value) with warmer regions corresponding to lower *P*-values after correction for the false discovery rate. LOE, late-onset epilepsy; MD, mean diffusivity.

Table 2. Outliers and cerebrovascular lesions by LOE status.

	LOE− (*n* = 1224)	LOE+ (*n* = 27)	*P*-value
Large cortical stroke, *n* (%)	51 (4.2)	1 (3.7)	1.00
Small cortical stroke, *n* (%)	88 (7.2)	5 (18.5)	0.04
Superficial siderosis, *n* (%)	25 (2)	1 (3.7)	0.4
Lobar CMB, *n* (%)	113 (9.2)	6 (22.2)	0.04
Temporoparietal meta-ROI thinning, *n* (%)	43 (3.5)	3 (11.1)	0.07
Total outlier count (gray matter), median IQR	1.0 (0.0–2.0)	2.0 (0.0–9.0)	0.003
Total outlier count (white matter FA), median IQR	0 (0.0–2.0)[1]	2.0 (0.0–6.0)	0.012
Total outlier count (white matter MD), median IQR	0 (0.0–2.0)[1]	3.0 (0.0–13.0)	<0.001

CMB, cerebral microbleed; FA, fractional anisotropy; IQR, interquartile range; LOE, late-onset epilepsy; MD, mean diffusivity; ROI, region of interest.
[1]Non-LOE group (*n* = 1204).

Discussion

The main findings of this study are that participants with incident LOE have considerably higher levels of both gray and white matter pathology, present prior to LOE diagnosis, when compared to demographically similar individuals without LOE. At the group level, the proportion of outliers was higher in white matter (25/70 [36%] areas with abnormally increased diffusivity in LOE) compared to cortex (13/68 [19%] areas with cortical thinning in LOE) or subcortical gray matter (no difference in outlier proportion). In longitudinal analyses, the outlier count for both gray matter and white matter diffusivity were predictive of incident LOE after controlling for demographic factors, risk factors for cerebrovascular disease, stroke, and dementia.

These findings build upon prior work from ARIC linking brain MRI abnormalities with incident epilepsy. Using ARIC Visit 3 MRI data, Johnson et al.[32] demonstrated that white matter hyperintensities (WMHs) are associated with incident LOE. Since the etiology of WMHs is diverse and can include cerebral small vessel disease and dementia, the authors controlled for these covariates. In the model including vascular risk factors as covariates, the hazard ratio for LOE in association with WMH was 1.28 (95% confidence interval [CI]: 1.06–1.54). When participants were censored at the time of stroke or dementia diagnosis, the association between WMH and LOE persisted (HR: 1.34, 95% CI: 1.07–1.67). WMHs provide only a crude estimate of white matter integrity. Whereas WMHs provide a binary assessment for the presence or absence of white matter lesions, diffusion tensor imaging provides more specific data on white matter microstructural integrity with continuous variables such as fractional anisotropy and mean diffusivity, which give a better view of the role of white matter abnormalities in epilepsy risk and thus provide a more robust link between white matter abnormalities and incident epilepsy.

Table 3. Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for risk for development of late-onset epilepsy (LOE).

