Progressive Cortical Thinning in Patients With Focal Epilepsy

Marian Galovic, MD; Victor Q. H. van Dooren, MSc; Tjardo S. Postma, MD; Sjoerd B. Vos, PhD; Lorenzo Caciagli, MD; Giuseppe Borzì, MD; Juana Cueva Rosillo, MD; Khue Anh Vuong, MSc; Jane de Tisi, BA(Hon); Parashkev Nachev, PhD; John S. Duncan, FRCP; Matthias J. Koepp, PhD

IMPORTANCE It is controversial whether epilepsy is a static or progressive disease. Evidence of progressive gray matter loss in epilepsy would support early diagnosis, rapid treatment, and early referral for surgical interventions.

OBJECTIVE To demonstrate progressive cortical thinning in patients with focal epilepsy distinct from cortical thinning associated with normal aging.

DESIGN, SETTING, AND PARTICIPANTS A case-control neuroimaging study was conducted from August 3, 2004, to January 26, 2016, among 190 patients with focal epilepsy at a tertiary epilepsy referral center (epilepsy data) and 3 independent comparison cohorts matched for age and sex (healthy volunteer data; n = 141).

EXPOSURES Two or more high-resolution T1-weighted magnetic resonance imaging scans at least 6 months apart (mean [SD] interval, 2.5 [1.6] years).

MAIN OUTCOMES AND MEASURES Global and vertexwise rate of progressive cortical thinning.

RESULTS A total of 190 people with focal epilepsy (99 women and 91 men; mean [SD] age, 36 [11] years; 396 magnetic resonance imaging scans) were compared with 141 healthy volunteers (76 women and 65 men; mean [SD] age, 35 [17] years; 282 magnetic resonance imaging scans). Widespread highly significant progressive cortical thinning exceeding normal aging effects, mainly involving the bilateral temporal lobes, medial parietal and occipital cortices, pericentral gyri, and opercula, was seen in 146 individuals with epilepsy (76.8%; 95% CI, 58%-95%). The mean (SD) annualized rate of global cortical thinning in patients with epilepsy was twice the rate of age-associated thinning observed in healthy volunteers (0.024 [0.061] vs 0.011 [0.029] mm/y; P = .01). Progression was most pronounced in adults older than 55 years and during the first 5 years after the onset of seizures. Areas of accelerated cortical thinning were detected in patients with early onset of epilepsy and in patients with hippocampal sclerosis. Accelerated thinning was not associated with seizure frequency, history of generalized seizures, or antiepileptic drug load and did not differ between patients with or without ongoing seizures. Progressive atrophy in temporal (n = 101) and frontal (n = 28) lobe epilepsy was most pronounced ipsilaterally to the epileptic focus but also affected a widespread area extending beyond the focus and commonly affected the contralateral hemisphere. For patients with temporal lobe epilepsy, accelerated cortical thinning was observed within areas structurally connected with the ipsilateral hippocampus.

CONCLUSIONS AND RELEVANCE Widespread progressive cortical thinning exceeding that seen with normal aging may occur in patients with focal epilepsy. These findings appear to highlight the need to develop epilepsy disease-modifying treatments to disrupt or slow ongoing atrophy. Longitudinal cortical thickness measurements may have the potential to serve as biomarkers for such studies.


Published online July 1, 2019.
For more than 100 years it has been hypothesized that “seizures beget seizures,” but it remains controversial whether epilepsy is a static or progressive disease. Knowledge about whether epilepsy in humans is associated with ongoing neuronal damage has important practical implications for rapid diagnosis and early treatment. Evidence of progressive neurodegeneration in drug-resistant epilepsy would support early surgical interventions, with an incentive to reduce the mean delay of 18 to 23 years between the onset of seizures and referral for surgery and further stimulate the search for disease-modifying therapies.

