

Original Research

MRI-Negative Temporal Lobe Epilepsy: A Study of Brain Structure in Adults Using Surface-Based Morphological Features

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Abstract

Background: This research aimed to delve into the cortical morphological transformations in patients with magnetic resonance imaging (MRI)-negative temporal lobe epilepsy (TLE-N), seeking to uncover the neuroimaging mechanisms behind these changes. **Methods:** A total of 29 individuals diagnosed with TLE-N and 30 healthy control participants matched by age and sex were selected for the study. Using the surface-based morphometry (SBM) technique, the study analyzed the three-dimensional-T1-weighted MRI scans of the participants' brains. Various cortical structure characteristics, such as thickness, surface area, volume, curvature, and sulcal depth, among other parameters, were measured. **Results:** When compared with the healthy control group, the TLE-N patients exhibited increased insular cortex thickness in both brain hemispheres. Additionally, there was a notable reduction in the curvature of the piriform cortex (PC) and the insular granular complex within the right hemisphere. In the left hemisphere, the volume of the secondary sensory cortex (OP1/SII) and the third visual area was significantly reduced in the TLE-N group. However, no significant differences were found between the groups regarding cortical surface area and sulcal depth ($p < 0.025$ for all, corrected by threshold-free cluster enhancement). **Conclusions:** The study's initial findings suggest subtle morphological changes in the cerebral cortex of TLE-N patients. The SBM technique proved effective in identifying brain regions impacted by epileptic activity. Understanding the microstructural morphology of the cerebral cortex offers insights into the pathophysiological mechanisms underlying TLE.

Keywords: magnetic resonance imaging; MRI-negative temporal lobe epilepsy; structural imaging; surface-based morphology

1. Introduction

Temporal lobe epilepsy (TLE) is the predominant form of focal epilepsy in adults. However, about 30% of individuals with TLE do not exhibit detectable abnormalities on standard magnetic resonance (MR) scans, a condition termed magnetic resonance imaging (MRI)-negative TLE (TLE-N) [1]. The etiology of epilepsy is multifaceted, with its primary cause attributed to the secondary effects of aberrant synchronous neural discharges [2]. These epileptiform discharges can inflict damage on diverse cortical and subcortical structures [3]. Research indicates that 40% of non-lesional patients, despite having normal MRI and histopathology results, can achieve seizure freedom [4]. Treating TLE-N remains particularly challenging due to its low remission rates [5]. Chronic recurrent seizures lead to high disability rates, compelling most patients to rely on lifelong medication, which significantly deteriorates their quality of life and imposes a severe psychological toll on them and their families. Thus, early diagnosis, comprehensive evaluation, and timely surgical intervention are crucial for managing TLE-N effectively.

Surface-based morphometry (SBM) is a sophisticated image processing technique that analyzes MR imaging data of brain structures. It quantifies gray matter morphology by assessing parameters such as cortical thickness, surface area, volume, curvature, and sulcal depth. This method can detect various types, stages, and severities of neurological conditions, revealing subtle gray matter differences that conventional brain images might miss [6,7]. Prior studies have uncovered significant brain morphological abnormalities and cortical atrophy in the hemispheres of TLE patients [8,9]. In TLE patients, SBM has identified increased complexity in temporal and frontal cortical folding distant from the epileptic focus, along with widespread cortical thinning in regions connected to the hippocampus [10]. As we all know, TLE has strong heterogeneity and numerous subtypes, among which the surgical success rate of TLE-N is low. There is a paucity of research on the brain morphology of TLE-N patients. Our study utilizes high-resolution three-dimensional-T1-weighted image (3D-T1WI) sequences to employ the SBM method in analyzing cerebral cortex structures from multiple parameter perspectives, aiming to identify structural differences in the cortical regions of TLE-N.



patients. By doing so, we seek to evaluate the brain areas impacted by epileptiform discharges in TLE-N and elucidate the underlying pathophysiological mechanisms.

