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Structural Brain Changes Are Linked to Clinical and Cognitive Outcomes in Anti-LGI1 Encephalitis

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Abstract

Background and Objectives

Anti–leucine-rich glioma–inactivated 1 encephalitis (LGI1E) is traditionally considered as limbic encephalitis, but emerging evidence characterizes LGI1E as a whole-brain disorder. Furthermore, most neuroimaging studies have relied on cross-sectional designs and purely volumetric measures. Here, we integrate volume and fractal dimensionality (FD), a novel measure of structural complexity, to investigate cross-sectional and longitudinal brain changes in LGI1E and their associations with clinical and cognitive outcomes.

Methods

This observational study included 3T MRI, clinical evaluations, and comprehensive cognitive assessments at Charité – Universitätsmedizin Berlin. Patients with LGI1E underwent up to 3 study visits at median disease durations of 10, 46, and 58 months. Disease severity was rated using the modified Rankin Scale (mRS) and the Clinical Assessment Scale in Autoimmune Encephalitis (CASE). T1-weighted MRI was processed using FreeSurfer to extract volumetric data, alongside fractal analysis to estimate FD. Dominance analysis determined the relative importance of FD and volume. Longitudinal changes were examined using linear mixed-effects models in relation to age at onset, disease duration, and relapses.

Results

We studied 34 patients with LGI1E (median age: 67 years; 29% female; 52 study visits) and 34 age-matched and sex-matched healthy controls. Patients showed clinical improvement in both mRS and CASE scores from peak illness to first study visit. Morphological analyses revealed reduced FD in fronto-temporo-parietal cortices and reduced FD and volume in subcortical areas, with FD more frequently emerging as the more important measure in affected areas. Furthermore, reduced FD in the pallidum at the first study visit was associated with less mRS improvement since peak illness, while reduced accumbens volume was linked to less CASE improvement. Reductions in both FD and volume in frontotemporal cortices and subcortical areas were associated with impaired overall cognition, with FD more frequently emerging as the dominant measure in brain-cognition associations. Finally, longer disease duration and relapses were associated with longitudinal reductions in FD and volume in subcortical areas.

Discussion

LGI1E is characterized by widespread morphological brain alterations beyond the limbic system, with meaningful associations to clinical outcomes, cognitive function, and longitudinal disease course. FD emerged as the more comprehensive imaging marker, capturing unique morphological brain characteristics undetected by volumetry analyses.

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Supplementary Material

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Glossary

CASE = Clinical Assessment Scale in Autoimmune Encephalitis; **FBDS** = faciobrachial dystonic seizure; **FD** = fractal dimensionality; **FG** = fusiform gyrus; **HC** = healthy control; **ICU** = intensive care unit; **ICV** = intracranial volume; **IQR** = interquartile range; **ITG** = inferior temporal gyrus; **LGI1E** = anti–leucine-rich glioma–inactivated 1 encephalitis; **LMM** = linear mixed-effects model; **MOFC** = medial orbital frontal cortex; **MPRAGE** = magnetization-prepared rapid gradient-echo; **mRS** = modified Rankin Scale; **MTG** = middle temporal gyrus; **MTL** = medial temporal lobe; **POP** = pars opercularis; **PTR** = pars triangularis; **STG** = superior temporal gyrus; **TTC** = transverse temporal cortex.

Introduction

Anti–leucine-rich glioma–inactivated protein 1 encephalitis (LGI1E) is the second most common type of autoimmune encephalitis.[1] Clinical manifestations of LGI1E often evolve dynamically and include seizures, particularly the pathognomonic faciobrachial dystonic seizures (FBDSs), as well as behavioral changes and cognitive impairment.[1-3] Consistent with this evolving clinical course, routine clinical MRI typically demonstrates disease stage-dependent alterations.[4] During the FBDS stage, imaging is frequently unremarkable, although some patients show T1 and/or T2 hyperintensity of the basal ganglia contralateral to the side of FBDS.[5-7] In the subsequent encephalitic stage, approximately 70% of patients develop unilateral or bilateral T2/fluid-attenuated inversion recovery (FLAIR) hyperintensities in the medial temporal lobes (MTLs).[2,7-10] Independent of these acute MTL alterations, most patients later develop hippocampal atrophy, the extent of which correlates with the severity of memory impairment.[9,11,12] Owing to these characteristic MTL abnormalities, LGI1E has traditionally been classified as a limbic encephalitis. However, accumulating evidence from advanced MRI studies indicates more widespread brain involvement. In particular, resting-state fMRI and diffusion-weighted imaging studies have revealed alterations in both functional and structural connectivity extending beyond the limbic system.[10,13,14] These findings demonstrate a reorganization of large-scale brain networks, suggesting that LGI1E should be conceptualized as a whole-brain network disorder rather than a purely focal limbic encephalitis.[10,14]

Previous structural MRI studies have predominantly relied on volumetric analyses, most consistently reporting atrophy of the hippocampus and its subfields.[9-12] Although these findings underscore focal MTL involvement, they contrast with the brain-wide alterations revealed by recent network-based approaches, highlighting the need for more sensitive morphological measures to capture the subtle structural brain changes that may drive widespread network alterations. In addition, the relationships between structural brain alterations and extra-limbic cognitive impairments as well as broader clinical outcomes remain incompletely understood.

In this context, recent advances have highlighted fractal dimensionality (FD) as a novel morphological measure of structural complexity that is sensitive to brain shape characteristics and capable of detecting subtle structural changes beyond volumetric alterations.[15,16] In general, although volume reliably reflects the size of a brain structure, derived from the voxel counts of its segmentation mask, it does not account for how this structure is arranged in space. Consequently, 2 structures can have identical volumes but markedly different FD values, depending on differences in their morphology or, more intuitively, their shapes. Computationally, such differences are estimated from the spatial scaling properties of the voxel-indexed segmentation mask, as extensively validated in previous studies.[15-18] In healthy populations, FD has been shown to complement and often outperform standard morphological measures in detecting age-related brain changes.[15,17-20] Accumulating evidence has also shown systematic FD alterations in patients with various neurologic conditions, along with clinical and cognitive associations.[21-24] Although FD represents a promising new morphological measure, it has not yet been investigated in LGI1E. Consequently, it remains unclear whether these 2 morphological dimensions—fractal and volumetric brain changes—converge on shared structural alterations in patients and to what extent each measure uniquely captures clinical and cognitive outcomes in LGI1E. Finally, most previous studies on LGI1E have been cross-sectional,[9-12,25,26] limiting the ability to assess structural brain changes over the disease course. It thus remains largely unclear how the longitudinal trajectories of brain morphology relate to key clinical variables, including age at onset, disease duration, and clinical relapses.

