Patterns of subregional mesiotemporal disease progression in temporal lobe epilepsy

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ABSTRACT

Objective: Evidence for disease progression in the mesiotemporal lobe is mainly derived from global volumetry of the hippocampus. In this study, we tracked progressive structural changes in the hippocampus, amygdala, and entorhinal cortex in drug-resistant temporal lobe epilepsy at a subregional level. Furthermore, we evaluated the relation between disease progression and surgical outcome.

Methods: We combined cross-sectional modeling of disease duration in a large cohort of patients ($n = 134$) and longitudinal analysis in a subset that delayed surgery ($n = 31$). To track subregional pathology, we applied surface-shape analysis techniques on manual mesiotemporal labels.

Results: Longitudinal and cross-sectional designs showed consistent patterns of progressive atrophy in hippocampal CA1, anterolateral entorhinal, and the amygdalar laterobasal group bilaterally. These regions also exhibited more marked age-related volume loss in patients compared with controls. We found a faster progression of hippocampal atrophy in patients with a seizure frequency ≥ 6 per month. High rates of contralateral entorhinal cortex atrophy predicted post-surgical seizure relapse.

Conclusion: We observed progressive atrophy in hippocampal, amygdalar, and entorhinal subregions that frequently display neuronal loss on histology. The bilateral character of cumulative atrophy highlights the importance of early surgery. In patients who nevertheless delay this procedure, serial scanning may provide markers of surgical outcome. *Neurology*® 2013;81:1840-1847

GLOSSARY

FDR = false discovery rate; **SPHARM-PDM** = spherical harmonics-point distribution model; **TLE** = temporal lobe epilepsy; **TLE-HA** = temporal lobe epilepsy-hippocampal atrophy; **TLE-NV** = temporal lobe epilepsy-normal hippocampal volume.

In drug-resistant temporal lobe epilepsy (TLE), MRI studies have established that structural brain abnormalities extend beyond the hippocampus to involve other mesiotemporal structures.^{1,2} The high diagnostic yield of MRI to identify mesiotemporal sclerosis, the histopathologic hallmark of TLE, has greatly streamlined the surgical workup of patients.³

Cross-sectional MRI volumetric analysis has provided preliminary evidence for disease progression, manifesting as cumulative mesiotemporal atrophy in relation to duration of epilepsy or seizure frequency.^{4,5} Because patients with drug-resistant TLE rarely refuse surgery, only one study has assessed longitudinal volumetric changes in a small cohort, limited to the hippocampus⁶; results suggested adverse effects of progressive atrophy on postsurgical outcome. The longitudinal impact of seizures on other key limbic structures, such as the entorhinal cortex and amygdala, has not been evaluated. Moreover, as previous work utilized global volumetric assessments, patterns of atrophy in subregions of mesiotemporal structures remain unknown. Spatially more refined evidence for cumulative damage across multiple mesiotemporal structures would reinforce motivation and possibly better guide early surgery in drug-resistant TLE.⁷

Our objective was to track progressive mesiotemporal pathology and its impact on postsurgical outcome in drug-resistant TLE. We combined cross-sectional mapping of epilepsy

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duration effects in a large cohort of patients and longitudinal analysis of within-subject changes in a subset that initially delayed surgery. To localize disease progression at a subregional level, we applied our previously developed and validated method based on spherical harmonic shape descriptors.⁸

METHODS Subjects. We studied 134 patients referred to our hospital for the investigation of drug-resistant TLE. Patient selection was done in randomized fashion from our database, with the constraint to include similar proportions of patients with unilateral left TLE ($n = 64$) and unilateral right TLE ($n = 70$). To study effects of epilepsy unconfounded by other pathologies, we excluded patients with 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 were determined by a comprehensive evaluation including detailed history, neurologic examination, review of medical records, video-EEG recordings, and MRI evaluation in all patients. Within our cohort, 23 of 134 patients (17%) underwent invasive recording. This procedure was undertaken to exclude either a temporal neocortical seizure generator (unilateral implantation; 8/23) or a bilateral temporal seizure onset (15/23). In the latter, in 7 of 15, stereo-EEG showed a unilateral seizure onset, whereas in the remaining 8, there was a late involvement of the contralateral mesial structures, including the entorhinal cortex.

