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Cortical thickness analysis in temporal lobe epilepsy

Reproducibility and relation to outcome

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ABSTRACT

Objective: To assess the reproducibility of neocortical atrophy and its clinical significance across the spectrum of temporal lobe epilepsy (TLE), in particular with respect to postsurgical outcome.

Methods: MRI-based cortical thickness measurement was obtained in 105 patients. A total of 58 had hippocampal atrophy on magnetic resonance volumetry (TLE-HA) and 47 had normal hippocampal volumes (TLE-NV). Twenty-seven patients had repeated scans with a mean interval of 28 months. Patients were compared to 48 age- and sex-matched healthy controls. We used linear models to assess cortical thinning and the effect of seizure control after surgery. Reproducibility of finding cortical atrophy was statistically evaluated using bootstrap simulations.

Results: Cross-sectional and longitudinal analyses revealed highly similar topology and rates of neocortical thinning in both TLE groups, predominantly in frontocentral, temporal, and cingulate regions. Bootstrap methods showed that at least 20 subjects per group were necessary to reliably observe these patterns of atrophy in TLE. Moreover, power analysis showed that even with sample sizes of 80 subjects per group, differences in thickness between TLE-HA and TLE-NV would be marginal. With respect to postsurgical outcome, we found an association between residual seizures and atrophy in temporopolar and insular cortices in TLE-HA, and in the posterior quadrant in TLE-NV.

Conclusion: We demonstrated with a high degree of confidence that static and dynamic effects of epilepsy impact similarly the neocortex of patients with hippocampal atrophy and patients with normal hippocampal volumes. On the contrary, areas predicting unfavorable postsurgical outcome were distinct, suggesting different configurations of epileptogenic networks in these 2 groups. *Neurology*® 2010;74:1776–1784

GLOSSARY

CLASP = Constrained Laplacian Anatomic Segmentation using Proximity; **GM** = gray matter; **HA** = hippocampal atrophy; **LTLE** = left temporal lobe epilepsy; **NV** = normal hippocampal volumes; **RTLE** = right temporal lobe epilepsy; **TLE** = temporal lobe epilepsy; **WM** = white matter.

In temporal lobe epilepsy (TLE),[1] an in vivo hallmark of hippocampal sclerosis is hippocampal atrophy on MRI,[2,3] which is found in about 75%–85% of patients[4] and is generally associated with favorable postsurgical outcome. In these patients, volumetry has demonstrated additional atrophy in temporo-limbic regions, including the entorhinal, temporopolar, and lateral temporal cortices, as well as the thalamus.[5–8] Moreover, whole-brain morphometry has shown distant changes mainly in frontocentral regions.[9–12] These findings indicate that pathology in patients with hippocampal atrophy (TLE-HA) involves a wide corticosubcortical network. The relation of such changes to postsurgical outcome, however, remains unclear.

Despite improvements in conventional MRI, in up to 25% of patients with unambiguous electroclinical features of refractory TLE, hippocampal volumetry is unremarkable,[13,14] even though several studies have reported mild increases in T2 signal.[15,16] The absence of large-scale MRI features of hippocampal sclerosis has led to a somewhat diverse nomenclature for this

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group, including MRI-negative,[17] paradoxical,[18] TLE-no,[19] cryptogenic,[20] or normal hippocampal volume (TLE-NV).[14,15]

Histology of surgical specimens in TLE-NV has shown a lesser degree of neuronal loss in CA1 than TLE-HA,[13,14,21] but similar temporal cortical thinning.[22] Moreover, we have shown severe entorhinal cortex and thalamic atrophy in these 2 groups.[5,7] Whole-brain analysis, however, has provided conflicting results regarding neocortical damage and its topographic distribution.[19,20,23]

Our purpose was to assess patterns of cortical atrophy in TLE-HA and TLE-NV in an attempt to clarify its clinical significance, in particular with respect to postsurgical outcome. In addition to cross-sectional analysis, we performed a longitudinal evaluation to disentangle possible differences in pathologic trajectories between these 2 groups. Moreover, we assessed the reproducibility of cortical atrophy with respect to sample size using a bootstrap simulation approach.

METHODS

Subjects. Based on manual hippocampal volumetry,[5] we classified patients with medically intractable TLE from our database into TLE-HA and TLE-NV. TLE-HA had hippocampal volumes or an interhemispheric hippocampal asymmetry beyond 2 SD of the corresponding mean of healthy controls. We then selected patients with TLE-NV (n = 47) and TLE-HA (n = 58), with the constraint that there were no differences in age and gender distributions across patient and control groups. Patients with TLE-HA had a younger age at seizure onset ($t = 3.4$, $p < 0.002$), a longer duration of epilepsy ($t = 3.2$, $p < 0.002$), and a higher incidence of febrile convulsions (Fisher exact test, $p < 0.001$) than TLE-NV. None of the patients had a mass lesion (malformations of cortical development, tumor, or vascular malformations) or traumatic brain injury.