	Covariates	Stroke and dementia as time-varying covariates	HR (95% CI)	*P*-value
Gray matter abnormalities (dichotomized as high or low based on median split) and risk for development of LOE after MRI at Visit 5				
Model 1	Age, sex, and race	No	2.7 (1.3–5.8)	0.01
Model 2		Yes	2.3 (1.1–5.1)	0.04
Model 3	Covariates from Models 1 and 2 plus education level, hypertension, diabetes, smoking	No	2.6 (1.2–5.5)	0.01
Model 4	status (ever/never)	Yes	2.3 (1.0–4.9)	0.04
Model 5	Covariates from Models 3 and 4 plus prevalent stroke and MCI/dementia	No	2.2 (1.0–4.9)	0.05
White matter FA abnormalities (dichotomized as high or low based on median split) and risk for development of LOE after MRI at Visit 5				
Model 1	Age, sex, and race	No	2.1 (0.9–4.7)	0.07
Model 2		Yes	2.0 (0.9–4.5)	0.1
Model 3	Covariates from Models 1 and 2 plus education level, hypertension, diabetes, smoking	No	2.0 (0.9–4.6)	0.09
Model 4	status (ever/never)	Yes	1.9 (0.9–4.4)	0.1
Model 5	Covariates from Models 3 and 4 plus prevalent stroke and MCI/dementia	No	1.8 (0.8–4.2)	0.1
White matter MD abnormalities (dichotomized as high or low based on median split) and risk for development of LOE after MRI at Visit 5				
Model 1	Age, sex, and race	No	3.1 (1.3–7.4)	0.01
Model 2		Yes	2.9 (1.2–7.0)	0.02
Model 3	Covariates from models 1 and 2 plus education level, hypertension, diabetes, smoking	No	3.2 (1.3–7.6)	0.01
Model 4	status (ever/never)	Yes	3.0 (1.2–7.3)	0.02
Model 5	Covariates from Models 3 and 4 plus prevalent stroke and MCI/dementia	No	2.8 (1.2–6.9)	0.02

FA, fractional anisotropy; LOE, late-onset epilepsy; MCI, mild cognitive impairment; MD, mean diffusivity.

Similar to WMHs, white matter diffusivities abnormalities are nonspecific, and are common in individuals with vascular risk factors, where they are thought to be the result of cerebral small vessel disease.[33] White matter lesions are also common in neurodegenerative diseases where they may reflect axonal degeneration.[34–37] Similar to the study by Johnson et al.[32] the association between white matter diffusivity and incident LOE persisted after controlling for vascular risk factors, stroke, and dementia diagnosis suggesting that the association between white matter microstructural abnormalities and incident epilepsy is not dependent solely on concomitant clinically observable neurodegenerative or cerebral small vessel disease. This is in keeping with recent findings from the ENIGMA consortium that found widespread white matter abnormalities across the common epilepsies in younger adults.[11] From a mechanistic perspective, animal models of demyelination demonstrate a mechanistic link between axonal injury and subsequent neuronal excitability and epileptogenesis.[38]

Among those with incident epilepsy, we observed the highest rates of cortical thinning in temporal lobe regions of interest (Table S2). In a study by Kaestner et al.,[39] older individuals (age > 55) with temporal lobe epilepsy had a similar profile of gray matter atrophy compared to patients with amnestic mild cognitive impairment, the prodromal phase of Alzheimer's disease. The atrophy pattern was similar among individuals with early and late-onset of epilepsy with atrophy in the medial temporal and precentral regions. However, among those with LOE, atrophy was more pronounced and widespread, extending to frontal, temporal neocortical, and paracentral regions. In this study, we observed similar patterns of cortical thinning in individuals with LOE compared to that observed in ENIGMA, a large-scale effort characterizing structural neuroimaging abnormalities among over 2000 individuals (under age 55) with common epilepsies.[6] Areas of overlap included: precentral gyrus, inferior and middle frontal gyrus, transverse temporal gyrus, temporal pole, and entorhinal cortex (Table S2). Of note, we did not observe group level differences in hippocampal volumes. This is likely related in part to the heterogeneity of the cohort in terms of epilepsy etiologies and also to the comparison/control group. With regard to the latter, almost 40% of the no-LOE controls had either prevalent mild cognitive impairment or dementia, which is also associated with hippocampal atrophy. This is in agreement with the study by Kaestner et al.[39] who found that hippocampal volumes among those with amnestic mild cognitive impairment were lower than healthy controls, but statistically similar to older adults with temporal lobe epilepsy.