The hippocampus, amygdala, and entorhinal cortex were segmented manually on the baseline MRI by the same rater (N.B.), blinded to the subject's category (patient, control) according to our previously published protocol.¹⁹ We have previously shown excellent intra- and interreliability in the measurement of these structures.⁹ Based on a manual volumetric assessment that takes into account absolute volume and interhemispheric asymmetry, we classified patients into those with hippocampal atrophy (TLE-HA, $n = 72$) and those with normal hippocampal volume (TLE-NV, $n = 62$). Patients with TLE-HA had a younger age at seizure onset ($t = 3.7, p < 0.0005$), a longer duration of epilepsy ($t = 3.2, p < 0.005$), and a higher incidence of prolonged febrile seizures (Fisher exact test, $p < 0.0005$) than those with TLE-NV.

Within our TLE population, a subset of 31 patients (19 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. Sixteen of them eventually followed our recommendation and were subsequently operated. In total, 67 serial MRI scans with 2 to 4 scans per subject were available. All images were acquired on the same scanner. The mean $\pm$ SD interval between the first and last MRI was 2.5 ± 1.4 years (range = 1–9.2 years). 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.

Ninety patients underwent a selective amygdalohippocampectomy. Mean $\pm$ SD follow-up time was 3.4 ± 3.1 years. We determined postsurgical seizure outcome according to Engel modified classification.¹⁰ Sixty-two patients (69%) had class I outcome, 7 (8%) class II, 13 (14%) class III, and 8 (9%) class IV. Although the proportion of seizure-free patients (i.e., those with class I outcome) was higher in TLE-HA (76%) than in TLE-NV (54%), this difference was only marginally significant ($p = 0.08$, Fisher exact test). After qualitative histopathologic analysis, hippocampal sclerosis was detected in all 66 patients in whom specimens were

available. In the remaining 24 patients, hippocampal specimens were either incomplete or unsuitable for examination due to subpial aspiration.

The control group for cross-sectional analysis consisted of 47 age- and sex-matched healthy individuals (23 males; mean $\pm$ SD age 32 ± 12 years; range = 20–66 years). Demographic and clinical data of all subjects are presented in tables 1 and 2.

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 scans of all subjects were acquired on a 1.5T Gyroscan (Philips Medical Systems, Eindhoven, Netherlands) using a 3-dimensional T1 fast field echo sequence (repetition time = 18 milliseconds; echo time = 10 milliseconds; number of excitations = 1; flip angle = 30°; matrix size = 256×256 ; field of view = 256 mm; slice thickness = 1 mm) that provides isotropic 1 mm³ voxels. Each scan underwent automated correction for intensity nonuniformity and intensity standardization.¹¹ Each baseline scan (i.e., first scans of the longitudinal cohort and all scans from the cross-sectional cohort) was linearly registered to the MNI152 template.¹² Longitudinal analysis was based on a 3-step process. First, follow-up scans were linearly registered to baseline scans of the same subject in native space. These mutually registered scans were linearly registered to stereotaxic space using the transformation parameters of the baseline scans, and finally nonlinearly registered to the baseline scan using a multiscale deformation that performs a global-to-local warping.¹³ Using the inverse of the nonlinear transform, mesiotemporal labels obtained on the baseline scans were mapped to each follow-up scan. The accuracy of the segmentation was verified in all subjects before further analysis.

Surface-based mapping of mesiotemporal subregional volumes. We have previously developed and validated a method to localize subregional structural changes.⁸ In brief, mesiotemporal labels of the baseline scan were converted to surface meshes and parameterized using spherical harmonics with a point distribution model (SPHARM-PDM).¹⁴ For each mesiotemporal structure, SPHARM-PDM surfaces of each individual were rigidly aligned to a template (constructed from the mean surface of controls and patients) with respect to the centroid and the longitudinal axis of the first-order ellipsoid. To correct for differences in overall head size, each surface was inversely scaled with respect to intracranial volume.¹⁴

To compute cross-sectional volume changes, we applied the heat equation to interpolate the vertex-wise displacement vectors within the volume enclosed by the SPHARM-PDM surface boundary.⁸ The Jacobian determinant of the resulting vector field was projected back onto the surface. By subtracting 1 from the Jacobian determinant, we quantified growth ($J > 0$) or shrinkage ($J < 0$) of a unit-size cube along the surface-normal direction.