Measurements of cortical thickness with structural magnetic resonance imaging (MRI) scans are a quantitative, reproducible, and biologically valid biomarker of neurodegeneration. Neuromaging studies have demonstrated widespread patterns of neocortical atrophy in people with epilepsy. The predominantly cross-sectional design of these studies did not allow determination of whether gray matter loss was static or progressive. Some cross-sectional studies correlated morphologic changes with duration of epilepsy, but this approach is inherently confounded by the effects of aging because disease duration is highly correlated with age.

Longitudinal structural neuroimaging provides an objective and statistically powerful framework to assess disease progression. Few whole-brain longitudinal studies have been performed in epilepsy. Several of these studies were restricted to small cohorts and did not directly compare patients with epilepsy with healthy controls, thus failing to differentiate possible disease progression in epilepsy from normal aging. A previous population-based study from our center detected new neocortical volume loss using visual analysis of subtracted images during a 3.5-year period in 54% of patients with chronic epilepsy, 39% of newly diagnosed patients, and 24% of healthy controls. The observed changes were widespread, could be remote from the putative epileptic focus, and were not associated with frequency of seizures. Overall cerebral and cerebellar volume losses were similar in the control and patient groups, concluding that more sensitive methods are required to quantitatively assess progression of epilepsy. Two recent meta-analyses identified an urgent need for large longitudinal neuroimaging studies in epilepsy.

We evaluated changes in cortical thickness over time in a large neuroimaging data set of people with focal epilepsy and matched healthy controls, with the aim to separate out the effects of epilepsy-associated progression from normal aging.

Methods

Participants
We analyzed anonymized data from August 3, 2004, to January 26, 2016, of people with focal epilepsy from a cohort of consecutive patients undergoing follow-up at the National Hospital for Neurology and Neurosurgery, London, United Kingdom. We identified individuals who had at least 2 high-resolution T1-weighted MRI scans performed on the same scanner more than 6 months apart (mean [SD] interscan interval, 3.0 [1.8] years). We excluded individuals with brain lesions other than hippocampal sclerosis, those with insufficient MRI scan quality, and, where available (108 of 190 [56.8% of the sample]), video electroencephalography telemetry or ambulatory long-term electroencephalography monitoring. Ambiguous or unclear lateraization or localization was classified as undetermined. The study was classified by the National Hospital for Neurology and Neurosurgery Institutional Review Board as a service evaluation involving further anonymized analysis of previously acquired data that did not require individual participant consent. The institutional review board approved the project as a service evaluation.

Several online repositories include publicly available anonymized MRI scan data of healthy volunteers, but most of these cohorts are cross-sectional and involve young (<20 years) or old (>70 years) individuals. We selected 3 longitudinal data sets (eAppendix 2 and eTable 1 in the Supplement) with data on healthy volunteers aged between 20 and 70 years, each having 2 high-resolution T1-weighted scans more than 6 months apart (mean [SD] interscan interval, 1.7 [0.7] years). We matched the healthy volunteers with the epilepsy data set for age and sex.

MRI Preprocessing
Cortical thickness was estimated using the fully automated, validated, and reliable Computational Anatomy Toolbox (CAT12) with an inverse-consistent longitudinal surface registration approach. Cortical thickness maps were smoothed with a 15-mm surface-based kernel. All data were quality controlled according to procedures implemented in CAT12 and scans with misalignment, misregistration, or inaccurate thickness estimation were excluded. Image quality ratings were estimated by scaling image noise, inhomogeneities, and resolution to a single score within the CAT12 quality assurance framework.

Statistical Analysis
Categorical variables are displayed as numbers and percentages and were analyzed with the Fisher exact test. Continuous variables are displayed as mean (SD) and were analyzed using...
Progressive Cortical Thinning in Patients With Focal Epilepsy