Demographic and clinical data were obtained through interviews with the patients and their relatives. TLE diagnosis and lateralization of the seizure focus into left TLE (LTLE) and right TLE (RTLE) were determined by a comprehensive evaluation including detailed history, neurologic examination, review of medical records, and video-EEG recordings in all patients.

Sixty-two (22 TLE-NV and 40 TLE-HA) patients were operated. Seven TLE-NV patients and 30 TLE-HA patients underwent a selective amygdalohippocampectomy. The remaining patients (i.e., 10 TLE-HA and 15 TLE-NV) underwent an anterior temporal lobe resection. We determined surgical outcome according to the Engel classification scheme[24] at a mean follow-up time of 3.9 ± 3.1 years. Thirty-three (53%) patients had an outcome Class I (28 Class Ia, 5 Class Ib), 10 (16%) Class II, 12 (19%) Class III, and 2 (3%) Class IV; 5 patients were lost to follow-up. Although the proportion of seizure-free patients was slightly higher in TLE-HA (58%) than in TLE-NV (45%), this difference was not significant (Fisher exact test). While proportions of patients who underwent a selective procedure were more elevated in TLE-HA than in TLE-NV (75% vs 32%, Fisher exact test, $p < 0.003$), the rate of seizure-free patients did not differ between the 2 surgical approaches. Following qualitative histopathologic analysis, hippocampal sclerosis was detected in 22/27 (81%) of available specimens in patients with TLE-HA and in 11/17 (64%) patients with TLE-NV. Degrees of cell loss and gliosis were generally more marked in patients with TLE-HA. None of the patients showed histopathologic evidence of cortical dysplasia. Due to subpial aspiration, specimens were unsuitable for histopathology in 18 (29%) patients.

Within our TLE population, a subset of 27 patients (15 TLE-HA, 12 TLE-NV) refused to undergo surgery at the first evaluation made by our epilepsy team. These patients, however, agreed to have follow-up MRI scans. Twelve of them eventually followed our recommendation and were operated at subsequent hospitalizations. In total, 57 serial MRI scans with 2 to 4 scans per subject were available. All images were acquired on the same scanner. The interval between the first and last scan was 28 ± 19 months (range = 7 to 90 months).

The control group consisted of 48 age- and sex-matched healthy individuals. Detailed information on patients and controls is presented in the table.

Standard protocol approvals, registrations, and patient consents. The Ethics Committee of the Montreal Neurological Institute and Hospital approved the study and written informed consent was obtained from all participants.

MRI acquisition and processing. MRI were acquired on a 1.5 T Gyroscan (Philips Medical Systems, Eindhoven, Netherlands) using a 3-dimensional T1-fast field echo sequence (repetition time = 18 msec; echo time = 10 msec; number of

Table Demographic and clinical data[a]

Group	Hippocampal volume (z scores)	Male	Age, y	Onset, y	Duration, y	Febrile convulsions	Surgery	Engel I[b]
Controls (n = 48)	0.0 ± 1.0	21	33 ± 12 (20-66)	—	—	—	—	—
LTLE-NV (n = 24)	0.3 ± 1.7	12	36 ± 12 (17-57)	22 ± 13 (2-54)	14 ± 10 (1-37)	2	9	3
LTLE-HA (n = 28)	−4.0 ± 1.4	13	33 ± 9 (19-52)	12 ± 9 (1-35)	22 ± 10 (6-42)	12	20	12
RTLE-NV (n = 23)	0.1 ± 1.0	8	35 ± 11 (17-63)	19 ± 12 (1-49)	16 ± 10 (1-35)	1	13	7
RTLE-HA (n = 30)	−3.4 ± 1.2	12	35 ± 11 (18-52)	14 ± 12 (1-38)	21 ± 12 (5-45)	13	20	11

Abbreviations: HA = hippocampal atrophy; LTLE = left temporal lobe epilepsy; NV = normal hippocampal volumes; RTLE = right temporal lobe epilepsy.

[a] Age, age at seizure onset, and duration of epilepsy are mean ± SD (range).

[b] Engel I: seizure-free, i.e., Class I postsurgical outcome in Engel's classification.