The neuropathologic basis for neurodegeneration in epilepsy is likely multifactorial. For example, in a postmortem analysis evaluating for Alzheimer's pathology in 138 patients (mean age at death 56.5 years) with primarily focal drug resistant epilepsy with a diverse age of epilepsy onset (mean age at first seizure: 10.23 [range: 0.3–78]), higher Braak stages were noted in older patients as well as those with stigmata of traumatic brain injury and cerebrovascular disease. Among patients with cognitive decline, Braak stage was low, implicating non-Alzheimer's pathology in cognitive decline. Overall, their results suggest that brain atrophy in epilepsy is multifactorial.[40] We observed that brain atrophy predates LOE diagnosis after accounting for demographics, vascular risk factors, stroke, macroscopic infarction, and dementia. Although brain atrophy could be attributable to a neurodegenerative process (e.g., amyloid, tau pathology) another potential etiologic factor is cerebral microinfarction. Cerebral microinfarcts may be the result of cerebral small vessel disease, microemboli, and hypoperfusion; range from 100 micrometers to a few millimeters in size; and are often not visible on standard clinical MRI.[41] Their presence is associated with smaller brain volumes in a dose-dependent fashion.[42] The relative importance of brain atrophy related to neurodegeneration and cerebrovascular disease in epilepsy risk is unknown and warrants further study.

The strengths of this study include a large normative cohort and high-quality longitudinal data on participant health status and comorbid conditions. A major limitation of this study is the reliance on ICD-9/10 codes to define epilepsy. The use of ICD-9/10 codes leads to a risk for misclassification, including misclassification of epilepsy as non-epileptic events or acute symptomatic seiuzres.[1] However, we expect misclassification bias to lean toward the null as misclassification would minimize differences between groups. In prior work, use of two or more ICD codes for epilepsy classification had 94.4% sensitivity and 91.7% specificity, validated with chart review.[43,44] Information on epilepsy phenotype (e.g., etiology, classification, lateralization, and localization of seizures) is not possible with use of ICD codes; however, some inferences about etiology are possible. For example, the majority of participants with LOE had either an antecedent stroke or developed cognitive impairment during the follow-up period. Of note, one participant with LOE with prevalent dementia at Visit 5 had superficial siderosis and lobar cerebral microhemorrhages identified on MRI raising the possibility of a diagnosis of cerebral amyloid angiopathy. Another limitation is the small number of incident epilepsy cases. Finally, given that the primary outcome of the study, incident LOE, was defined using clinical data, there remains a possibility that onset of seizures occurred before the first seizure or epilepsy diagnosis code, as a result of either subclinical seizures or a delay in diagnosis of clinical seizures.

In this study, we demonstrate considerable gray and white matter pathology among individuals who later developed LOE, compared with demographically similar individuals without LOE. White matter pathology was more widespread than cortical pathology at both the group level and participant level. Finally, burden of cortical thinning and white matter diffusivity were each predictive of incident LOE after controlling for demographic factors, risk factors for cerebrovascular disease, stroke, and dementia. Taken together, this study provides important insights into the role of neurodegeneration, both of gray and white matter, and the risk of epilepsy in the elderly.

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Author contributions

JG: conception and design of the study, acquisition and analysis of data, and drafting a significant portion of the manuscript or figures; AEW: drafting a significant portion of the manuscript or figures; RDA: drafting a significant portion of the manuscript or figures; JH: drafting a significant portion of the manuscript or figures; CRJ: drafting a significant portion of the manuscript or figures; RR: drafting a significant portion of the manuscript or figures; AMK-N: drafting a significant portion of the manuscript or figures; RFG: acquisition and analysis of data, drafting a significant portion of the manuscript or figures; ALCS: acquisition and analysis of data, drafting a significant portion of the manuscript or figures; ELJ: acquisition and analysis of data, drafting a significant portion of the manuscript or figures.

Potential conflicts of interest

ALCS reports being an Associate Editor at the journal Neurology outside of the submitted work.

Data availability statement

A public-use ARIC dataset is available through BioLINCC. Additional data are available to researchers who submit a manuscript proposal to the ARIC publications committee (https://sites.cscc.unc.edu/aric/desc).

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Characteristics of individuals with LOE.
Table S2. Proportion of participants with cortical thinning.
Table S3. Proportion of participants with abnormal * subcortical volume.
Table S4. Proportion of participants with low white matter FA.
Table S5. Proportion of participants with high white matter MD.
Table S6. Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for risk for development of late-onset epilepsy (LOE), defined by a single seizure code.
Table S7. Adjusted hazard ratios (HRs) and 95% confidence intervals (CI) for risk for development of late-onset epilepsy (LOE), excluding all patients with prevalent stroke or dementia.