To address these gaps, we conducted a comparative morphological neuroimaging study, combining cross-sectional and longitudinal analyses of fractal and volumetric brain changes, alongside detailed clinical characterization and cognitive assessment. Specifically, the study aimed to (1) characterize morphological brain alterations in patients with LGI1E compared with healthy controls, (2) explore the relationship between brain morphology and clinical as well as cognitive outcomes, (3) investigate the longitudinal trajectories of brain morphology during the postacute disease phase, and (4) systematically compare FD and volume in identifying disease-related brain changes and their associations with clinical and cognitive outcomes.

Methods

Participants

We prospectively enrolled 34 patients with LGI1E at Charité – Universitätsmedizin Berlin, Berlin, Germany. The median age was 67 years (interquartile range [IQR] 52–72);

10 patients (29%) were female, and 24 (71%) were male. Patients were enrolled in the postacute disease phase, defined as the period after discharge from acute hospitalization, and participated in a total of 52 study visits between June 2013 and July 2023. Baseline data were available for all patients, and 14 patients had at least 1 longitudinal follow-up visit. At each visit, patients underwent neurologic examination, neuropsychological testing, and MRI. Clinical information across the disease course was extracted from patients' medical records, including data on hospital admission, intensive care unit (ICU) treatment, and relapses.

All patients met the current diagnostic criteria for LGI1E, including detection of LGI1 autoantibodies in serum and/or CSF through cell-based assays.[27] Patients were included on referral to our reference center for autoimmune encephalitis, without predefined time-based inclusion criteria. We also included 34 healthy control (HC) participants matched to patients for age and sex using nearest neighbor matching in the R package MatchIt.[28] The median age of HCs was 66 years (IQR 50–70); 11 (32%) were female, and 23 (68%) were male. After matching, the groups were well matched for age ($Z = 0.546$, $p = 0.585$) and sex ($\chi^2 = 0.069$, $p = 0.793$).

Image Acquisition

T1-weighted images were acquired on a 3T Siemens Trio MRI scanner (Siemens, Erlangen, Germany) using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence. During the study period, the MRI hardware and acquisition protocol underwent a routinely planned upgrade. This upgrade included a transition from a 20-channel to a 64-channel head coil, along with adjustments in the repetition time from 1900 ms to 2500 ms, echo time from 3.03 ms to 2.64 ms, inversion time from 900 ms to 1000 ms, and flip angle from 9° to 8°. The resolution of the MPRAGE sequences remained consistent at $1 \times 1 \times 1$ mm^3 isotropic voxels, with a field of view of 256×256 mm^2 and 176 sagittal slices in both protocols. Given the protocol change, we conducted a control analysis to assess whether the new protocol had any systematic effect on brain measures. To this end, a subset of HCs from the old protocol were age and sex matched to HCs from the new protocol. No group differences in FD and volume were observed between protocols (eFigure 1).

Morphological Analysis

T1-weighted images were processed using the longitudinal processing pipeline in FreeSurfer 7.3.2,[29] yielding volumetric data of brain structures through cortical reconstruction and volumetric segmentation, based on the Desikan-Killiany atlas.[30] Intracranial volume (ICV) was estimated to control for the confounding effect of overall brain size. In addition, FD was computed for each brain structure using fractal analysis applied to the intermediate aparc+aseg.mgz files generated by FreeSurfer. To this end, we applied the dilation algorithm for filled volumes from the calcFD toolbox[15,18] in MATLAB, using canonical spatial ranges 2^k with k = 0, 1,…,4.

Clinical Outcomes

Neurologic function was assessed using the modified Rankin Scale (mRS) and the Clinical Assessment Scale in Autoimmune Encephalitis (CASE).[31] Scores were assessed at peak illness and at each postacute study visit. Changes in mRS and CASE scores from peak illness to each study visit were computed to quantify clinical outcomes.

Neuropsychological Assessment

All patients underwent comprehensive neuropsychological testing across 5 cognitive domains: (1) verbal episodic memory, assessed using the Rey Auditory Verbal Learning test; (2) visuospatial memory, assessed using the Rey-Osterrieth Complex Figure test; (3) working memory, assessed using the Digit Span Forward and Backward test; (4) executive function, assessed using the Stroop Color and Word test; and (5) attention, assessed using the Test Battery for Attention Performance. Cognitive composite scores at the first study visit were computed by first standardizing individual subscores, then averaging them within each cognitive domain, and finally averaging across all tests to obtain an overall cognition score. Reaction times were inverted to ensure that higher scores consistently express better performance. No associations were observed between years of education and overall cognition or any cognitive domain (eTable 1).

Statistical Methods

All statistical tests were performed using R version 4.4.0. Statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. Categorical data were expressed as proportions, while continuous data were expressed as either mean (SD) or median (IQR), depending on the distribution. After matching, sex differences between patients with LGI1E and HCs were examined using the χ^2 test. Owing to the skewed distribution, age differences were examined using the Wilcoxon rank-sum test. Moreover, mRS and CASE scores from peak illness to first study visit were paired and compared using the Wilcoxon signed-rank test.