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excitations = 1; flip angle = 30°; matrix size = 256 × 256; field of view = 256 × 256 mm^2; slice thickness = 1 mm), providing an isotropic voxel of volume = 1 mm^3. Each image underwent automated correction for intensity nonuniformity and intensity standardization.[25] Images were linearly registered into a standardized stereotaxic space based on the Talairach atlas.[26]

For cortical thickness measurements, images were classified into gray matter (GM), white matter (WM), and CSF. To generate a model of the cortical surface and to measure cortical thickness across thousands of surface-spanning vertices, we applied the Constrained Laplacian Anatomic Segmentation using Proximity (CLASP) algorithm.[27] CLASP iteratively warps a surface mesh to fit the boundary between WM and GM in the classified image. It then expands the WM/GM boundary along a Laplacian map to generate a second outer surface that runs along the GM/CSF boundary. Extracted surfaces were nonlinearly aligned using a 2-D registration procedure that improves the anatomic correspondence of vertices in all subjects.[28] As in previous work,[29] thickness data were blurred using a surface-based diffusion-smoothing kernel of 20 mm FWHM that preserves cortical topologic features.

Statistical analysis. Statistical analysis was conducted using the SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat/) for Matlab (R2007a, The Mathworks, Natick, MA).

Cross-sectional analysis of atrophy. We assessed whether cortical thickness was reduced in each TLE group (i.e., *LTLE-HA, LTLE-NV, RTLE-HA, RTLE-NV*) relative to controls using 1-tailed *t* tests at each vertex.

In a separate analysis, we directly compared TLE-HA to TLE-NV using 2-tailed *t* tests. Finally, we performed an analysis restricted to patients who were completely seizure-free after surgery (i.e., Engel Class Ia). Thickness data from LTLE and RTLE were combined and analyzed relative to the epileptogenic lobe (i.e., ipsilateral and contralateral to the seizure focus) to increase statistical power.

Cross-sectional reproducibility and power analysis. We assessed the reproducibility of finding atrophy in TLE with respect to sample size using a bootstrap approach. For each TLE group and healthy controls, we randomly subsampled 15, 20, or 25 subjects with replacement 100 times. In sampling with replacement, after randomly drawing an individual from the original sample, this individual is put back before drawing the next one. At each iteration, we then performed vertex-wise 1-tailed *t* tests between the random TLE subsample and a subsample of controls. Finally, we mapped the probability of significant atrophy onto each vertex across all 100 iterations.

We estimated the sample size needed to detect a significant atrophy in TLE-HA relative to TLE-NV using vertex-wise power analysis.

Longitudinal analysis of atrophy. To examine dynamic changes in thickness in patients with multiple scans, we fitted linear mixed-effects models containing a fixed time from baseline scan and random subject term on cortical thickness at each vertex. We tested for a negative effect of time from baseline scan. We then assessed differences in progressive thinning between TLE-HA and TLE-NV using linear mixed-effects interaction models.

In addition, we assessed the interaction between seizure frequency and progressive cortical thinning. Based on the median seizure frequency of 7.5 seizures/month (range 0.1–102), we divided our longitudinal group into those with many seizures (>7.5 seizures/month) and few seizures (≤7.5 seizures/month).

Outcome analysis. We assessed the effects of complete seizure freedom (i.e., Engel Class Ia compared to Engel Ib–IV) following surgery on cross-sectional and longitudinal cortical thickness changes in TLE-HA and TLE-NV using linear models.

Correction for multiple comparisons. We corrected significances from vertex-wise analyses using random field theory for nonisotropic images on a cluster level.[30] This controls the chance of ever reporting a false positive finding to be below 0.05. To illustrate trends, significances were also displayed at an uncorrected threshold of $p < 0.005$.

RESULTS

Cross-sectional group analysis. Results are shown in figure 1. Compared to controls, TLE-HA and TLE-NV had similar patterns of neocortical atrophy. LTLE-NV had cortical thinning in bilateral frontal ($p < 0.004$), ipsilateral lateral temporal ($p < 0.002$), and bilateral temporo-occipital regions ($p < 0.04$). A trend was also observed in the ipsilateral entorhinal area. LTLE-HA had atrophy in bilateral frontal ($p < 0.0001$), lateral temporal ($p < 0.02$), temporo-occipital (ipsilateral $p < 0.03$; contralateral trend $p < 0.005$ uncorrected), and ipsilateral mesial-temporal (hippocampal, entorhinal, temporopolar $p < 0.0001$). Trends were seen in contralateral orbitofrontal and temporopolar regions. In RTLE, the pattern of changes was similar to LTLE with the exception of lateral temporal thinning that was present contralateral to the seizure focus in both TLE-HA and TLE-NV. Moreover, the distribution of atrophy was less widespread.

Comparison between TLE-HA and TLE-NV. The direct comparison of groups revealed no differences in overall mean cortical thickness in TLE-HA relative to TLE-NV (−1.5%, $t = 1.57$, $p = 0.13$). The direct vertex-wise contrast of TLE-HA to TLE-NV revealed also no neocortical differences, but ipsilateral mesiotemporal thinning in TLE-HA ($p < 0.01$) (figure e-1A on the *Neurology*® Web site at www.neurology.org). Power analysis based on these results showed that, even for a low power of 0.75 ($\alpha = 0.005$, minimum cluster size 20 vertices), we would have needed a total sample size of more than 160 subjects to detect marginal differences in neocortical thickness between these 2 groups (figure e-1B).