Table. Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Epilepsy (n = 190)</th>
<th>Healthy Volunteers (n = 141)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td>.75</td>
</tr>
<tr>
<td>Male</td>
<td>91 (47.9)</td>
<td>65 (46.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>99 (52.1)</td>
<td>76 (53.9)</td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline MRI scan</td>
<td>36 (11)</td>
<td>35 (17)</td>
<td></td>
</tr>
<tr>
<td>At seizure onset</td>
<td>16 (12)</td>
<td>NA</td>
<td>.56</td>
</tr>
<tr>
<td>Duration of epilepsy at baseline MRI scan, mean (SD), y</td>
<td>22 (13)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Laterализation of epilepsy, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>72 (37.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Right</td>
<td>68 (35.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bilateral</td>
<td>21 (11.1)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Undetermined</td>
<td>29 (15.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Localization of epilepsy, No.%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>101 (53.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Frontal</td>
<td>28 (14.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Parietal</td>
<td>5 (2.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Multilobar</td>
<td>7 (3.7)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Undetermined</td>
<td>49 (25.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hippocampal sclerosis, No. (%)</td>
<td>38 (20.0)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure frequency/mo, mean (SD)</td>
<td>29 (145)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>No seizures, No. (%)</td>
<td>14 (7.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Less than once a month, No. (%)</td>
<td>29 (15.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Once a month to once a week, No. (%)</td>
<td>62 (32.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Once a week to daily, No. (%)</td>
<td>63 (33.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Daily seizures, No. (%)</td>
<td>22 (11.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Generalized tonic-clonic seizures, No. (%)</td>
<td>92 (48.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>No. of AEDs, mean (SD)</td>
<td>2 (1)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiepileptic drug; MRI, magnetic resonance imaging; NA, not applicable.

Results

We included 190 people with focal epilepsy with 396 MRI scans and 141 healthy volunteers with 282 MRI scans. Patients and controls were comparable for mean (SD) age (36 [11] vs 35 [17] years; P = .56), sex (99 women [52.1%] vs 76 women [53.9%]; P = .75), and mean (SD) image quality rating scores (2.04 [0.14] vs 2.05 [0.17]; P = .66). Demographic characteristics of the patients with epilepsy and the controls are displayed in the Table.

Annualized Cortical Thinning

People with epilepsy had a higher mean (SD) overall yearly rate of global cortical thinning compared with healthy volunteers (0.024 [0.061] vs 0.011 [0.029] mm/y; P = .01; Figure IA). The mean (SD) rate of yearly cortical thinning increased in people with epilepsy older than 55 years (aged 18 to <35 years: n = 83, 0.021 [0.066] mm/y; P = .07 compared with the oldest group; aged 35 to <55 years: n = 95, 0.023 [0.055] mm/y; P = .04 compared with the oldest group; aged 55 to <75 years: n = 12, 0.058 [0.060] mm/y; Figure IB). There were no differences between age groups in seizure frequency, number of antiepileptic drugs (AEDs) taken, or history of secondarily generalized seizures. Clinical characteristics of patients with epilepsy aged 55 years or older are displayed in eAppendix 5 and eTable 2 in the Supplement. For aging-associated thinning in healthy volunteers, see eAppendix 6 in the Supplement.

Progressive Cortical Thinning Associated With Epilepsy

When comparing progressive cortical thinning in epilepsy with aging-associated thinning in healthy volunteers, we found with 2-sample t tests. Calculations were done in SPSS, version 24.0 (IBM Corp.).

Vertexwise cortical thickness measurements were analyzed with SurfStat within Matlab (http://www.math.mcgill.ca/keith/surfstat). We fitted linear mixed-effects models, a flexible framework for longitudinal analysis of multiple repeated measurements per participant with irregular measurement intervals. To test for differences between groups (eg, patients vs controls) or the influence of clinical variables (eg, seizure frequency) on change of cortical thickness over time, we tested for a main effect of an interaction between the variable of interest (ie, group allocation or clinical variable) and age at MRI scan. All models were corrected for a random effect of participant and fixed effects of age at scan, sex, and group. With this approach, we were able to test for within-participant thickness changes over time while correcting for baseline demographic differences and for different interscan intervals. We report findings considered significant at P < .05 corrected for multiple comparisons using random field theory for nonisotropic images on a cluster level.26

Annualized cortical thinning was determined by subtracting vertexwise thickness values of aligned baseline and follow-up MRI scan pairs and dividing by the interscan interval. Mean annualized thinning was calculated in age subgroups with approximately 20-year intervals (18 to <35, 35 to <55, and 55 to <75 years) and subgroups of short (<5 years) and long (≥5 years) duration of epilepsy.

