Longitudinal and cross-sectional analysis of atrophy in pharmacoresistant temporal lobe epilepsy

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ABSTRACT

Background: Whether recurrent epileptic seizures induce brain damage is debated. Disease progression in epilepsy has been evaluated only in a few community-based studies involving patients with seizures well controlled by medication. These studies concluded that epilepsy does not inevitably lead to global cerebral damage.

Objective: To track the progression of neocortical atrophy in pharmacoresistant temporal lobe epilepsy (TLE) using longitudinal and cross-sectional designs.

Methods: Using a fully automated measure of cortical thickness on MRI, we studied a homogeneous sample of patients with pharmacoresistant TLE. In the longitudinal analysis ($n = 18$), fixed-effect models were used to quantify cortical atrophy over a mean interscan interval of 2.5 years (range = 7 to 90 months). In the cross-sectional analysis ($n = 121$), we correlated epilepsy duration and thickness. To dissociate normal aging from pathologic progression, we compared aging effects in TLE to healthy controls.

Results: The longitudinal analysis mapped progression in ipsilateral temporopolar and central and contralateral orbitofrontal, insular, and angular regions. In patients with more than 14 years of disease, atrophy progressed more rapidly in frontocentral and parietal regions than in those with shorter duration. The cross-sectional study showed progressive atrophy in the mesial and superolateral frontal, and parietal cortices.

Conclusions: Our combined cross-sectional and longitudinal analysis in patients with pharmacoresistant temporal lobe epilepsy demonstrated progressive neocortical atrophy over a mean interval of 2.5 years that is distinct from normal aging, likely representing seizure-induced damage. The cumulative character of atrophy underlies the importance of early surgical treatment in this group of patients. *Neurology*® 2009;72:1747-1754

GLOSSARY

GM = gray matter; **TLE** = temporal lobe epilepsy; **WM** = white matter.

In temporal lobe epilepsy (TLE), a considerable body of MRI studies has established that structural brain abnormalities extend beyond the hippocampus to involve other mesial and limbic structures.^{1,2} Although the pathogenesis of such changes is not fully understood, experimental³ and human cognitive studies⁴ suggest that they may be related to recurrent seizures.⁵

MRI provides a unique tool to evaluate the effects of disease progression in vivo using cross-sectional and longitudinal designs.⁶ Due to the difficulty in obtaining reliable estimates of seizure counts, cross-sectional studies usually correlate morphometric measurements with duration of epilepsy. The drawback of this approach is the confounding effect of age, because it is highly correlated to duration. On the other hand, correcting for age may fail to yield significant results due to decreased effect size. However, cross-sectional studies generally offer the advan-

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Table 1 Demographic and clinical data in the cross-sectional sample

Group	Age, y	Male	Duration, y	SF	HA, n (%)	Surgery	Engel I
Controls (41)	33 ± 12 (20-66)	19	NA	NA	NA	NA	NA
L TLE (54)	34 ± 10 (16-54)	19	15 ± 11 (0-42)	8 (1-150)	40 (74)	43	28
R TLE (49)	35 ± 10 (18-55)	21	15 ± 11 (0-49)	7 (1-330)	30 (61)	38	29

Age and duration of epilepsy are presented as mean ± SD (range); SF is presented as median (range) seizure frequency per month.

SF = seizure frequency; HA = number of patients with hippocampal atrophy ipsilateral to the seizure focus (percentage of patients in the group); Engel I = seizure-free, i.e. Class I postsurgical outcome in Engel's classification; TLE = temporal lobe epilepsy.

tage of large sample sizes. Longitudinal designs based on relatively short interscan intervals remove potential aging confounds. Moreover, as they control for intersubject variability, statistical sensitivity to detect subtle changes increases. Importantly, they allow the quantification of morphologic changes over time, thus inferring causality.

In patients with pharmacoresistant TLE, longer disease duration has been consistently associated with progressive atrophy of mesiotemporal lobe structures, including the hippocampus and entorhinal cortex.⁷⁻⁹ Whether recurrent seizures in these patients induce neocortical damage remains unclear. Since patients with intractable seizures rarely refuse surgical treatment, only one previous longitudinal study has been performed in this cohort.⁹ Thus, progressive neocortical damage has been evaluated only in a few community-based studies involving patients with seizures well controlled by medication.^{10,11} These studies concluded that epilepsy does not inevitably lead to global cerebral damage, which may develop insidiously over a period longer than 3.5 years.