Brain morphology comparisons between patients with LGI1E and HCs at first study visit were conducted using a two-sample permutation test based on mean differences. For these comparisons, morphological measures were adjusted for age and sex, and volumetric data were additionally adjusted for ICV. Effect sizes of between-group differences were quantified as Cohen's d (EnvStats and rstatix packages). The association between morphological measures and clinical outcomes on the mRS and CASE was assessed using a permutation test on Spearman's rank correlations (jmuOutlier and stats packages). Moreover, we analyzed the association between morphological measures and cognitive scores using a permutation test on product-moment correlations (jmuOutlier and stats packages). Dominance analysis was conducted to assess the relative contributions of FD and volume in identifying disease-related brain changes and morphology-cognition associations. To this end, the standardized dominance

statistic was calculated as the percentage of the general dominance statistic relative to the overall fit statistic (dominanceanalysis package).

To explore the longitudinal trajectories of brain morphology in LGI1E, we applied linear mixed-effects models (LMMs). Fixed effects included age at onset, disease duration measured from symptom onset to each study visit, sex, and relapse. ICV was included as an additional fixed effect when analyzing volumetric trajectories. Patient identity was incorporated as a random effect to account for individual variability. The effect size of each fixed effect was calculated using Cohen's *d* (lme4 and EMAtools packages). All permutation-based tests were performed with 5,000 simulations. To adjust for multiple comparisons, we applied the Benjamini-Hochberg method to control the false discovery rate (FDR) within tissue compartments because of the nested data structure of the segmentations.

Standard Protocol Approvals, Registrations, and Participant Consents

All participants provided written informed consent. Our study followed the STROBE guidelines, adhered to the Declaration of Helsinki, and was approved by the ethics committee of Charité – Universitätsmedizin Berlin (EA4/011/19).

Data Availability

Anonymized data may be shared upon request from qualified investigators by contacting the corresponding author.

Results

Clinical Trajectories of Patients With LGI1E

Figure 1 shows the clinical trajectories of individual patients. The baseline study visit for all 34 patients was conducted a median of 10 months after symptom onset (IQR 5–20). The second visit was conducted in 14 patients at 46 months (IQR 34–54), and a third study visit was conducted in 4 patients at 58 months (IQR 56–62). Two patients (6%) required ICU treatment for severe hyponatremia during the acute phase. Eight patients (24%) experienced a relapse, with the median time to relapse of 9 months after symptom onset (IQR 5–10). Immunotherapy exposure across study visits was as follows: 27 of 29 patients (93%) were receiving immunotherapy at the first study visit, 4 of 12 patients (33%) at the second study visit, and 1 of 3 patients (33%) at the third study visit. Additional treatment characteristics are summarized in eTable 2.

Clinical Outcomes

Figure 2 shows clinical outcomes of patients. The median mRS scores assessed at peak illness and during the 3 study visits were as follows: peak illness (n = 34): 3 (IQR 2–3), first study visit (n = 34): 1 (IQR 1–2), second study visit (n = 14): 1 (IQR 1–2), and third study visit (n = 4): 1 (IQR 0–1). A notable reduction in mRS scores was observed from peak illness to the first study visit (n = 34, $Z = 4.551$, $p < 0.001$; Figure 2A). Similarly, the median CASE scores were as follows: peak illness (n = 33): 5 (IQR 4–6), first study visit (n = 32): 2 (IQR 1–2), second study visit (n = 12): 2 (IQR 1–2), and third study visit (n = 4): 1 (IQR 0–1). A reduction in CASE scores was also observed from peak illness to the first study visit (n = 31, $Z = 4.888$, $p < 0.001$; Figure 2B).

Alterations of Brain Morphology in LGI1E

Compared with HCs, patients exhibited widespread morphological alterations across cortical and subcortical areas at the first study visit (Figure 3). In the cortex, alterations were observed exclusively for FD, encompassing a distributed pattern of reductions. The affected regions involved a frontotemporo-parietal cluster comprising the left pars opercularis (POP), pars triangularis (PTR), middle temporal gyrus (MTG), inferior temporal gyrus (ITG), precuneus cortex, and the bilateral inferior parietal cortex, as well as the left isthmus cingulate cortex. In subcortical areas, reductions were observed in both FD and volume in the bilateral hippocampus and accumbens (Figure 3, left). Among the 12 affected brain areas, FD and volume showed higher standardized dominance in 7 and 1 cortical areas, respectively, whereas both measures showed greater respective contributions in 2 subcortical areas (FD range: 44.3–80.5%; volume range: 19.5–55.7%) (Figure 3, right).

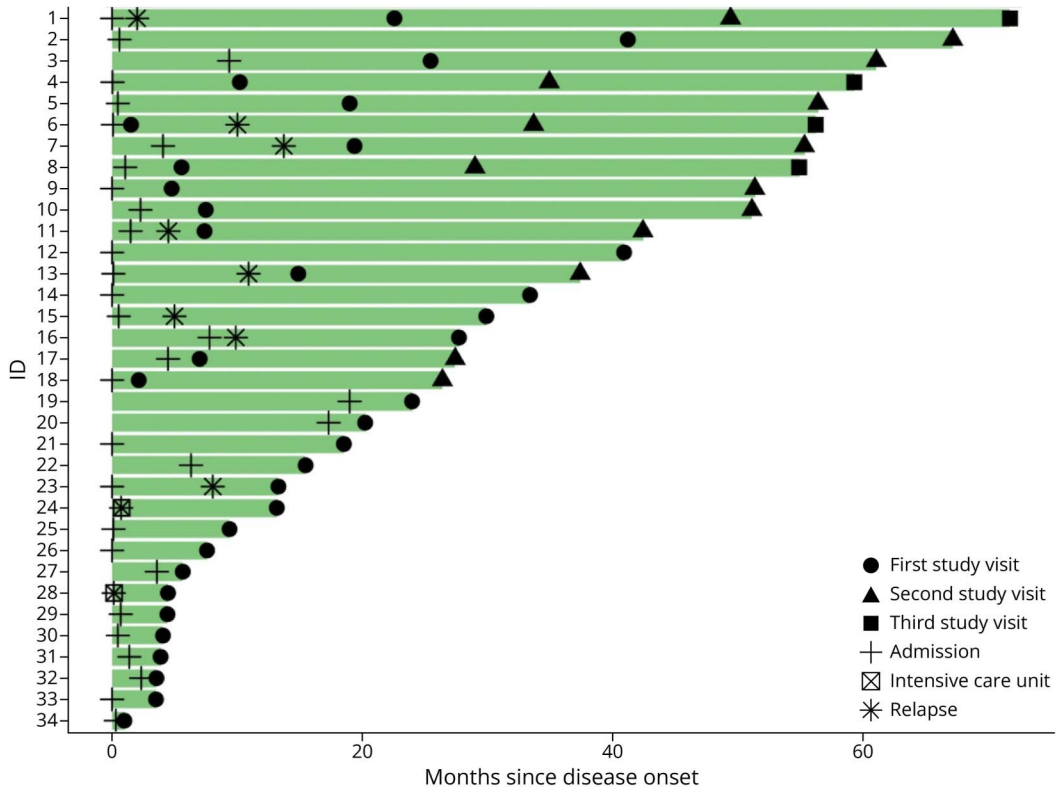
Associations Between Brain Morphology and Clinical Outcomes