We fitted a machine-learning model (Bayesian logistic ridge regression) to separate (classify) epilepsy cases from healthy controls based on their annualized cortical thinning. We trained the model using the top 100 principal components describing the vertexwise data (1000 posterior and 1000 burnin samples), adjusted for age and sex, and tested it using a 10-fold cross-validation procedure. We used t-distributed stochastic neighbor embedding to visualize high-dimensional differences (100 dimensions, perplexity 30) between progressive thinning in patients and controls in 2-dimensional space.

We performed structural connectivity analyses using 10 diffusion-weighted data sets from healthy volunteers included in BCBtoolkit, measuring the regional proportion of voxels connected with the hippocampus. The detailed methods are given in eAppendix 4 and eFigures 1 and 2 in the Supplement.
widespread areas of greater progressive atrophy developing in those with focal epilepsy (right-sided cluster involving 63,884 vertices; \( P < .001 \); largest left-sided cluster involving 37,189 vertices, \( P < .001 \); Figure 1C). Areas that were affected bilaterally included the lateral and posterior temporal lobes, posterior cingulate gyri, occipital lobes, pericentral gyri, and the opercula. The ventrolateral prefrontal cortex and the inferior parietal lobule were affected more in the right hemisphere than the left hemisphere.

To analyze whether the spatial patterns of progressive thinning reflect areas of connectivity to the epileptic focus, we performed structural connectivity measurements based on data from 10 healthy volunteers (eAppendix 4 and eFigures 1 and 2 in the Supplement). We found that the distribution of progressive thinning in all patients with epilepsy was similar to regions connected to both hippocampi (Figure 1C). The results were largely unchanged after adjustment for number of AEDs taken between the 2 MRI scans (eAppendix
and healthy volunteers. We performed a sensitivity analysis excluding data from a healthy control cohort involving Asian volunteers (n = 69) and the results remained similar (eAppendix 8 and eFigure 4 in the Supplement). Post hoc analyses also showed that the multisite character of the healthy volunteer cohort and the Parkinson Progression Marker Initiative study in particular did not increase the variability of cortical thickness measurements compared with patients with epilepsy and thus cannot explain our findings (eAppendix 9 and eFigure 5 in the Supplement). There were no areas of greater cortical thinning in controls than in people with epilepsy.

To detect the frequency of progressive changes in individual participants, we fitted a machine-learning model (pseudo-$R^2 = 0.55$; C statistic, 0.74; 95% CI, 0.52-0.97). The model separated annualized cortical thinning in epilepsy from normal aging in 242 of 331 participants (73.1%; 95% CI, 58%-88%), with a sensitivity of 77% (95% CI, 58%-95%) and specificity of 69% (95% CI, 35%-100%). A dimensionality-reduction plot (eFigure 6 in the Supplement) shows 2 separable but overlapping clusters between people with epilepsy and healthy volunteers.

**Localization and Lateralization of Epilepsy**

To assess the association between epilepsy localization and lateralization and the spatial patterns of progressive atrophy, we compared cortical thinning in patients with left and right temporal lobe epilepsy (TLE), patients with left and right frontal lobe epilepsy (FLE), and healthy volunteers (Figure 2). Those with left TLE (n = 46; 93 MRI scans; Figure 2A) showed progressive cortical thinning in the left precuneus, cuneus, fusiform, lingual, postcentral, and superior temporal gyri. Those with right TLE (n = 36; 77 MRI scans; Figure 2A) showed progressive atrophy in bilateral fusiform and lingual gyri and bilateral precunei. The distribution of accelerated cortical thinning in patients with left and right TLE was similar to areas structurally connected with the ipsilateral hippocampus (Figure 2B). Comparing the effects of TLE lateralization (eFigure 7A in the Supplement), patients with left TLE showed more progressive thinning in the left postcentral gyrus than did those with right TLE.