To localize longitudinal changes, we projected the voxel-wise displacement vector field obtained between the follow-up and baseline scans to the baseline SPHARM-PDM surface of each mesiotemporal structure. This procedure guaranteed point-wise correspondence across subjects. The signed surface-normal components of these vectors corresponding to inward/outward deformation signify atrophy/hypertrophy, respectively.

Statistical analysis. Analysis was performed using SurfStat (<http://www.math.mcgill.ca/keith/surfstat/>) for MATLAB (R2011a; MathWorks, Natick, MA).¹⁵ The analysis framework in the current work closely follows the methodologic steps of a study that assessed the neocortex in TLE.¹⁶

Table 1 Demographic and clinical data of the cross-sectional cohort

Group	Age	Males	Duration	SF ^a	HA ^b	Surgery, n	Engel I ^c
Controls (n = 47)	33 ± 12 (20-66)	23	NA	NA	NA	NA	NA
LTLE (n = 64)	36 ± 12 (17-57)	30	19 ± 12 (0-42)	4 (1-150)	35 (55%)	39	24
RTLE (n = 70)	35 ± 10 (17-63)	27	20 ± 11 (0-45)	6 (1-330)	37 (53%)	51	38

Abbreviations: HA = hippocampal atrophy; LTLE = left temporal lobe epilepsy; NA = not applicable; RTLE = right temporal lobe epilepsy; SF = seizure frequency.

Age and duration of epilepsy are presented in years ± SD (range).

^aMedian (range) seizure frequency per month.

^bNo. of patients with hippocampal atrophy ipsilateral to the seizure focus (percentage of patients in the group).

^cEngel I = seizure-free, i.e., class I postsurgical outcome in Engel classification.

Cross-sectional analysis. We assessed effects of disease duration on mesiotemporal volumes (global and vertex-wise) using linear models. To examine interaction between duration of epilepsy and seizure frequency, we factorized seizure frequency with respect to its median (6/mo) into low (<6/mo) and high (>6/mo). We fitted a linear model with the factorized seizure frequency and its interaction with duration as additional terms.

Similarly, we assessed differences in the rate of progression between TLE-HA and TLE-NV using an interaction model (which contained effects of *group*, TLE-HA and TLE-NV, *duration*, and a *group* × *duration* interaction). Finally, we assessed effects of age in patients and controls, and analyzed differences in age-related volume change between patients and controls using interaction models (which contained effects of *group*, TLE and controls, *age*, and a *group* × *age* interaction).

Longitudinal analysis. To examine the effects of the inter-scan interval in patients who had longitudinal data available (n = 31), we fitted linear mixed-effects models containing *time from baseline-scan* as a fixed effect and *subject* intercept as random effect on mesiotemporal volumes (global and vertex-wise), and tested for a negative effect of *time from baseline-scan*. To assess differences in disease progression between TLE-HA and TLE-NV, we tested for interaction of *group* × *scan interval*.

Relationship to outcome. We used linear models to assess the relation between vertex-wise volume changes and postsurgical outcome. This analysis was performed in the cross-sectional and longitudinal cohorts separately.

Correction for multiple comparisons. We corrected our findings for multiple comparisons using the false discovery rate (FDR) correction at $q < 0.05$.¹⁷ To ascertain a uniform threshold and to control for the overall FDR, we applied a pooled correction approach across all structures tested.

Localization of findings. To facilitate the anatomical localization of results, we schematically outlined hippocampal,¹⁸ entorhinal,¹⁹ and amygdalar²⁰ subdivisions on the surface template according to histologic parcellation atlases.

RESULTS Cross-sectional analysis. Effects of duration.

Surface-based analysis showed that longer duration of epilepsy was associated with atrophy in bilateral hippocampal CA1 subfields, bilateral anterior and lateral entorhinal subdivisions, and the ipsilateral amygdalar laterobasal nuclear group ($t > 2.6$, FDR < 0.05). Effects of hippocampal atrophy were more marked ipsilaterally ($t = 3.9$, FDR < 0.05). We found a faster progression of hippocampal atrophy in patients with a high seizure frequency (≥ 6 /mo) compared with those who had a low seizure frequency (<6/mo) both ipsilateral and contralateral ($t > 2.6$, FDR < 0.05) to the seizure focus (figure 1).