Analyzing cortical thickness on high-resolution MRI offers a reliable, direct, and biologically meaningful index to quantify neocortical atrophy.¹² Moreover, combining thickness measurement¹³ with powerful surface-based registration achieves optimal preservation of local surface topology and anatomic correspondence between individuals.¹⁴ Using such techniques in TLE, we have previously shown widespread atrophy in the temporal and frontocentral cortices.¹⁵

Our purpose was to track progression of neocortical atrophy in intractable TLE on MRI using longitudinal and cross-sectional designs.

METHODS Subjects. We randomly selected from our database 121 patients referred to our hospital for the investigation of medically intractable TLE and no mass lesion (malformations of cortical development, tumor, or vascular malformations). Demographic and clinical data were obtained through interviews with the patients and their relatives. TLE diagnosis and lateralization of the seizure focus were determined by a comprehensive evaluation including detailed history, video-EEG telemetry, and neuropsychological assessment in all patients. The hippocampus was segmented manually on MRI according to our previously described protocols.² Based on a volumetric assessment that takes into account absolute volume and interhemispheric asymmetry, we classified patients into those with hippocampal atrophy and those with normal hippocampal volume.

Eighteen patients refused to undergo surgery at the first evaluation by our epilepsy team. These patients, however, agreed to have repeated MRI scans. Seven of them eventually followed our recommendation and were operated at subsequent hospitalizations.

For patients who underwent surgery, we determined surgical outcome according to Engel's modified classification scheme.¹⁶ Qualitative pathologic examination¹⁷ of the resected tissue revealed hippocampal sclerosis in 59 (65%) patients and temporal cortex gliosis in 12 (13%). Due to subpial aspiration, specimens were unsuitable for histopathology in 20 (22%) patients.

In total, 42 serial MR scans with at least 2 scans (range = 2 to 5) per subject were available. All images were acquired on the same MR scanner. The interval between the first and last scan was 31 ± 21 months (range = 7 to 90). These scans were examined in the longitudinal analysis. We analyzed the remaining 103 patients together with the first scan of the longitudinal sample in the cross-sectional analysis.

The control group for cross-sectional analysis consisted of 41 age- and sex-matched healthy individuals (19 men; age 20–66 years, mean 33 ± 12 years). The Ethics Committee of the Montreal Neurological Institute and Hospital approved the study and written informed consent was obtained from all participants. Demographic and clinical data of all subjects are shown in tables 1 and 2.

MRI acquisition and processing. MR images were acquired on a 1.5 T Gyroscan (Philips Medical Systems, Eindhoven, Netherlands) using a three-dimensional T1-fast field echo sequence providing an isotropic voxel size of 1 mm³. Images underwent correction for intensity nonuniformity¹⁸ and were linearly registered into a standardized stereotaxic space based on the Talairach atlas.¹⁹

For cortical thickness measurements, registered images were classified into gray matter (GM), white matter (WM), and CSF. We applied the Constrained Laplacian Anatomic Segmentation using Proximity algorithm¹³ that iteratively warps a surface mesh to fit the boundary between WM and GM in the classified im-

Table 2 Demographic and clinical data in the longitudinal sample

Group	Age, y	Male	Duration, y	SF	HA, n (%)	Surgery	Engel I
L TLE (8)	27 ± 10 (17-46)	6	16 ± 13 (1-39)	10 (2-30)	4 (50)	3	2
R TLE (10)	35 ± 12 (17-48)	6	20 ± 12 (7-43)	6 (4-330)	8 (80)	7	5

Age and duration of epilepsy are presented as mean ± SD (range); SF is presented as median (range) seizure frequency per month.

SF = seizure frequency; HA = number of patients with hippocampal atrophy ipsilateral to the seizure focus (percentage of patients in the group); Engel I = seizure-free, i.e. Class I postsurgical outcome in Engel's classification; TLE = temporal lobe epilepsy.

age. It then expands the WM/GM boundary along a Laplacian map to generate an outer surface along the GM/CSF boundary. Surfaces were nonlinearly aligned to a surface template²⁰ using a 2D registration procedure.¹⁴ We applied the inverse of the linear registration matrix and measured cortical thickness in native space as the distance between corresponding vertices of inner and outer surface across 40,962 points in each hemisphere. Thickness data were blurred using a surface-based diffusion smoothing kernel of 20 mm FWHM that preserves cortical topology.²¹

Statistical analysis. Analyses were conducted using the SurfStat (<http://www.math.mcgill.ca/keith/surfstat/>) toolbox for Matlab.

Cross-sectional analysis. We correlated disease duration and seizure frequency with mean hemispheric cortical thickness and thickness at each vertex. As seizure frequency followed a highly right-skewed distribution, it was log-transformed before analysis. Hemispheres were pooled together according to side of seizure focus to increase statistical power. To correct for potential effects of age, we correlated age with cortical thickness in patients and controls separately. Linear models for mean hemispheric thickness and vertex-wise analysis contained a group and age main effect term, and a group × age interaction effect term. We assessed age-related differences in cortical thickness between groups by testing the significance of the interaction term.