Patients with left FLE (n = 11; 25 MRI scans; Figure 2C) showed progressive cortical thinning in bilateral posterior cingulate gyri and precunei, bilateral posterior lateral temporal lobes, and bilateral frontoparietal opercula, whereas the effects were more pronounced in the left hemisphere. Those with right FLE (n = 11; 23 MRI scans; Figure 2C) showed progressive atrophy in a large cluster affecting most of the right hemisphere but not involving the right medial and ventral temporal lobe. Patients with right FLE also showed progressive atrophy in the left hemisphere, including the lateral temporal lobe, superior frontal gyrus, frontoparietal operculum, cuneus, and superior parietal lobule. Cortical thinning was more progressive in those with right than with left FLE, particularly in several right parieto-temporal and right frontal areas (eFigure 7B in the Supplement).

Comparing the patterns of progressive atrophy between patients with a temporal vs frontal epileptic focus (Figure 2D), those with FLE showed more progressive thinning in a large right fronto-parieto-occipital and posterolateral temporal cluster and in the right cingulate gyrus, left operculum, and left lateral temporal lobe. Patients with TLE showed more progressive thinning in both parahippocampal gyri, but these small clusters did not reach the threshold after random field theory correction.

**Clinical Characteristics and Progressive Cortical Thinning**

We analyzed the association of clinical characteristics in people with epilepsy with the rate and spatial extent of progressive cortical thinning (Figure 3). An earlier age at onset of epilepsy correlated with accelerated thinning in the left posterior cingulate gyrus and left precuneus (Figure 3A). In those with epilepsy and hippocampal sclerosis, areas of accelerated cortical thinning were detected in the left supramarginal gyrus, left inferior parietal lobule, and right middle frontal gyrus (Figure 3B).

There was no association of the rate of cortical thinning with seizure frequency, history of secondarily generalized seizures, or the number of AEDs taken between scans. There was no difference in the rate of atrophy between patients with epilepsy with (n = 176) vs without (n = 14) ongoing seizures.

**Duration of Epilepsy and Cortical Thinning**

People with a short (<5 years) duration of epilepsy had a higher yearly mean (SD) rate of cortical thinning (n = 14; 0.053 [0.102] mm/y; Figure 4) compared with those with an onset of epilepsy 5 years or more ago (n = 176; 0.022 [0.056] mm/y; P = .049). There were no between-group differences in seizure frequency, number of AEDs, or history of secondary generalized seizures. For analyses of an interaction between short epilepsy duration and older age, see eAppendix 10 and eTable 3 in the Supplement.

**Discussion**

We used a large longitudinal neuroimaging data set to demonstrate that morphologic abnormalities in focal epilepsy are dynamic rather than static. We showed that progressive cerebrocortical thinning may occur in epilepsy that is widespread and exceeds gradual atrophy associated with normal aging.

A total of 76.8% of people with epilepsy in our cohort showed progressive cortical thinning that was distinct from that seen with normal aging, suggesting that epilepsy-associated progressive atrophy is a common phenomenon in patients with epilepsy undergoing follow-up in a tertiary epilepsy center. Our annualized cortical thinning estimates are comparable with those in previous reports that documented thinning of 0.02 to 0.05 mm/y in people with epilepsy and between 0.001 and 0.008 mm/y in healthy adults. The most likely cause of cortical thinning is neuronal loss, suggesting that these measurements are a surrogate marker for neurodegeneration. In our study, the yearly rate of cortical thinning in epilepsy was double that of normal aging in people younger than 55 years and almost 4-fold in those older than 55 years (Figure 1A). This significant increase of epilepsy-associated gray matter loss in older adults suggests a higher vulnerability of...
Figure 2. Localization and Lateralization of Epilepsy and Their Association With Progressive Cortical Thinning

A. Temporal lobe epilepsy vs healthy controls

Left TLE (n=46, 93 scans)  
Right TLE (n=36, 77 scans)  