A separate analysis of the 19 TLE-HA and 9 TLE-NV patients with Class Ia postsurgical outcome confirmed ipsilateral mesiotemporal thinning ($p < 0.01$) as the only difference between these 2 groups.

Longitudinal analysis. Vertex-wise analysis (figure 2) revealed clusters of progressive cortical thinning in bilateral frontal (orbitofrontal, lateral frontal), posterior parietal, temporal (lateral and basal), and contralateral cingulate regions ($p < 0.01$). In each of the significant clusters, negative effects on mean cortical thickness ranged from 0.02 to 0.05 mm/year. Negative effects were highly similar in TLE-HA and TLE-NV. Indeed, the interaction analysis did not indicate

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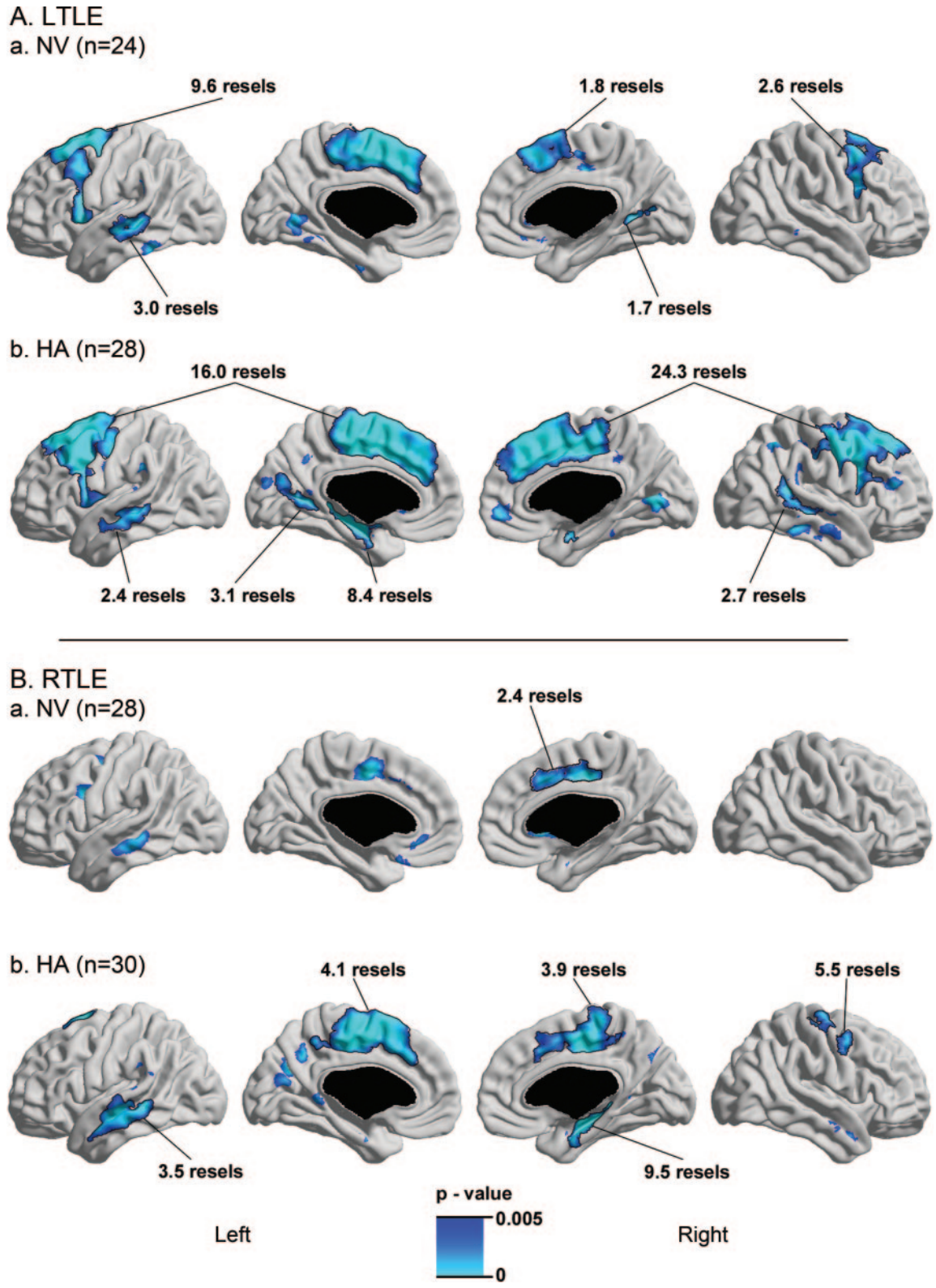
Figure 1 Cross-sectional analysis



Areas of thinning in patients with TLE compared to 48 healthy controls are presented by seizure focus lateralization and by group (A, left temporal lobe epilepsy; B, right temporal lobe epilepsy). Significant clusters ($t > 2.6$, extent > 1.5 resels), thresholded using random field theory, are indicated. Significances are also displayed at an uncorrected threshold of $p < 0.005$. TLE-NV = temporal lobe epilepsy with normal hippocampal volume; TLE-HA = temporal lobe epilepsy with hippocampal atrophy.