Longitudinal analysis. To examine the effects of the inter-scan interval, we fitted linear fixed-effects models containing time from baseline scan and subject intercept as effects on mean hemispheric cortical thickness and thickness at each vertex. We tested for a negative effect of time from baseline scan. Hemispheres were pooled together according to side of seizure focus to increase statistical power.

To examine interactions between duration of epilepsy and disease progression, we factorized duration of epilepsy with respect to its median (14 years) into short (i.e., <14 years) and long (i.e., ≥14 years). We then fitted a fixed-effects model as above with the factorized duration as an additional term, and tested on the interaction between time from baseline scan and factorized duration.

Correction for multiple comparisons. In all vertex-wise analyses, we used random-field theory for nonisotropic images to detect significant clusters.²² This controlled the chance of ever reporting a false positive to be below 0.05. Cortical significance maps were also displayed at an uncorrected level of $p < 0.005$.

RESULTS Cross-sectional analysis. Effects of duration.

Duration of epilepsy was negatively correlated with mean hemispheric cortical thickness ipsilateral ($t = -2.0$, $p < 0.03$) and contralateral ($t = -2.7$, $p < 0.01$) to the seizure focus (figure 1A). Vertex-wise analysis (figure 1B) revealed cortical thinning in ipsi-

lateral mesiotemporal, orbitofrontal ($p < 0.0001$), and parietal ($p < 0.02$) regions, as well as in a large portion of the contralateral frontal lobe convexity ($p < 0.0001$), including the prefrontal, premotor, and central areas.

Effects of seizure frequency. Seizure frequency was negatively correlated with mean hemispheric cortical thickness ipsilateral to the seizure focus ($t = -1.99$, $p < 0.05$). Vertex-wise analysis (figure e-1 on the *Neurology*[®] Web site at www.neurology.org) revealed cortical thinning in ipsilateral centroparietal regions ($p < 0.001$). Further trends ($p < 0.005$) were seen in ipsilateral posterior cingulate and frontal cortices bilaterally.

Effects of age. In controls, there were no negative effects of aging on mean left and right hemispheric cortical thickness (figure e-2A). In patients with TLE, aging was associated with decreased cortical thickness in the left (LTLE: $t < -4.48$, $p < 0.0001$; RTLE: $t < -4.08$, $p < 0.001$) and right hemisphere (LTLE: $t < -3.16$, $p < 0.002$; RTLE: $t < -3.15$, $p < 0.002$). In the left hemisphere, the slope in both TLE groups was steeper than in controls (LTLE: $t < -1.95$, $p < 0.03$; RTLE: $t < -1.89$, $p < 0.04$). Similar effects were seen in the right hemisphere, but did not reach significance.

Vertex-wise analysis (figure e-2B) in controls showed a cluster of negative age effects in left inferior frontal cortex ($p < 0.0001$). The effects of aging were similar in both TLE groups. In LTLE, clusters of negative age effects were located bilaterally in frontal and central ($p < 0.0001$), left posterior insular ($p < 0.05$), posterior mesiotemporal ($p < 0.05$), and right prefrontal and cuneal ($p < 0.05$) cortices. In RTLE, clusters of negative age effects were found bilaterally in frontal and central ($p < 0.0001$), parietal ($p < 0.0001$), temporo-occipital ($p < 0.04$), and left prefrontal ($p < 0.005$) cortices.

Vertex-wise analysis of differences in aging (figure e-2C) revealed multiple areas in frontal and occipital areas, with stronger effects in patients compared to controls. In LTLE, a cluster was found in left medial frontal and central regions ($p < 0.01$). In RTLE, clusters of

Figure 1 Cross-sectional analysis

A Mean cortical thickness

B Cortical thickness at each vertex

Effects of duration on (A) mean cortical thickness (black dots represent individual patients with temporal lobe epilepsy; the solid black line describes the linear regression model) and (B) thickness at each vertex. Significances have been thresholded at $p < 0.005$. Peak positions and resolution elements (i.e., resels) of significant clusters after random field theory correction are shown (cluster threshold $t > 3.2$, cluster extent threshold 0.8 resels).

steeper aging effects were found in the left medial and lateral frontal ($p < 0.002$), left occipital ($p < 0.0001$), and right parietal ($p < 0.0001$) cortices.