TLE-subgroup analysis showed that patients with TLE-HA had higher rates of atrophy in the ipsilateral hippocampus and amygdala than those with TLE-NV ($t > 2.8$, FDR < 0.05). However, ipsilateral entorhinal cortex atrophy and contralateral changes in all 3 structures progressed at a similar rate in both groups ($t < 1.2$, FDR > 0.05).

Effects of age. Post hoc analysis in clusters of significant disease duration effects (see figure 1) revealed stronger negative aging effects in patients than controls in all mesiotemporal structures ipsilaterally, and nearly all contralaterally ($t > 2.6$, FDR < 0.05). In fact, the only structures that did not show evidence for stronger aging in patients were the contralateral hippocampus in left TLE and the contralateral entorhinal cortex in right TLE ($t < 1.4$, FDR > 0.2) (figure e-1 on the *Neurology*[®] Web site at www.neurology.org).

Table 2 Demographic and clinical data in the longitudinal sample

Group	Age	Males	Duration	SF ^a	HA ^b	Surgery	Engel I ^c
LTLE (n = 12)	32 ± 12 (17-50)	8	16 ± 11 (1-42)	4 (2-60)	7 (58%)	4	2
RTLE (n = 19)	32 ± 11 (17-48)	9	17 ± 12 (1-49)	8 (4-330)	12 (63%)	12	7

Abbreviations: HA = hippocampal atrophy; LTLE = left temporal lobe epilepsy; RTLE = right temporal lobe epilepsy; SF = seizure frequency.

Age and duration of epilepsy are presented in years ± SD (range).

^aMedian (range) seizure frequency per month.

^bNo. of patients with hippocampal atrophy ipsilateral to the seizure focus (percentage of patients in the group).

^cEngel I = seizure-free, i.e., class I postsurgical outcome in Engel classification.

Figure 1 Surface-based analysis of progressive mesiotemporal structural changes in TLE: Cross-sectional findings

Effects of duration of epilepsy on local volume changes are mapped on the hippocampus (A), entorhinal cortex (B), and amygdala (C). For each structure, linear regression fits are shown. Significances are thresholded at $FDR < 0.05$. *Faster progression of atrophy in TLE-HA (i.e., with hippocampal atrophy) relative to TLE-NV (i.e., with normal hippocampal volume). For each structure, schematic boundaries of subdivisions are outlined on the template. C = caudal; CA = cornu ammonis; CI = caudal limit; CM = centromedial nuclear group; DG = dentate gyrus; FDR = false discovery rate; Int = intermediate; LB = laterobasal nuclear group including lateral, basolateral, basomedial, and accessory basal nuclei; Lc = lateral caudal; Lr = lateral rostral; O = olfactory; R = rostral; SF = superficial nuclear group including cortical nuclei; TLE = temporal lobe epilepsy; TLE-HA = TLE-hippocampal atrophy; TLE-NV = TLE-normal hippocampal volume.

Longitudinal analysis. Results of the effect of interscan interval on changes in mean global hippocampal, entorhinal cortex, and amygdalar volume are shown in figure e-2.

Surface-based analysis localized progressive atrophy in hippocampal CA1 (ipsilateral: -0.034 ± 0.009 mm^3/y , $t = 7.4$; contralateral: -0.031 ± 0.013 mm^3/y , $t = 4.1$; figure 2A), entorhinal lateral subdivision (ipsilateral: -0.040 ± 0.012 mm^3/y , $t = 8.2$; contralateral: -0.033 ± 0.009 mm^3/y , $t = 6.2$; figure 2B), and the amygdalar laterobasal nuclear group (ipsilateral: -0.040 ± 0.018 mm^3/y , $t = 3.1$; contralateral: -0.036 ± 0.013 mm^3/y , $t = 4.3$; figure 2C).

Compared with TLE-NV, patients with TLE-HA showed higher rates of atrophy in the ipsilateral

hippocampus and amygdala ($t > 2.7$, $FDR < 0.05$), whereas ipsilateral entorhinal atrophy as well as contralateral changes progressed at a similar rate in both groups.

Relationship between disease progression and surgical outcome.