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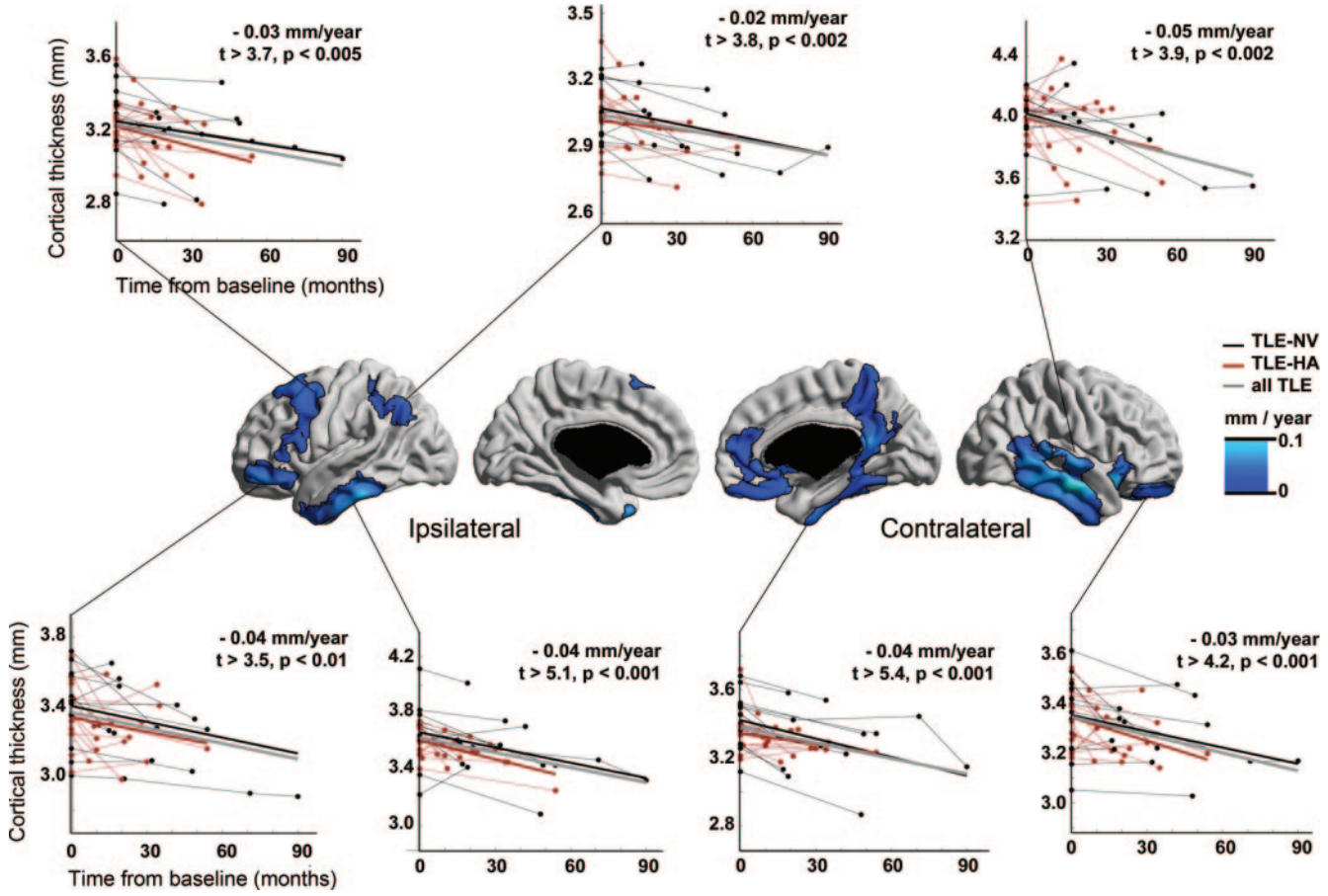
Figure 2 Longitudinal analysis



Progression of cortical thinning in temporal lobe epilepsy. For each significant cluster, the vertex-wise mean annual rate of cortical thinning (in mm/year) is shown. The insets display mixed-effects models on mean thickness in each cluster; the model for temporal lobe epilepsy with normal hippocampal volume (TLE-NV) is plotted as a solid black line, the model for temporal lobe epilepsy with hippocampal atrophy (TLE-HA) as a solid red line, and the model for both groups combined as a solid gray line. Cluster significance ($t > 2.0$, extent > 3.0 resels) was determined using random field theory.

any difference in slopes between the 2 TLE groups ($t < 1.3$, $p < 0.18$).