Region | Vertices | P Value | Region | Vertices | P Value
--- | --- | --- | --- | --- | ---
Left precuneus and cuneus | 7604 | <1 × 10⁻⁶ | Left fusiform and lingual gyrus | 8233 | <1 × 10⁻⁶
Left fusiform and lingual gyrus | 4263 | 7 × 10⁻⁶ | Right fusiform and lingual gyrus | 2230 | .004
Left postcentral gyrus | 3268 | .001 | Right precuneus | 1948 | <.001
Left superior temporal gyrus | 2127 | .009 | Left precuneus | 1667 | .03

B. Regions with high structural connectivity with the hippocampus

Voxels connected with the left hippocampus  
Voxels connected with the right hippocampus  

Proportion of Connected Voxels, %

C. Frontal lobe epilepsy vs healthy controls

Left FLE (n=11, 25 scans)  
Right FLE (n=11, 23 scans)  

Region | Vertices | P Value | Region | Vertices | P Value
--- | --- | --- | --- | --- | ---
Left posterior cingulate and precuneus | 6998 | <1 × 10⁻⁶ | Large right-hemispheric cluster (frontoparieto-occipital, lateral temporal) | 116,046 | <1 × 10⁻⁶
Left posterior lateral temporal lobe | 5627 | <1 × 10⁻⁶ | Left lateral temporal lobe | 7732 | <1 × 10⁻⁶
Left frontoparietal operculum | 4918 | 5 × 10⁻⁶ | Left superior frontal gyrus | 5706 | 2 × 10⁻⁵
Right posterior cingulate and precuneus | 2359 | .007 | Left frontoparietal operculum | 2909 | .002
Right posterior lateral temporal lobe | 1779 | <.001 | Left cuneus | 2149 | .003
Right lingual gyrus | 1512 | .03 | Left superior parietal lobule | 2094 | .005

D. Temporal vs frontal lobe epilepsy

More progressive thinning in TLE  
More progressive thinning in FLE  

Region | Vertices | P Value | Region | Vertices | P Value
--- | --- | --- | --- | --- | ---
Left parahippocampal gyrus | 704 | 4 × 10⁻⁶ (uncorrected) | Right fronto-parieto-occipital and posterior temporal cluster | 42,708 | <1 × 10⁻⁶
Right parahippocampal gyrus | 246 | .001 (uncorrected) | Right posterior cingulate gyrus | 1060 | .001
Left frontoparietal operculum | 2578 | .001 | Left lateral parietal lobe | 1811 | .02
Left medial and inferior temporal gyr | 1931 | <.001 | Left cuneus | 1931 | <.001
Right anterior cingulate gyrus | 1811 | .02 | Right lateral parietal lobe | 2094 | .005

A. Comparison of left and right temporal lobe epilepsy vs healthy controls.
B. Structural connectivity with the left and right hippocampi in 10 healthy volunteers is presented as the regional proportion of connected voxels.
C. Comparison of left and right frontal lobe epilepsy vs healthy controls.
D. Comparison of temporal vs frontal lobe epilepsy. Significant clusters (P < .05; random field theory corrected) are displayed on hemispheric surface templates and in overview tables. FLE indicates frontal lobe epilepsy; FWE, familywise error; and TLE, temporal lobe epilepsy.
Progressive morphologic changes in epilepsy were most pronounced in the first 5 years after the onset of seizures (Figure 4A), with a doubling of the progression rate within the first 5 years after epilepsy onset compared with the later disease course. This finding supports the need for early diagnosis, rapid treatment, and reduction of delays of surgical referral to the aging brain to cortical damage caused by epilepsy. Alternatively, it could reflect a concomitant preclinical neurodegenerative condition in these cases, whereas none of the patients in our study had confirmed dementia at time of scanning. It is unlikely that the increased rate of atrophy in older individuals would be explained by a higher severity of epilepsy because there were no differences in seizure frequency or number of AEDs between age groups.