In the cross-sectional analysis, patients with residual seizures showed a more marked progression of atrophy in the contralateral entorhinal lateral subdivision relative to those who became seizure-free (-0.06 mm^3/y vs -0.01 mm^3/y , $t = 2.8$; figure 3A). This region was also predictive of surgical outcome in the longitudinal analysis, although bilaterally, with rates of atrophy approximately 4 orders of magnitude higher in patients with residual seizures compared with those who

Figure 2 Surface-based analysis of progressive mesiotemporal structural change in TLE: Longitudinal findings

Regions of significant atrophy (in mm^3/y) are mapped on the hippocampus (A), entorhinal cortex (B), and amygdala (C). For each significant cluster, mixed-effects model fits are shown. Significances are thresholded at $\text{FDR} < 0.05$. *Faster progression of atrophy in TLE-HA relative to TLE-NV. C = caudal; CA = cornu ammonis; Cl = caudal limit; CM = centromedial nuclear group; DG = dentate gyrus; FDR = false discovery rate; Int = intermediate; LB = laterobasal nuclear group including lateral, basolateral, basomedial, and accessory basal nuclei; Lc = lateral caudal; Lr = lateral rostral; O = olfactory; R = rostral; SF = superficial nuclear group including cortical nuclei; TLE = temporal lobe epilepsy; TLE-HA = TLE-hippocampal atrophy; TLE-NV = TLE-normal hippocampal volume.

became seizure-free (ipsilateral: $-0.042 \text{ mm}^3/\text{y}$ vs $-0.012 \text{ mm}^3/\text{y}$, $t = 2.9$; contralateral: $-0.039 \text{ mm}^3/\text{y}$ vs $-0.014 \text{ mm}^3/\text{y}$, $t = 3.2$; figure 3B).

Assessing simple effects of seizure frequency and epilepsy duration on surgical outcome did not reveal any differences between patients who were seizure-free and those who were not.

DISCUSSION We combined cross-sectional and longitudinal analysis of structural MRI to track progressive atrophy within the main constituents of the mesiotemporal TLE network, i.e., the hippocampus, the amygdala, and the entorhinal cortex. Contrary to previous work that focused on global volumetry,^{4,5} in the current study, we mapped subregional patterns of mesiotemporal atrophy. To this end, we used an MRI

postprocessing technique that quantified salient shape characteristics of the surface representation of each mesiotemporal structure while guaranteeing anatomical correspondence across subjects.^{8,14} This analysis localized progressive atrophy in hippocampal CA1, anterolateral entorhinal cortex, and the laterobasal amygdala bilaterally. Moreover, we were able to show more marked progressive entorhinal cortex atrophy in patients with seizure recurrence after surgery compared with those who became seizure-free. Finally, both our longitudinal and cross-sectional analyses yielded strikingly comparable patterns of anomalies, providing an important internal cross-validation of results.

Our results showed progressive atrophy in bilateral mesiotemporal regions, albeit changes were more marked ipsilateral to the seizure focus. Increased

Figure 3 Surface-based predictors of surgical outcome

(A) Cross-sectional mapping of the interaction between duration of epilepsy and postsurgical outcome. (B) Longitudinal mapping of the interaction between interscan interval and postsurgical outcome. Maps display regions where progressive atrophy is more marked in non-seizure-free (NSF) patients (Engel class II–IV) relative to seizure-free (SF) patients (Engel class I); inset scatter plots show the post hoc mean effect in significant clusters. See figure 1 for details on the statistical thresholding. C = caudal; CI = caudal limit; FDR = false discovery rate; Int = intermediate; Lc = lateral caudal; Lr = lateral rostral; O = olfactory; R = rostral.

sensitivity to detect contralateral atrophy compared with previous work^{4,5,21} likely stems from combined effects of studying a larger population, as well as performing a point-wise analysis of atrophy across the surface manifold. In the current work, while pathologic analysis confirmed hippocampal sclerosis in all patients, adequate tissue sample was not available for a systematic cross-validation of mesiotemporal subregions. Given that progressive atrophy occurs preferentially in areas displaying neuronal loss on histology,^{22,23} our results emphasize the ability of advanced structural MRI processing to unveil lesional tissue and progressive structural damage otherwise not detected on visual evaluation or global volumetry.²⁴