Next, we investigated the relationships between brain morphology and clinical outcomes measured by mRS and CASE at the first study visit. Overall, reductions in FD and volume were associated with less clinical improvement. Specifically, FD uniquely correlated with clinical improvement in the mRS score in the bilateral pallidum (n = 34; left: $\rho = 0.510$, $P_{FDR} = 0.022$; right: $\rho = 0.466$, $P_{FDR} = 0.035$), whereas volume uniquely correlated with clinical improvement in CASE score in the bilateral accumbens (n = 31; left: $\rho = 0.480$, $P_{FDR} = 0.042$; right: $\rho = 0.483$, $P_{FDR} = 0.042$).

Associations Between Brain Morphology and Cognitive Performance

At the first study visit, FD and volume reductions were consistently associated with poorer cognitive performance. For the overall cognition composite score, FD showed more correlations in the cortex than volume. Shared correlation areas were observed for FD and volume in a frontotemporal cluster comprising the left superior temporal gyrus (STG), the right medial orbital frontal cortex (MOFC), PTR, transverse temporal cortex (TTC), and fusiform gyrus (FG), and the bilateral POP, as well as the left insula and postcentral gyrus. In subcortical areas, FD and volume correlated with overall cognition in the left pallidum, the right hippocampus, and the bilateral accumbens, amygdala, and thalamus, with additional associations for FD in the right pallidum and for volume in the left hippocampus (Figure 4A, left). Across the 31 brain areas showing morphology-cognition associations, FD exhibited higher standardized dominance in 19 areas,

Figure 1 Disease Course and Study Visits



The swimmer plot depicts the clinical course from disease onset to the most recent follow-up for each of the 34 patients with LGI1E. Icons indicate hospital admission, treatment in the intensive care unit, clinical relapse, and study visits. LGI1E = anti–leucine-rich glioma–inactivated 1 encephalitis.

compared with 12 for volume (FD: 31.3–83.7%; volume: 16.3–68.7%) (Figure 4A, right).

Beyond overall cognition, domain-specific analyses consistently revealed correlations unique to FD that were not observed with volume. In subcortical areas, both FD and volume correlated with verbal episodic memory in the right hippocampus and the bilateral accumbens. In addition, FD showed unique correlations in the left pallidum, the right caudate and putamen, and the bilateral thalamus. In the cortex, verbal episodic memory was correlated with FD and volume in the left postcentral gyrus and the right MOFC and TTC (Figure 4B, left). Among the 18 brain areas associated with verbal episodic memory, FD and volume exhibited higher standardized dominance in 11 and 7 areas, respectively (FD: 25.6–86.2%; volume: 13.8–74.4%) (Figure 4B, right). For working memory, correlations were exclusively observed for FD in the cortex, predominantly within a frontoparietal cluster and extending to distinct areas in the cingulate, insular, and temporal lobes (eFigure 2A, left). FD exhibited higher standardized dominance in 7 cortical areas, while volume was dominant in only 1 (eFigure 2A, right). Similarly, executive function showed unique cortical correlations with FD across 6 brain areas in the frontal, parietal, and insular lobes (eFigure 2B, left), with FD exhibiting higher standardized dominance across all these regions (eFigure 2B, right).

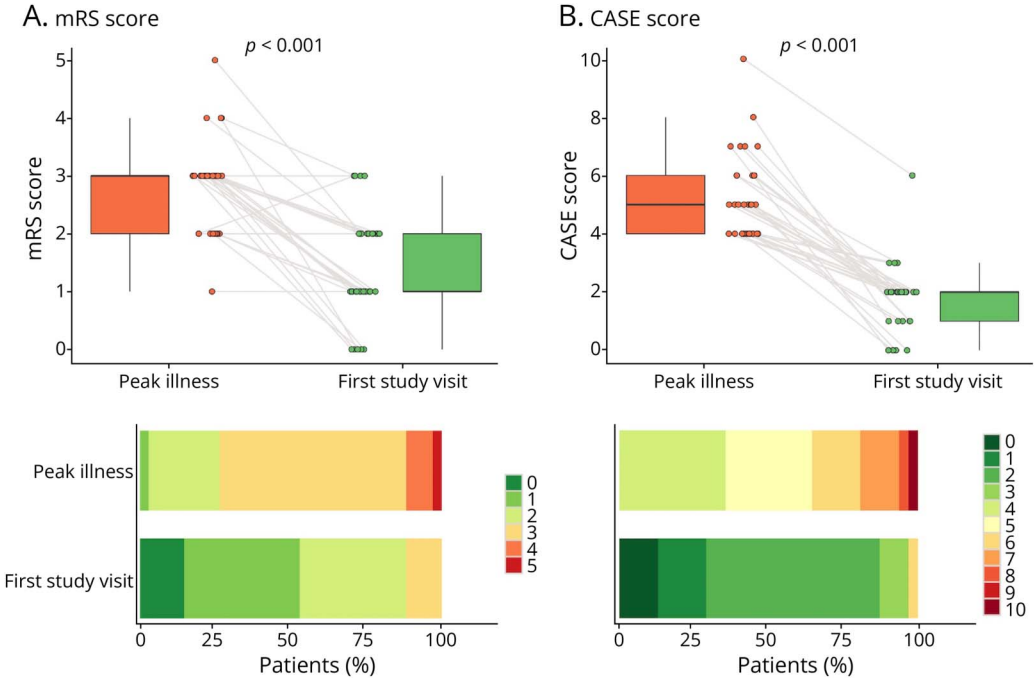
Determinants of Longitudinal Changes in Brain Morphology in LGI1E