Progressive morphologic changes in epilepsy were most pronounced in the first 5 years after the onset of seizures (Figure 4A), with a doubling of the progression rate within the first 5 years after epilepsy onset compared with the later disease course. This finding supports the need for early diagnosis, rapid treatment, and reduction of delays of surgical referral to the aging brain to cortical damage caused by epilepsy. Alternatively, it could reflect a concomitant preclinical neurodegenerative condition in these cases, whereas none of the patients in our study had confirmed dementia at time of scanning. It is unlikely that the increased rate of atrophy in older individuals would be explained by a higher severity of epilepsy because there were no differences in seizure frequency or number of AEDs between age groups.

Progressive morphologic changes in epilepsy were most pronounced in the first 5 years after the onset of seizures (Figure 4A), with a doubling of the progression rate within the first 5 years after epilepsy onset compared with the later disease course. This finding supports the need for early diagnosis, rapid treatment, and reduction of delays of surgical referral to the aging brain to cortical damage caused by epilepsy. Alternatively, it could reflect a concomitant preclinical neurodegenerative condition in these cases, whereas none of the patients in our study had confirmed dementia at time of scanning. It is unlikely that the increased rate of atrophy in older individuals would be explained by a higher severity of epilepsy because there were no differences in seizure frequency or number of AEDs between age groups.

Progressive morphologic changes in epilepsy were most pronounced in the first 5 years after the onset of seizures (Figure 4A), with a doubling of the progression rate within the first 5 years after epilepsy onset compared with the later disease course. This finding supports the need for early diagnosis, rapid treatment, and reduction of delays of surgical referral to the aging brain to cortical damage caused by epilepsy. Alternatively, it could reflect a concomitant preclinical neurodegenerative condition in these cases, whereas none of the patients in our study had confirmed dementia at time of scanning. It is unlikely that the increased rate of atrophy in older individuals would be explained by a higher severity of epilepsy because there were no differences in seizure frequency or number of AEDs between age groups.

Progressive morphologic changes in epilepsy were most pronounced in the first 5 years after the onset of seizures (Figure 4A), with a doubling of the progression rate within the first 5 years after epilepsy onset compared with the later disease course. This finding supports the need for early diagnosis, rapid treatment, and reduction of delays of surgical referral to the aging brain to cortical damage caused by epilepsy. Alternatively, it could reflect a concomitant preclinical neurodegenerative condition in these cases, whereas none of the patients in our study had confirmed dementia at time of scanning. It is unlikely that the increased rate of atrophy in older individuals would be explained by a higher severity of epilepsy because there were no differences in seizure frequency or number of AEDs between age groups.

Progressive morphologic changes in epilepsy were most pronounced in the first 5 years after the onset of seizures (Figure 4A), with a doubling of the progression rate within the first 5 years after epilepsy onset compared with the later disease course. This finding supports the need for early diagnosis, rapid treatment, and reduction of delays of surgical referral to the aging brain to cortical damage caused by epilepsy. Alternatively, it could reflect a concomitant preclinical neurodegenerative condition in these cases, whereas none of the patients in our study had confirmed dementia at time of scanning. It is unlikely that the increased rate of atrophy in older individuals would be explained by a higher severity of epilepsy because there were no differences in seizure frequency or number of AEDs between age groups.

Progressive morphologic changes in epilepsy were most pronounced in the first 5 years after the onset of seizures (Figure 4A), with a doubling of the progression rate within the first 5 years after epilepsy onset compared with the later disease course. This finding supports the need for early diagnosis, rapid treatment, and reduction of delays of surgical referral to the aging brain to cortical damage caused by epilepsy. Alternatively, it could reflect a concomitant preclinical neurodegenerative condition in these cases, whereas none of the patients in our study had confirmed dementia at time of scanning. It is unlikely that the increased rate of atrophy in older individuals would be explained by a higher severity of epilepsy because there were no differences in seizure frequency or number of AEDs between age groups.