We did not find significant effects of seizure frequency on cortical thinning after correction for random field theory. However, there were small trends ($p < 0.005$ uncorrected) for faster cortical thinning in patients with high seizure frequency in the ipsilateral inferior temporal gyrus and contralateral central areas.

Relationship of neocortical atrophy to surgical outcome. Comparing the mean cortical thickness in clusters of atrophy between each TLE group and controls (see figure 1), we did not observe any difference ($t < 1.3$, $p > 0.15$) between seizure-free (Class Ia) and non–seizure-free individuals (Class Ib–IV). On the other hand, in TLE-NV vertex-wise comparison of non–seizure-free relative to seizure-free individuals revealed ipsilateral posterior laterotemporal, and contralateral parietal and occipital thinning ($p < 0.025$ uncorrected). In TLE-HA, non–seizure-free patients displayed ipsilateral temporopolar and bilateral insular atrophy ($p < 0.05$, figure 3). Trends were observed in the ipsilateral orbitofrontal and anterior cingulate regions.

In the longitudinal analysis, we noted more marked progressive bilateral frontocentral thinning in the 4 non–seizure-free relative to the 8 seizure-free individuals ($p < 0.01$) irrespective to the TLE grouping.

Reproducibility analysis. Bootstrap reproducibility analysis revealed that patterns of atrophy were reproducible in more than 75% of the simulations when sample sizes of at least 20 individuals per group were used (figure 4). On the other hand, at smaller group sizes, reproducibility dropped below chance level.

DISCUSSION To discriminate patterns of cortical atrophy, we performed separate cross-sectional comparisons of TLE-HA and TLE-NV to controls, and observed severe and highly reproducible neocortical thinning in both groups, predominantly in frontocentral and lateral temporal regions. The direct comparison between the 2 patient populations revealed more marked atrophy only in mesiotemporal regions

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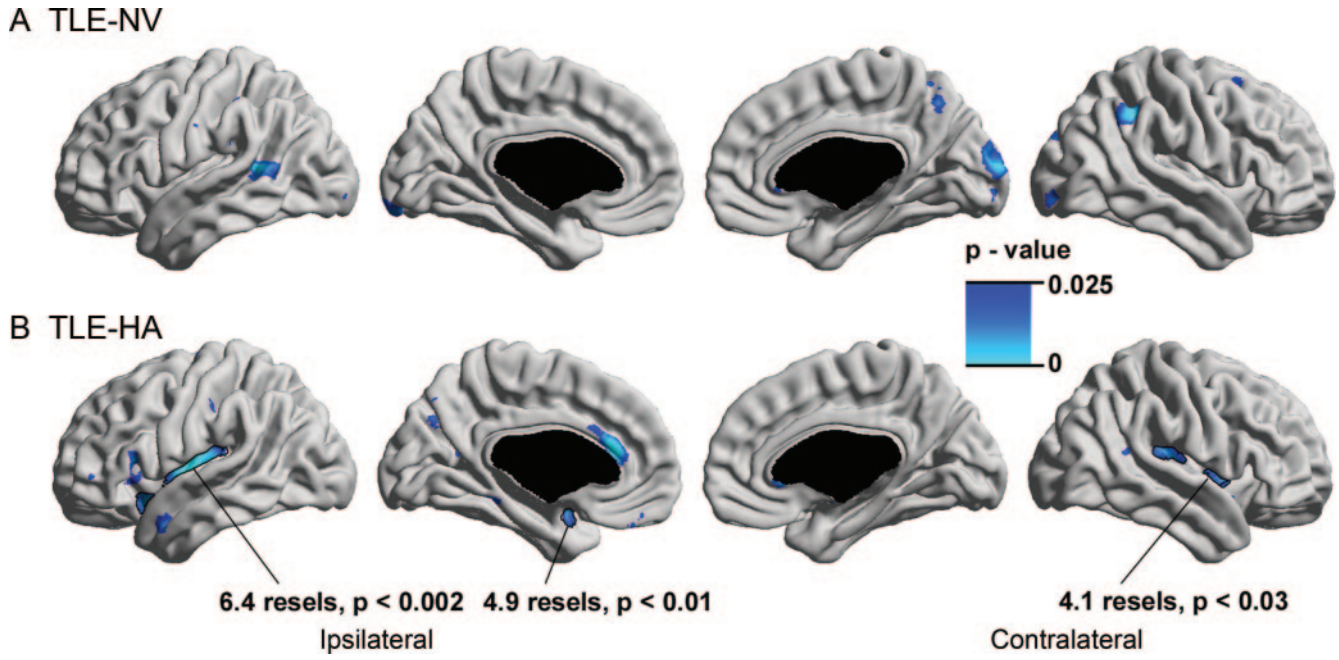
Figure 3 Predictors of surgical outcome