Longitudinal analyses of brain morphology are summarized in Figure 5. Specifically, longer disease duration was associated with greater morphological declines in FD and volume in subcortical areas, including the left accumbens, caudate, and putamen, as well as the bilateral thalamus. In addition, FD showed a unique association with disease duration in the right amygdala (Figure 5A). Longitudinal trajectories of FD and volume across disease duration in the bilateral thalamus are additionally illustrated for patients with follow-up visits (eFigure 3).

Clinical relapses were associated with morphological deterioration in both FD and volume in subcortical areas. The right accumbens was the only area affected across both measures. In addition, relapses were uniquely associated with FD reductions in the right caudate and with volume reductions in the left caudate and putamen (Figure 5B).

Finally, we observed that older age at onset was associated with reductions in both FD and volume throughout cortical and subcortical areas. In both compartments, FD showed associations across a broader range of brain areas, fully encompassing those identified by volume. In the cortex, shared association areas involved a frontotemporal cluster comprising the left ITG; the right rostral middle frontal gyrus, MOFC, and TTC; and the

Figure 2 Clinical Outcomes of Patients With LGI1E on mRS and CASE Scores



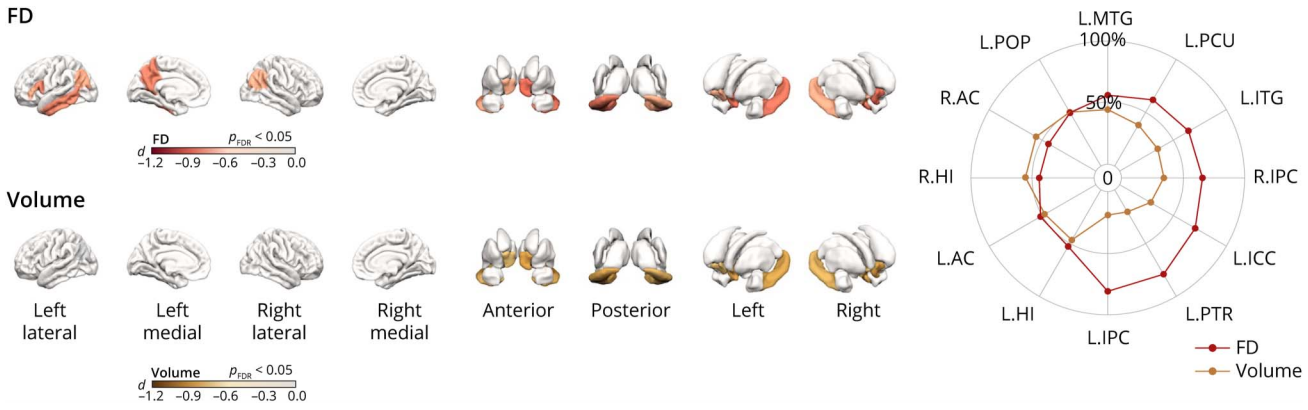
(A) Paired comparisons of the modified Rankin Scale (mRS) from peak illness to the first postacute follow-up visit (n = 34). The bottom panel shows the proportion of mRS scores at each time point (possible range: 0–6). (B) Paired comparisons of the Clinical Assessment Scale in Autoimmune Encephalitis (CASE) (n = 31). The bottom panel shows the proportion of CASE scores at each time point (possible range: 0–27). Both comparisons were assessed using the Wilcoxon signed-rank test. The median duration between peak illness and the first study visit was 7 months (interquartile range 4–16). LGI1E = anti–leucine-rich glioma–inactivated 1 encephalitis.

bilateral STG, MTG, and FG, as well as the left postcentral gyrus and posterior cingulate cortex, and the bilateral lateral occipital cortex. In subcortical areas, older age at onset was associated with reductions in both FD and volume in the left amygdala, and the bilateral accumbens and thalamus (Figure 5C).