A limitation of the current study is the absence of serial MRI data in healthy controls, which would have provided a better control for normal aging. To circumvent this, in the cross-sectional analysis, we statistically compared effects of age on mesiotemporal volumes between patients and controls, and found stronger negative effects in clusters of progressive atrophy in the former. Even in the absence of longitudinal control data, we are, thus, confident that progressive atrophy in the mesiotemporal lobe, similar to that seen in the neocortex,¹⁶ is distinct from aging. Because we studied only

patients with electroclinical features of unilateral TLE, the finding of bilateral progressive changes may therefore represent adverse effects of seizure spread. Previous intracranial EEG studies have shown that seizures originating in the ipsilateral mesiotemporal region may propagate to the contralateral temporal lobe directly along commissural pathways²⁵ or indirectly via other regions, such as the frontal lobes.²⁶ In areas of propagation, seizures may disrupt the balance between excitatory and inhibitory synaptic signaling, altering glutamatergic²⁷ and GABAergic circuits,²⁸ contributing to the maintenance of seizure activity. Ultimately, neuronal death and synaptic rearrangement may ensue in both seizure-generating regions and contralateral target regions.²⁸

The inclusion of both patients with TLE-HA and TLE-NV permits the generalizability of our findings to a wide spectrum of drug-resistant patients. Directly comparing the trajectories of progressive atrophy between these 2 cohorts, we observed higher rates of ipsilateral hippocampal and amygdalar atrophy in TLE-HA. However, contralateral atrophy in these structures and bilateral entorhinal atrophy progressed at similar rates. We have previously shown that approximately two-thirds of patients with TLE-NV present

with marked entorhinal cortex atrophy,²⁹ a proportion similar to that seen in TLE-HA.³⁰ Furthermore, data from our group and others have shown comparable degrees of static and progressive thinning and gray matter volume loss in neocortical regions in the 2 cohorts.^{31,32} Current findings further support the concept that TLE-HA and TLE-NV are part of the same pathologic continuum. They also emphasize that the structural substrate of TLE is more accurately defined by a network of multiple interconnected regions,³³ rather than solely dependent on hippocampal damage.

The degree of progressive entorhinal cortex atrophy predicted postsurgical seizure outcome, both in the cross-sectional and longitudinal analyses. These group-level findings could be valuable in guiding future work based on statistical pattern learning techniques, to establish predictors of surgical outcome in individual cases. Previous postsurgical lesion mapping studies have established a relationship between the extent of entorhinal cortex resection and the chance of seizure freedom, regardless of the type of surgery.^{34,35} Our results showed that the degree of progressive entorhinal cortex atrophy contralateral to the seizure focus also relates to surgical outcome. Contralateral changes may be an indicator of the severity of the underlying epileptogenic process, and have predictive value independent of the degree of atrophy or extent of ipsilateral entorhinal resection. Collectively, these findings emphasize the key role of this structure in the epileptic network of TLE.³⁶ Indeed, the anatomical connectivity profile of the entorhinal cortex naturally situates it as a gatekeeper of signaling between the hippocampus and neocortex.^{37,38} In TLE, it has a key role in the propagation of mesiotemporal seizures originating from the hippocampus and amygdala.³⁹ Electrophysiologic studies have also shown that a large proportion of seizures originate in the entorhinal cortex itself.³⁹ Furthermore, this structure often hosts marked high-frequency oscillations shortly after seizure onset, a marker of epileptogenicity.³³ It could be argued that a faster rate of entorhinal atrophy is mainly related to a more severe underlying disease, so that early surgery would not help. This important point can be properly addressed through a longitudinal design with the first MRI evaluation at the time of seizure onset. It is likely that in some patients the disease may be more severe with bilateral anomalies early on. Nevertheless, the dynamic nature of atrophy in noncontrolled epilepsy, as shown here and in other studies, advocates early surgery to prevent further loss of neuronal tissue. Recurrent seizures and progressive structural changes may lead to epileptic discharges and further damage in other mesiotemporal structures and, in turn, extend the epileptogenic network.^{28,33} In patients who nevertheless delay surgery, serial scanning may allow establishing biomarkers of outcome.

AUTHOR CONTRIBUTIONS

Boris C. Bernhardt: drafting manuscript for content, including medical writing; study concept and design; statistical analysis and interpretation of data. Hosung Kim: drafting manuscript for content, including medical writing; study concept and design; MRI processing; statistical analysis and interpretation of data. Neda Bernasconi: revising manuscript for content, including medical writing; study concept and design; interpretation of data; acquisition of data; study supervision; obtaining funding.

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