Areas of cortical thinning in patients with residual seizures (Engel Class Ib–IV) compared to seizure-free patients (Engel Class Ia) following surgery are shown. Significant clusters ($t > 2.6$, extent >1.5 resels), thresholded using random field theory, are indicated. Significances are also displayed at an uncorrected $p < 0.025$.

in TLE-HA. Confidence in our findings was provided by the vertex-wise power analysis demonstrating that our study was sufficiently powered and that the lack of dissociation in neocortical atrophy between these 2 groups was indeed due to negligible effect size. In our longitudinal analysis, we observed equivalent rates of marked bilateral frontal, temporal, and cingulate thinning in both TLE groups. Altogether, these findings indicate that TLE-HA and TLE-NV have similar patterns of static and dynamic pathology in neocortical regions remote from the seizure focus.

Contrary to previous whole-brain analyses that discriminated TLE groups based on qualitative analysis of the hippocampus,[19,20,23] we performed volumetry as an objective and sensitive mean to identify atrophy.[5,8,14] Our work also differs from previous studies with respect to clinical selection criteria. Indeed, while one report included patients with posttraumatic epilepsy,[19] none of our subjects had epilepsy related to head trauma, as they may present with different clinicopathologic features than nontraumatic TLE.[31] This excluded potential confounds related to structural changes due to the trauma itself.[32] On the other hand, our TLE subgroups differed with respect to clinical characteristics including age at seizure onset, duration of epilepsy, and the prevalence of a history of febrile convulsions, a finding also seen in previous studies.[18–20]

While there is overall agreement on widespread frontolimbic atrophy in TLE-HA,[33] the topographic distribution of neocortical damage in TLE-NV is subject to debate. It is likely that some of the variability encountered across various studies resulted from inadequate statistical power. Here, we evaluated the reproducibility of patterns of atrophy by carrying out a bootstrap resampling approach, thus approximating the variability of morphometric studies in TLE. Patterns of atrophy in our group comparisons were reproducible in at least 75% of simulations when using samples with more than 20 subjects per group. Reproducibility at smaller sample sizes, on the other hand, dropped below chance level. These results indicate that studies with relatively few subjects may suffer from low reproducibility, likely due to limited power and violations of the distributional assumptions when parametric statistics are used.

Our results showed a larger extent of structural abnormalities in LTLE, in accordance with data from voxel-based morphometry.[11,34] As suggested by diffusion MRI in healthy individuals, temporofrontal networks may be more extensively connected in the dominant (i.e., generally left) hemisphere, likely due to their involvement in language function.[35] Such increased anatomic connectivity may lead to more intense seizure propagation in the left hemisphere and more marked neuronal loss in LTLE.