Discussion

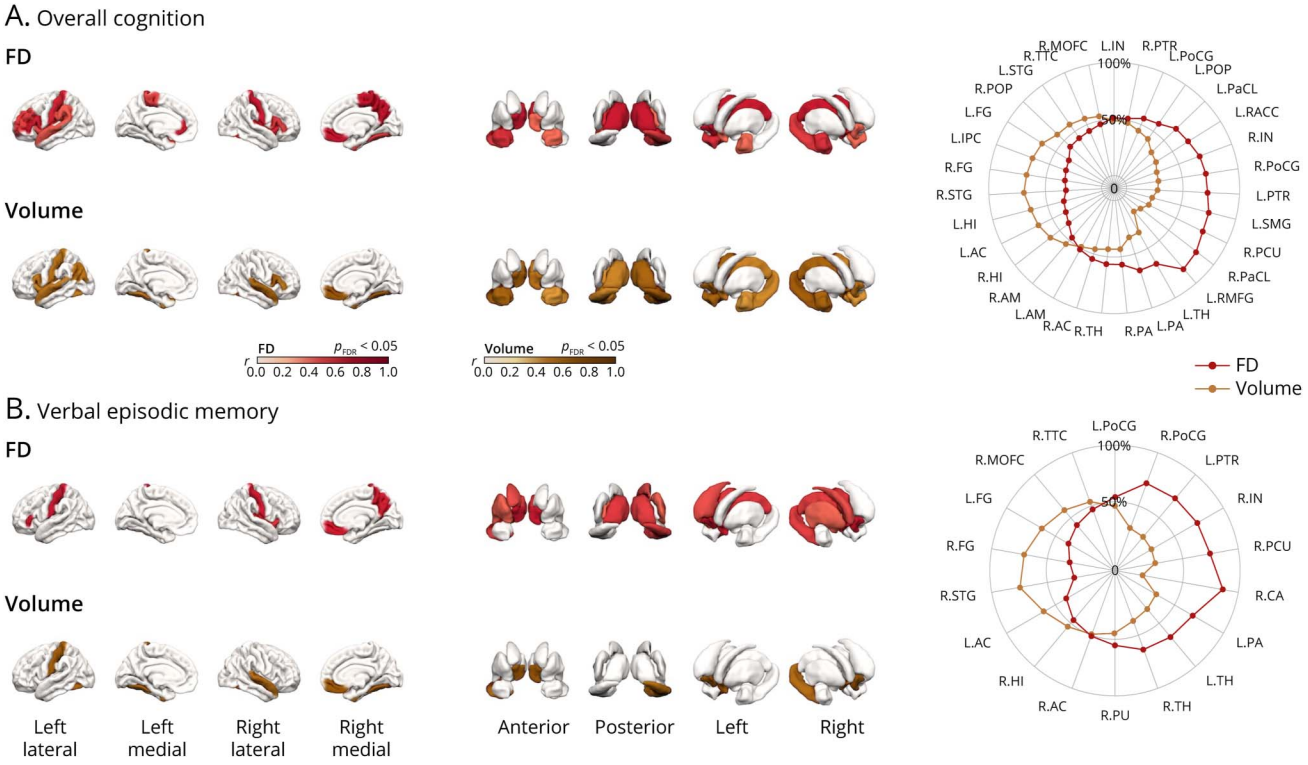
This structural neuroimaging study identified widespread morphological brain changes in LGI1E, which extended beyond the limbic system and showed meaningful associations

Figure 3 Morphological Brain Alterations in Patients With LGI1E at the First Study Visit



Morphological measures were compared between 34 patients with LGI1E and 34 healthy controls. Patients showed cortical reductions exclusively in FD and subcortical reductions in both FD and volume in the hippocampus and accumbens. Color bars illustrate the effect size (Cohen's *d*) for between-group differences at a threshold of $P_{FDR} < 0.05$ (left). Dominance analysis quantified the relative contributions of FD and volume across the 12 altered brain areas. FD and volume exhibited higher standardized dominance statistics in 9 and 3 areas, respectively. Subcortical areas are highlighted in gray (right). AC = accumbens; FD = fractal dimensionality; HI = hippocampus; ICC = isthmus cingulate cortex; IPC = inferior parietal cortex; ITG = inferior temporal gyrus; L. = left; LGI1E = anti–leucine-rich glioma–inactivated 1 encephalitis; MTG = middle temporal gyrus; PCU = precuneus cortex; POP = pars opercularis; PTR = pars triangularis; R. = right.

Figure 4 Morphological Associations With Overall Cognition and Verbal Episodic Memory in Patients With LGI1E