Longitudinal analysis. Effects of interscan interval. We found a progressive decrease in mean cortical thickness in the hemisphere ipsilateral (-0.016 ± 0.009 mm/year; $t = -2.20$, $p < 0.02$) and contralateral to the focus (-0.022 ± 0.009 mm/year; $t = -2.88$, $p < 0.01$) (figure 2A). Annual rates of cortical atrophy (figure 2B) exceeded 0.05 mm/year in bilateral prefrontal, insular, frontocentral; ipsilateral entorhinal; and contralateral temporal and posterior cingulate regions.

Vertex-wise analysis (figure 2C) revealed progressive cortical atrophy in contralateral insular and posterior cingulate ($p < 0.05$) regions. Moreover, additional areas of atrophy were found in bilateral frontal (orbitofrontal and superior frontal), parietal, and temporal (ipsilateral temporopolar and contralateral lateral temporal) areas ($p < 0.005$, uncorrected).

Interaction between epilepsy duration and disease progression. We found a faster progression of atrophy in

patients with long duration of epilepsy (≥ 14 years) compared to those with shorter duration (< 14 years) in the hemisphere ipsilateral ($t = 2.12$, $p < 0.03$) and contralateral ($t = 1.84$, $p < 0.05$) to the focus (figure 3). Vertex-wise analysis showed that in patients with longer disease, cortical atrophy progressed faster in bilateral frontocentral (ipsilateral: $p < 0.002$; contralateral: $p < 0.04$) and ipsilateral parietal ($p < 0.01$) regions.

DISCUSSION This study combines both cross-sectional and longitudinal designs to assess the impact of disease progression on the neocortex in intractable TLE. In the cross-sectional study, we took advantage of a large sample of patients with a wide range of epilepsy durations and compared aging effects to healthy controls, dissociating pathologic progression from normal aging. In the longitudinal analysis, we used fixed-effect models to precisely quantify cortical change over time. Importantly, we applied conservative corrections for multiple comparisons using random field theory,

Figure 2 Longitudinal analysis

A Change in mean hemispheric cortical thickness

B Annual change in vertex-wise cortical thickness

C Vertex-wise decrease in cortical thickness

Effect of interscan interval on (A) changes in mean hemispheric cortical thickness (gray lines connect the MR scans, indicated as black dots; the mixed-effects model is plotted as a solid black line); (B) vertex-wise mean annual rate of cortical thinning (in mm/year) in blue; (C) regions of vertex-wise progressive thinning ($p < 0.005$) in blue. Peak positions and resolution elements (i.e., resels) of significant clusters after random field theory correction are shown (cluster threshold $t > 3.5$, cluster extent threshold 0.8 resels).

which ensures with 95% confidence that no reported result is a type 1 error despite the large number of tests performed.²²

The purpose of our cross-sectional analysis was to study the overall effect of duration of epilepsy on neocortical thickness. We found progressive atrophy in ipsilateral orbitofrontal, mesiotemporal, and post-central, as well as in contralateral prefrontal areas. In a previous cross-sectional study using cortical thickness, progressive atrophy was found in somatomotor and parahippocampal regions.²³ Aging effects, however, were not dissociated from those related to disease duration. As disease duration is highly correlated with age, statistically controlling for aging severely reduces the sensitivity to detect significant effects.

In our study, we opted to separate these effects by statistically comparing aging in patients to that in healthy controls. Similarly to previously reported data,²⁴

in controls we found neocortical atrophy related to aging in the inferior and middle frontal cortices. Aging effects in patients, while somewhat similar in topography to those of duration of epilepsy, were considerably more extensive and involved virtually the entire frontal lobe. However, after comparison to controls, differences became limited to smaller portions of the mesial frontal and superior frontal lobe convexity, as well as the parietal cortex. This analysis therefore confirms that progressive atrophy in TLE is distinct from aging.

Using relatively short follow-up periods in a longitudinal design allows controlling for aging effects. Since a subject is compared to his or her own baseline, such design provides a true measure of change over time required to infer causality between seizures and atrophy. However, adequately powered longitudinal analyses are difficult to perform as they entail the combination of several factors, such as repeated

Figure 3 Longitudinal analysis

Interaction between duration of epilepsy and disease progression. Superior view showing areas undergoing faster progression of atrophy ($p < 0.005$) in patients with longer disease duration (≥ 14 years). Peak positions and resolution elements (i.e., resels) of clusters after random field theory correction are shown (cluster threshold $t > 3.5$, cluster extent threshold 0.8 resels).

scans performed on the same hardware, reliable and sensitive image postprocessing, and availability of a relatively large group of patients.