Recently, MRI has gained widespread use in neuroimaging due to its non-invasive nature, high spatial resolution, and lack of ionizing radiation [11,12]. Among them, structural magnetic resonance imaging is valuable since it examines the morphological changes in the entire brain, providing valuable insights into the brain structure changes related to epilepsy. Study has observed that unilateral TLE patients experience extensive and progressive gray matter and subcortical atrophy [13]. Furthermore, white matter damage has been identified in these patients [13]. Diffusion tensor imaging studies have depicted significant abnormalities in fiber bundles related to epileptogenic foci within the temporal lobe, including the corpus callosum, cingulum, fornix, and thalamic cortex projection [14,15]. The damage to white matter fiber pathways could reflect alterations and structural connection changes in the brain. Some researchers have applied voxel-based morphological (VBM) analysis to quantitatively determine density or volume changes of gray and white matter at the voxel level [16]. SBM can simultaneously measure multiple morphological parameters such the thickness, volume, surface area, and curvature of the cerebral cortex, in contrast to VBM analyses, which primarily concentrate on minute variations in volume [17]. The SBM method compensates for this deficiency and enables a more comprehensive evaluation of the brain's morphological changes.

2. Materials and Methods

2.1 Participants

A total of 29 patients, clinically diagnosed with TLE-N, admitted to the Affiliated Brain Hospital of Nanjing Medical University between August, 2018 and August, 2022, were selected for the case group. Concurrently, 30 healthy volunteers recruited during the same timeframe formed the control group. The case group inclusion criteria were (1) no significant abnormalities on conventional brain MR images, (2) age between 15 and 65 years, and (3) clinical diagnosis confirmed by two senior neurologists based on the latest International League Against Epilepsy classification criteria. This diagnosis was corroborated by clinical symptoms, electrophysiological data, and clinical treatment evidence, with subsequent validation by pathology or stereoelectroencephalography (SEEG). Exclusion criteria included (1) presence of other neurological or psychiatric disorders, (2) severe physical ailments, and (3) contraindications to MRI scanning. For the control group, inclusion criteria were (1) no abnormalities on conventional brain MR images, (2) no history of neurological or psychiatric disorders, and (3) no family history of epilepsy.

Patients or their families/legal guardians were informed of the study's objectives and procedures and provided signed informed consent. The study protocol re-

ceived approval from the Affiliated Brain Hospital of Nanjing Medical University's medical ethics committee (Ethics Approval number: 2017-KY118-01).

2.2 Data Acquisition and Processing

All participants underwent MRI scans using a GE 3.0T Discovery MR750 scanner (GE, Chicago, IL, USA), with foam pads employed to minimize head movement. Participants were instructed to keep their eyes closed and remain still during the scan. Each participant had an initial MRI session, during which a three-dimensional fast low angle shot (3D-FLASH) sagittal scan was performed to obtain high-resolution 3D-T1WI of the entire brain. The scanning parameters were: repetition time = 2300 ms; echo time = 3.2 ms; flip angle = 12°; field of view = 100 × 100 mm²; matrix = 256 × 256; slice thickness = 1 mm; number of slices = 192.

The T1-weighted images were analyzed to measure cortical thickness, surface area, and curvature using DPABISurf_V1.8 software (<http://rfmri.org/DPABISurf>), a surface-based morphometry data analysis toolbox based on Linux 22.04 and matlab 2121b. The entire process was automated, starting with the dissemination of the T1-weighted (T1W) image using Advanced Normalization Tools (ANTs 2.2.0, <https://stnava.github.io/ANTs>) [18], followed by intensity non-uniformity (INU) correction with N4BiasFieldCorrection [19]. This T1W-reference was used throughout the workflow. Skull-stripping was performed using antsBrainExtraction.sh (ANTs 2.2.0) with the OASIS30ANTs template as the target. Brain surfaces were reconstructed using recon-all (FreeSurfer 6.0, <https://surfer.nmr.mgh.harvard.edu/fswiki/DownloadAndInstall>) [20], with enhancements to the brain mask through a proprietary method variation to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray matter of Mindboggle [21]. Spatial normalization to the ICBM 152 nonlinear asymmetrical template version 2009c was achieved using nonlinear registration with antsRegistration (ANTs 2.2.0). Segmentation of brain tissue into white matter (WM), gray matter (GM), and cerebrospinal fluid (CSF) was conducted using FSL (FSL 5.0.9, <https://fsl.fmrib.ox.ac.uk/fsl/docs/#/>) [22].