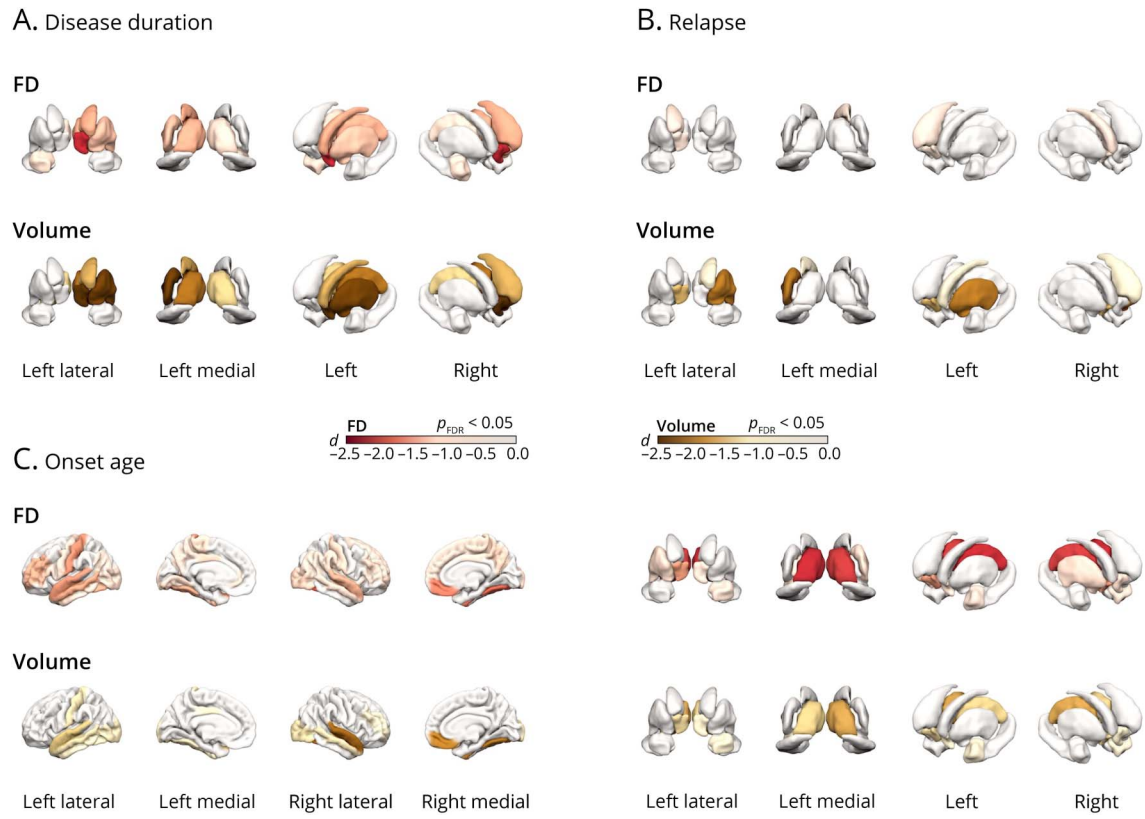


(A) Region-wise correlation analyses (left) showed that reductions in FD and volume in cortical and subcortical areas were associated with worse overall cognition (n = 32 patients). Color bars indicate the correlation coefficients, thresholded at $P_{FDR} < 0.05$. Dominance analyses (right) showed that FD and volume contributed more in 19 and 12 brain areas, respectively. Subcortical areas are highlighted in gray. (B) Reductions in FD and volume in cortical and subcortical areas were associated with worse verbal episodic memory (n = 31 patients). FD and volume contributed more in 11 and 7 areas, respectively. AC = accumbens; AM = amygdala; CA = caudate; FD = fractal dimensionality; FG = fusiform gyrus; HI = hippocampus; IN = insula; IPC = inferior parietal cortex; L. = left; LGI1E = anti–leucine-rich glioma–inactivated 1 encephalitis; MOFC = medial orbital frontal cortex; PA = pallidum; PaCL = paracentral lobule; PCU = precuneus cortex; PoCG = postcentral gyrus; POP = pars opercularis; PTR = pars triangularis; PU = putamen; RACC = rostral anterior cingulate cortex; RMFG = rostral middle frontal gyrus; R. = right; SMG = supramarginal gyrus; STG = superior temporal gyrus; TH = thalamus; TTC = transverse temporal cortex.

with clinical outcomes, neuropsychological performance, and disease course. To this end, our morphological analyses integrated traditional volumetry with FD, a more recent measure of structural complexity that captures brain shape characteristics and has shown high sensitivity to both age-related and disease-related brain changes in previous studies. Integrating fractal analysis identified a more comprehensive morphological signature of LGI1E that (1) captured widespread disease-related brain changes in both limbic and extra-limbic areas, (2) showed novel associations with clinical and cognitive outcomes, and (3) reflected broad associations with key aspects of the disease course, including disease duration, clinical relapses, and age at onset. Across all these analyses, FD emerged as a more comprehensive measure for characterizing structural brain features in LGI1E, detecting unique cortical morphological patterns not captured by volume, while showing comparable performance in subcortical regions. This was further corroborated by dominance analysis, which highlighted the substantial contribution of FD relative to volume, particularly in cortical areas. Together, these findings provide a more comprehensive understanding of structural brain changes in LGI1E and highlight FD as a promising neuroimaging marker for capturing disease-related structural characteristics.

Patients with LGI1E showed widespread alterations in brain morphology spanning both limbic and extra-limbic areas. These findings support the view that LGI1E is not restricted to a focal "limbic" encephalitis but rather represents a whole-brain disorder, in line with recent evidence.[10,13,14,32,33] Both FD and volume were reduced in patients, albeit with substantial variability in their respective spatial distributions. Specifically, FD showed widespread reductions across both cortical and subcortical areas, whereas volume changes were limited to subcortical structures. Notably, both FD and volume showed reductions in the hippocampus and accumbens, with hippocampal volume loss replicating previous cross-sectional findings in LGI1E.[9-12,25,26] However, volume appeared less sensitive to cortical alterations, consistent with previous findings from voxel-based morphometry in LGI1E.[9-11] By contrast, FD uniquely captured morphological alterations across the cortex and more frequently emerged as the dominant measure within these cortical regions. This may relate to the heterogeneous distribution of LGI1 expression across the brain, with strong enrichment in the hippocampus, whereas lower LGI1 expression across the cerebral cortex may yield more subtle morphological alterations that are detected by FD beyond overt volumetric loss.[34-36] The brain areas

Figure 5 Associations of Disease Duration, Relapse, and Age at Onset With Longitudinal Changes in Brain Morphology



Region-wise associations between disease course and longitudinal trajectories of brain morphology were estimated using linear mixed-effects models in patients with LGI1E. (A) Longer disease duration was associated with greater morphological declines in FD and volume in subcortical areas. (B) Clinical relapse was associated with morphological deterioration in FD and volume in subcortical areas. (C) Older age at onset was associated with morphological reductions in FD and volume across cortical and subcortical areas. Color bars indicate the effect sizes (Cohen's *d*) for each brain area, thresholded at $P_{FDR} < 0.05$. FD = fractal dimensionality; LGI1E = anti–leucine-rich glioma–inactivated 1 encephalitis.

exhibiting FD reductions have been linked to altered functional connectivity in previous fMRI studies of LGI1E,[10,13] particularly resembling disruptions within the default mode network. This overlap may indicate a link between structural and functional brain alterations in LGI1E. Furthermore, our structural analysis suggests a left-predominant alteration pattern in LGI1E, with FD reductions primarily identified in the left cortex and larger effect sizes for FD and volume reductions in left subcortical areas. This asymmetry is consistent with a previous study reporting asymmetrically distributed LGI1 expression in the human brain.[36]

Patients with LGI1E exhibited good clinical outcomes, with substantial reductions in both mRS and CASE scores from peak illness to the first study visit, consistent with previous clinical outcome studies in LGI1E.[14,37-39] Furthermore, we observed that reduced FD and volume were associated with less clinical improvement in a measure-specific and score-specific way. Specifically, mRS improvement was uniquely associated with FD in the pallidum, whereas CASE improvement was uniquely associated with accumbens volumes, both within the basal ganglia where LGI1 expression has been observed in the human brain.[36] The basal ganglia have been implicated in white matter network changes in LGI1E, suggesting convergent microstructural and macrostructural alterations.[14] Moreover, previous neuroimaging studies of LGI1E have reported an association between pallidal volume reduction and longer FBDS duration,[9] whereas an accumbens-centered metabolic network was associated with both CASE and cognitive dysfunction.[40] Taken together, these distinct morphological associations indicate the clinical relevance of both limbic and extra-limbic systems in LGI1E.