In our study, we specifically aimed to assess cortical changes in a homogeneous cohort of patients with pharmacoresistant TLE. We localized progressive thinning in ipsilateral temporopolar and central, as well as contralateral orbitofrontal, insular, and angular regions, over a mean interscan period of 2.5 years. Strongest effects were seen in prefrontal and frontal regions, with rates of atrophy in the order of 0.1 mm/year. As drug-responding patients with TLE are generally not referred to our tertiary center, we could not include a sizeable sample of these patients for comparison. A previous semiquantitative longitudinal MRI study over a median interval of 3.5 years¹⁰ failed to detect significant progression of cortical atrophy in patients with relatively benign, pharmacologically controlled forms of epilepsy. Although elevated proportions of patients with TLE had progressive subtle diffuse atrophy compared to healthy controls,¹¹ the authors concluded that these changes resulted mainly from an initial precipitating insult and aging, and not from the disease. There are a number of differences between these studies and our work. First, we have assessed progressive changes in a homogeneous group of patients with intractable TLE, while previous data^{10,11} were based on groups of community-based patients with various types of pharmacologically controlled epilepsy. From a methodologic point of view, our approach is more sensitive and more reproducible since it does not require any operator intervention.¹¹ Indeed, in contrast to a rater-based

measurement of change,¹⁰ automatically assessing cortical thickness is an unbiased and more direct measurement of atrophy. The algorithm used has been validated against phantom data, and cross-validated against other MRI surface extraction software, showing superior reproducibility.²⁵ Importantly, by avoiding surface self-intersection, it provides the most accurate geometry of the reconstructed surface, thus a topologically sound representation of the cortical mantle.²⁵ In our analysis, the use of a nonlinear 2D surface registration¹⁴ in addition to the linear volumetric registration ascertains optimal correspondence of thickness measurements from homologous regions across subjects, thus increasing the sensitivity to detect significant changes. Moreover, in contrast to volumetry, measuring thickness across thousands of points allows precise mapping of the topography of GM atrophy.

The pattern of progressive atrophy encompasses both group differences of frontocentral cortical thinning and alterations of limbic network organization in orbitofrontal and posterior cingulate and angular gyri that we recently reported in TLE.¹⁵ Seizures have been shown to increase markers of excitability, such as glutamate.²⁶ Furthermore, TLE has been associated with disruptions in cortical GABA-A-ergic circuits, potentially contributing to the genesis or maintenance of seizure activity.²⁷ Excessive metabolic activation resulting from a disrupted balance in these systems may in turn promote epileptogenicity and excitotoxicity, possibly through cellular reorganization.³ This may result in neuronal death and plasticity in both seizure-generating regions, and in neocortical circuits affected by seizure spread.²⁸ Thus, it is plausible that changes observed in the current study may be related to the combined effects of neuronal disconnection and seizure-related damage. However, the putative effects of genetic factors and antiepileptic drugs on atrophy progression cannot be ruled out. The genetic makeup of an individual is thought to influence susceptibility to precipitating events, development of plasticity in neuronal networks, and pharmacoresistance.^{29,30} On the other hand, we could not control for the effects of drugs since our patients had been on multiple and varying antiepileptic medication for several years. Effects of drugs on the neocortex are largely unknown. While some studies suggest that phenytoin³¹ induces cerebellar atrophy and valproic acid³² pseudoatrophy of the brain, others have shown that these drugs may have neuroprotective effects and promote neurogenesis.^{33,34}

A recent randomized controlled trial³⁵ demonstrated that 58% of surgically treated patients were seizure free at 1 year, compared with 8% of medically treated patients. The resulting practice guideline rec-

ommends that patients with partial seizures and failed first-line antiepileptic medications should be referred to an epilepsy surgery center, and that those who meet the criteria for temporal lobe resection should be offered surgery.³⁶ Referral for evaluation, however, tends to occur many years after medications have failed, despite the fact that further medication trials are ineffective once intractability sets in.³⁵ During this time, patients are at increased risk of mortality³⁷ and disability.

Neocortical atrophy in our patients with epilepsy for longer than 14 years progressed more rapidly than in those with shorter disease duration. Arguably, our results in pharmacoresistant patients may not directly apply to those amenable with optimized medical treatment. However, recent observations from prospective studies in community-based centers indicate that up to 35% of children with TLE may develop intractability.³⁸ Therefore, in light of functional data in humans showing progressive cognitive decline⁴ and evidence demonstrating that recurrent epileptic discharges provoke an extension of the epileptogenic network,³⁹ our findings support the view that early surgery should be offered to patients with pharmacoresistant TLE.⁴⁰

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by B. Bernhardt (Department of Neurology) and K. Worsley (Department of Mathematics).

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