The DPABISurf software V1.7. (<http://rfmri.org/DPABISurf>) provided mean thickness, surface area, and cortex curvature based on cerebral atlas labeling, using the Human Connectome Project (HCP) template for cortical division. Finally, a 10 mm Gaussian smoothing kernel (full width at half maximum) was applied to smooth the left and right cortices of the participants.

2.3 Statistical Analysis

Using SPSS version 23.0 (IBM, Armonk, NY, USA) independent sample *t*-test to compare the age differences between the TLE-N group and the healthy controls (HC) group, and using Chi-square test to compare the sex com-

position differences. $p < 0.05$ is considered statistically significant. Imaging data that did not meet quality standards due to artifacts or abnormal brain structures were excluded. If initial scans were flawed, a second scan was attempted, and data from participants whose scans still did not meet quality standards were discarded. Senior imaging experts and neurologists reviewed all subject images to ensure quality. In our study, two subjects' images were excluded due to artifacts.

Group-level analyses were conducted to identify brain regions with significant cortical abnormalities in TLE-N patients. Cortical maps from TLE-N patients were compared with those of HC using permutation-based statistical analysis with 10,000 permutations (two-tailed), accounting for age and sex as covariates. Statistical significance was set at $p < 0.025$ (left and right cerebral hemispheres separately), and based on previous research, we used threshold-free cluster enhancement (TFCE) for multiple comparisons [23,24].

3. Results

3.1 Comparison of Clinical Data between the Case and Control Groups

The study included a total of 29 patients with TLE in the case group and 30 healthy volunteers in the control group. The case group comprised 12 males and 17 females, with a mean age of 26.20 ± 5.63 years, whereas the control group comprised 12 males and 18 females, with a mean age of 23.76 ± 4.39 years. No significant difference was observed in age and sex between the groups ($p \geq 0.05$; Table 1).

3.2 Comparison of Cortical Thickness between the Case and Control Groups

Comprehensive analysis of whole brain cortical thickness revealed that patients with TLE-N exhibited increased cortical thickness in the posterior insular 1, Left Area a24, anterior ventral insular area and right middle insular area compared with healthy controls at baseline (Table 2, $p < 0.025$, corrected by TFCE). As shown in Fig. 1, the corrected SBM analysis revealed a predominant concentration of cortical thickness in the insular cortex among TLE-N patients (Fig. 1).

3.3 Comparison of Cortical Curvature between the Case and Control Groups

Analysis of cortical curvature in the right cerebral hemisphere demonstrated that patients with TLE-N had reduced cortical curvature in the Piriform Cortex ($t = -6.23$, cluster size = 139 mm^2) and the Insular Granular Complex area ($t = -6.20$, cluster size = 75 mm^2) compared with healthy controls at baseline (see Fig. 2 and Table 3, $p < 0.025$, corrected by TFCE).

3.4 Comparison of Cortical Volume between the Case and Control Groups

Cortical volume analysis of the left cerebral hemisphere indicated that patients with TLE-N had a lower cortical volume in the secondary sensory cortex (OP1/SII) area ($t = -6.03$, cluster size = 129 mm^2) and the third visual area ($t = -4.52$, cluster size = 60 mm^2) compared with healthy controls at baseline (see Fig. 3 and Table 4, $p < 0.025$, corrected by TFCE).

3.5 Comparison of Cortical Area and Sulcal Depth between the Case and Control Groups

Analysis of the cortical area and sulcal depth revealed no statistically significant difference between patients with

Table 1. Participant demographics.