Overall, both FD and volume reductions were associated with impaired cognitive performance in patients. These morphological associations were domain specific, involving verbal episodic memory, working memory, and executive function, but not visuospatial memory or attention. Similar domain-specific associations in LGI1E have been observed with other advanced neuroimaging techniques.[9,10,14,25] Our morphological analyses also identified shared association areas between FD and volume, highlighting their crucial roles in cognitive processing in LGI1E. Specifically, both FD and volume showed morphology-cognition associations in the hippocampus, paralimbic insular cortex, and extra-limbic STG, aligning well with previous neuroimaging findings in

LGI1E.[9-12,25] In addition, associations with overall cognition were observed for both measures in the MOFC, amygdala, and postcentral gyrus. Notably, prefrontal-amygdala circuits are increasingly recognized for their involvement in high-level cognitive functions, such as social cognition, decision making, and emotion regulation.[41,42] The postcentral gyrus, traditionally linked to somatosensory function, has also been increasingly recognized for its role in executive function as part of the frontoparietal control network, and in verbal episodic memory through functional connections to medial temporal regions.[43,44]

Beyond these shared signatures, FD demonstrated more extensive associations with cognitive performance than volume, yielding robust associations with overall cognition and 3 cognitive domains (i.e., verbal episodic memory, working memory, and executive function) that were not equally identified with volume. This was particularly evident for cortical effects in the cognitive domains of working memory and executive function, where morphology-cognition associations were exclusively observed with FD. In subcortical regions, FD and volume exhibited comparable associations with overall cognition and verbal episodic memory, whereas FD additionally revealed unique morphology-cognition associations in the thalamus and basal ganglia, aligning well with previous reports of altered structural and functional connectivity in these areas.[13,14] Regarding their relative contributions to morphology-cognition associations, FD more frequently emerged as the dominant measure for overall cognition in both cortical and subcortical areas. Across cognitive domains, FD consistently exhibited higher dominance effects, with particularly strong contributions in cortical regions.

Patients' longitudinal changes in brain morphology were systematically related to key clinical factors, including disease duration, clinical relapses, and age at onset. Specifically, longer disease duration was associated with more pronounced declines in both FD and volume in subcortical areas. The spatial distribution of these effects included not only the accumbens but also extra-limbic structures, such as the caudate, putamen, and thalamus, aligning well with LGI1 expression patterns reported in experimental and clinical studies.[34-36] The continuous reductions in FD and volume in these areas over time may thus reflect ongoing pathologic processes that contribute to the long-term symptoms of LGI1E, including persistent cognitive dysfunction, psychiatric disturbances, and seizures.[2,37,39] By contrast, we did not observe any associations between disease duration and cortical morphology, paralleling the previously reported normalization of cortical dysmetabolism during the convalescent phase.[32,33]

Our study population exhibited a relapse rate of 24%, which is comparable with the 14–35% reported in previous long-term LGI1E studies spanning over 2 years.[2,45] Here, clinical relapses were associated with morphological deterioration in both FD and volume in subcortical areas. The involvement of limbic areas such as the accumbens—along with extra-limbic structures such as the caudate and putamen—may reflect the diversity of recurring symptoms during relapses, such as cognitive impairment and seizures.[3,45] We observed fewer and less pronounced associations between clinical relapses and morphological measures compared with other fixed effects (i.e., disease duration or age at onset). This observation suggests a comparatively less pronounced impact of clinical relapses on longitudinal brain changes, which is paralleled by the fewer and milder symptoms reported during relapses compared with the initial episode in LGI1E.[45] Similarly, we observed no longitudinal effects of clinical relapses on cortical morphology.

Finally, older age at onset was associated with morphological reductions in both FD and volume across cortical and subcortical areas. Notably, FD encompassed all brain areas identified by volume in both compartments, reflecting its greater sensitivity regarding age-related changes across the brain in LGI1E. This high sensitivity of FD to age-related changes has consistently been reported in healthy populations[15,17-20] and may be particularly relevant in LGI1E, where older age is a prominent epidemiologic characteristic. These morphological associations, together with previous evidence that older age at onset predicts greater CNS involvement,[46] may help explain poorer clinical outcome associated with increasing age in patients with LGI1E.[47]

Our study has some limitations. First, patients were enrolled upon referral, resulting in variable postonset durations for each study visit among individual patients. Although this variability was statistically accounted for within LMMs, more homogeneous time intervals might allow for a more detailed understanding of longitudinal brain changes in LGI1E. Second, the relationship between cognitive scores and structural brain changes warrants further study in light of our findings, particularly regarding longitudinal cognitive trajectories, adjustments for age and years of education, and potential interaction effects between age-related and disease-related changes. Third, longitudinal neuroimaging data were not available for HCs, which limits our ability to compare the longitudinal brain trajectories of patients with healthy trajectories.

Because larger and more densely sampled longitudinal cohorts become increasingly available, future studies will be able to explore the potential effects of immunotherapy on the morphological alterations, as well as the morphological features that may predict long-term outcomes in individual patients. Furthermore, because our study focused on structural brain changes after the acute phase, future studies identifying these changes at earlier stages of the disease may facilitate earlier diagnosis and intervention, ultimately enhancing clinical translation.

In sum, this structural neuroimaging study integrating FD offers a more comprehensive understanding of brain

morphology in LGI1E and further supports its reconceptualization as a whole-brain disorder. Fractal analysis consistently identifies unique morphological signatures that are not detected by traditional volumetry, positioning FD as a promising new imaging marker for assessing disease progression and prognosis in patients with LGI1E.

Author Contributions

W. Zhao: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. K. Wurdack: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. F. Bartels: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. G. Cammà: major role in the acquisition of data; analysis or interpretation of data. A.E. Bozem: major role in the acquisition of data; analysis or interpretation of data. A. Romanello: study concept or design; analysis or interpretation of data. M.M. Mantwill: study concept or design; analysis or interpretation of data. H. Prüss: major role in the acquisition of data; study concept or design. F. Paul: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. C.J. Ploner: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. C.R. Madan: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. S. Krohn: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. C. Finke: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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