Progressive morphologic changes in epilepsy were most pronounced in the first 5 years after the onset of seizures (Figure 4A), with a doubling of the progression rate within the first 5 years after epilepsy onset compared with the later disease course. This finding supports the need for early diagnosis, rapid treatment, and reduction of delays of surgical referral to the aging brain to cortical damage caused by epilepsy. Alternatively, it could reflect a concomitant preclinical neurodegenerative condition in these cases, whereas none of the patients in our study had confirmed dementia at time of scanning. It is unlikely that the increased rate of atrophy in older individuals would be explained by a higher severity of epilepsy because there were no differences in seizure frequency or number of AEDs between age groups.
Strengths and Limitations

Strengths of our study are the inclusion of a large, diverse, and clinically representative tertiary center cohort of people with focal epilepsy and the use of a robust and statistically powerful longitudinal neuroimaging pipeline. A limitation is that data from patients with epilepsy and healthy volunteers were acquired on different 3-T MRI scanners. The statistical analyses focused on within-individual changes and all individuals were rescanned on the same equipment, potentially reducing the effect of between-cohort differences. Moreover, there were no between-group differences in image quality (combination of noise, inhomogeneities, and resolution), and a sensitivity analysis excluding a cohort of Asian volunteers produced largely unchanged results (eAppendix 8 and eFigure 4 in the Supplement). Posthoc analyses (eAppendix 9 and eFigure 5 in the Supplement) showed that our results cannot be explained by a reduced sensitivity to detect cortical thinning in healthy volunteers compared with patients with epilepsy. Future studies will, nevertheless, need to address this issue by acquiring longitudinal data from patients with epilepsy and healthy controls using the same MRI scanner.

A limitation inherent to most epilepsy studies is the possible influence of AED intake in patients compared with controls. It is unlikely, however, that our results could be explained by differences in medication only because a sensitivity analysis adjusting for AED intake produced largely similar results (eAppendix 7 and eFigure 3 in the Supplement), and we did not find any association of AED load with progressive atrophy. The subgroups of patients with epilepsy who were not taking AEDs (n = 14) and those with short disease duration (n = 14) were small and these findings will need to be replicated in larger cohorts specifically targeting these subgroups.

We acknowledge that there will have been a referral bias in the patients included in this study, with patients with more complicated cases being referred to our services and undergoing multiple MRI scans for clinical reasons, mainly for refractory seizures or concerns about cognitive impairment. Our findings, thus, apply to individuals receiving follow-up in a tertiary epilepsy center and cannot be readily generalized to the overall population. Previous population-based studies included less severely affected individuals, which may explain the lower magnitude and frequency of progressive changes observed in those studies. Although the patient and control groups were matched for age and sex, we did not have data on controls’ educational attainment or intelligence and we cannot be certain whether this factor may have contributed to our findings.

Conclusions

We provide evidence for widespread progressive neocortical atrophy in almost three-quarters of our cohort of patients with epilepsy, but it remains unknown how to prevent these morphologic changes. Our findings might apply to individuals receiving follow-up in a tertiary epilepsy center and cannot be readily generalized to the overall population. Previous population-based studies included less severely affected individuals, which may explain the lower magnitude and frequency of progressive changes observed in those studies. Although the patient and control groups were matched for age and sex, we did not have data on controls’ educational attainment or intelligence and we cannot be certain whether this factor may have contributed to our findings.

Figure 4. Duration of Epilepsy and Its Association With Progressive Cortical Thinning

A, Annualized rate of cortical thinning in people with epilepsy with disease duration of less than 5 years or 5 years or more after the onset of first seizure. B, Comparison of annualized cortical thinning rates in people with epilepsy with short and long disease duration (vertical lines indicate SEM).
Role of the Funder/Sponsor: The investigators within the Neuromorphometry by Computer Algorithm Chicago, Parkinson Progression Marker Initiative, and Southwest University Longitudinal Imaging Multimodal study contributed to the design and implementation of the respective data sets and/or provided data but did not participate in the analysis or writing of this report.

Disclaimer: The views expressed in this publication are those of the authors and not necessarily those of the Wellcome Trust.

REFERENCES