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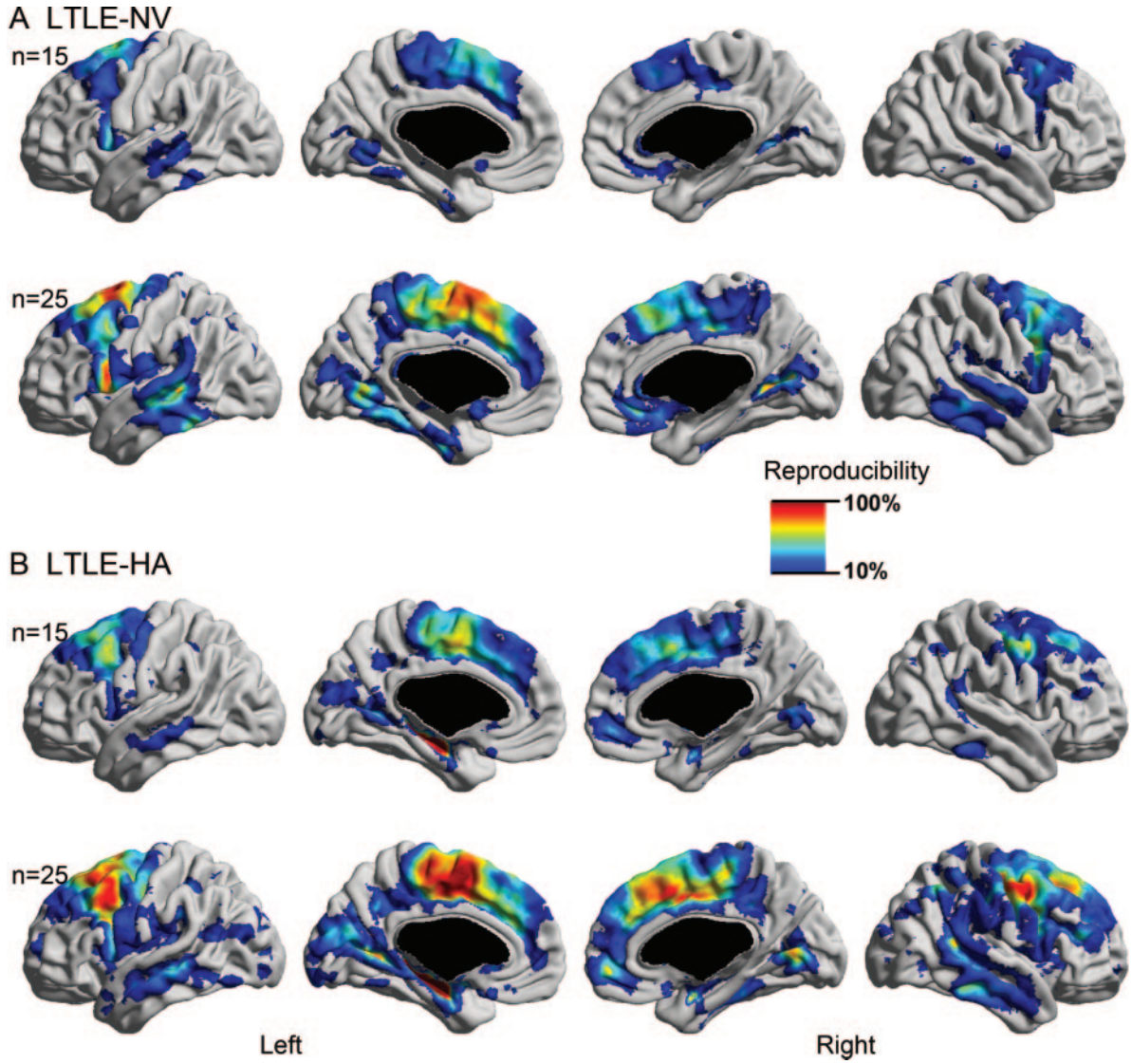
Figure 4 Reproducibility analysis of cortical thinning in temporal lobe epilepsy



The probability of observing atrophy ($p < 0.005$ uncorrected) throughout 100 random bootstrap resampling iterations (given a group size of n = 15 and n = 25) is shown at each vertex. Patterns of findings for right temporal lobe epilepsy were similar.

We performed a longitudinal evaluation to disentangle possible differences in pathologic trajectories between TLE-HA and TLE-NV that may have been missed by cross-sectional mapping. Longitudinal rates of thinning in these 2 groups were strikingly similar, encompassing bilateral frontal, central, cingulate, and lateral temporal cortices. Although the relatively small longitudinal sample may have limited the power to detect the full extent of damage within each TLE group, our finding of equivalent neocortical dynamics occurring despite different degrees of mesiotemporal lobe pathology further supports the concept that these 2 TLE entities are part of the same spectrum and that indeed longitudinal changes are most likely reflective of secondary effects of seizures.[36] We did not analyze the effect of seizure frequency and cortical thinning in the 2 TLE groups separately. However, when merging groups, we found trends for faster cortical thinning in patients with high seizure frequency in the ipsilateral inferior temporal and contralateral central cortices. Together with previous findings of cumulative structural and metabolic changes,[29,37,38] these results provide compelling evidence that TLE is likely a progressive disorder. We did not have longitudinal data available for our healthy controls. However, in a previous study,[29] we statistically highlighted cross-sectional differences in aging effects between patients with TLE and healthy controls and showed that cortical thinning in patients was considerably greater than normal aging across extended neocortical regions.

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Hippocampal atrophy is recognized as the most reliable structural MRI abnormality predicting favorable postsurgical outcome.[39,40] However, a relatively high proportion of TLE-HA patients with residual seizures after surgery motivate the search for additional morphometric surrogate markers for outcome prediction.

The predictive value of widespread neocortical damage with respect to surgery is unclear. Our post hoc evaluation in clusters of significant neocortical thinning detected by our cross-sectional group analysis did not reveal any relationship between the degree of neocortical atrophy and surgical outcome. However, regionally unbiased analysis across the entire cortex revealed an association between residual seizures and limbic atrophy encompassing temporopolar, insular, and cingulate cortices in TLE-HA, and posterior quadrant, particularly in the temporoparietal junction in TLE-NV. Thus, despite shared clinical semiology and patterns of neocortical atrophy, likely reflecting consequences of epilepsy, our findings suggest that mapping separately the configurations of epileptogenic networks is important to reliably determine seizure outcome after surgery in these 2 TLE groups.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by B.C. Bernhardt and Dr. N. Bernasconi.

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DISCLOSURE

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