	TLE-N (n = 29)	Controls (n = 30)	p value
Age (years)	26.20 ± 5.63	23.76 ± 4.39	0.068 ^a
Sex (female/male)	17/12	18/12	0.914 ^b

^at-test. ^bChi-squared test. TLE-N, magnetic resonance imaging (MRI)-negative temporal lobe epilepsy.

Table 2. Group differences in cortical thickness between case and control groups.

Location	HCP	Cluster size (mm ²)	MNI coordinate			t value
			X	Y	Z	
Right Area Posterior Insular 1	167	128	35.98	-19.06	-0.51	6.71
Right Middle Insular Area	109	89	38.61	0.97	-0.74	5.13
Right Anterior Ventral Insular Area	111	54	31.15	19.95	3.87	5.61
Left Area Posterior Insular 1	167	436	-35.28	-18.39	-0.57	8.11
Left Anterior Ventral Insular Area	111	219	-28.26	22.62	5.17	4.87
Left Area a24	61	128	-7.30	35.87	-7.47	5.32

HCP, Human Connectome Project; MNI, Montreal Neurological Institute. $p < 0.025$.

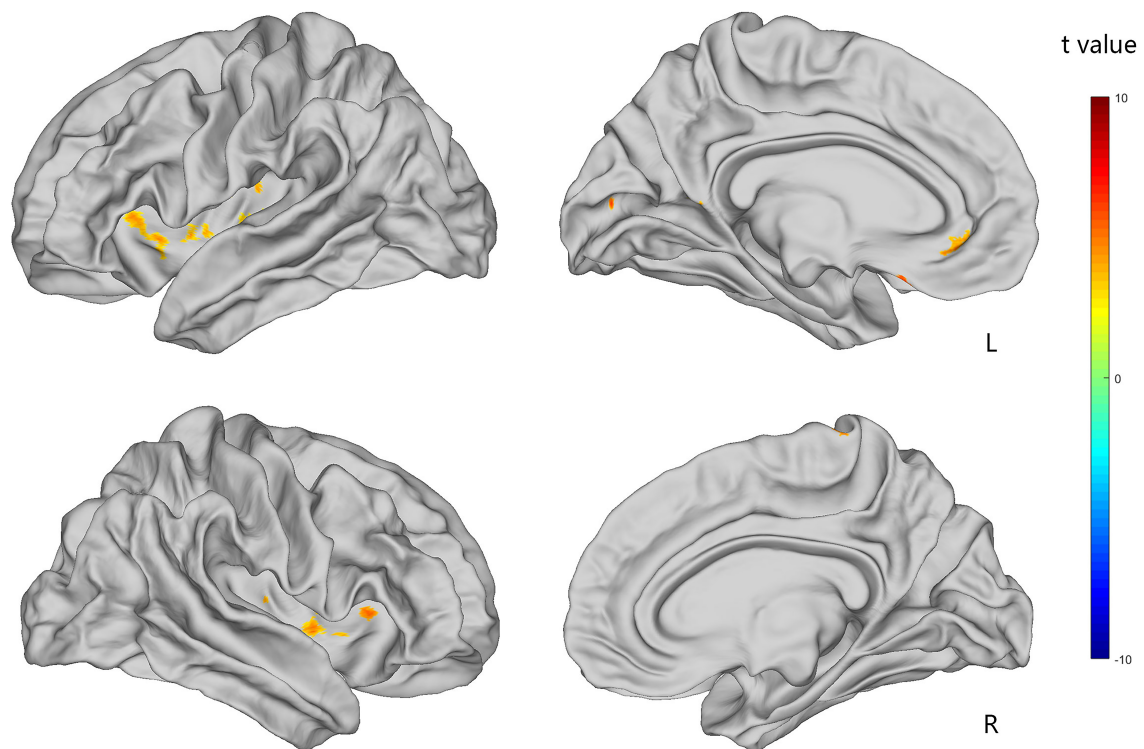


Fig. 1. Comparison of cortical thickness between HC group and TLE-N group. According to surface-based morphometry (SBM) analysis, the red area indicates an increase in cortical thickness compared to the healthy controls (HC) group.

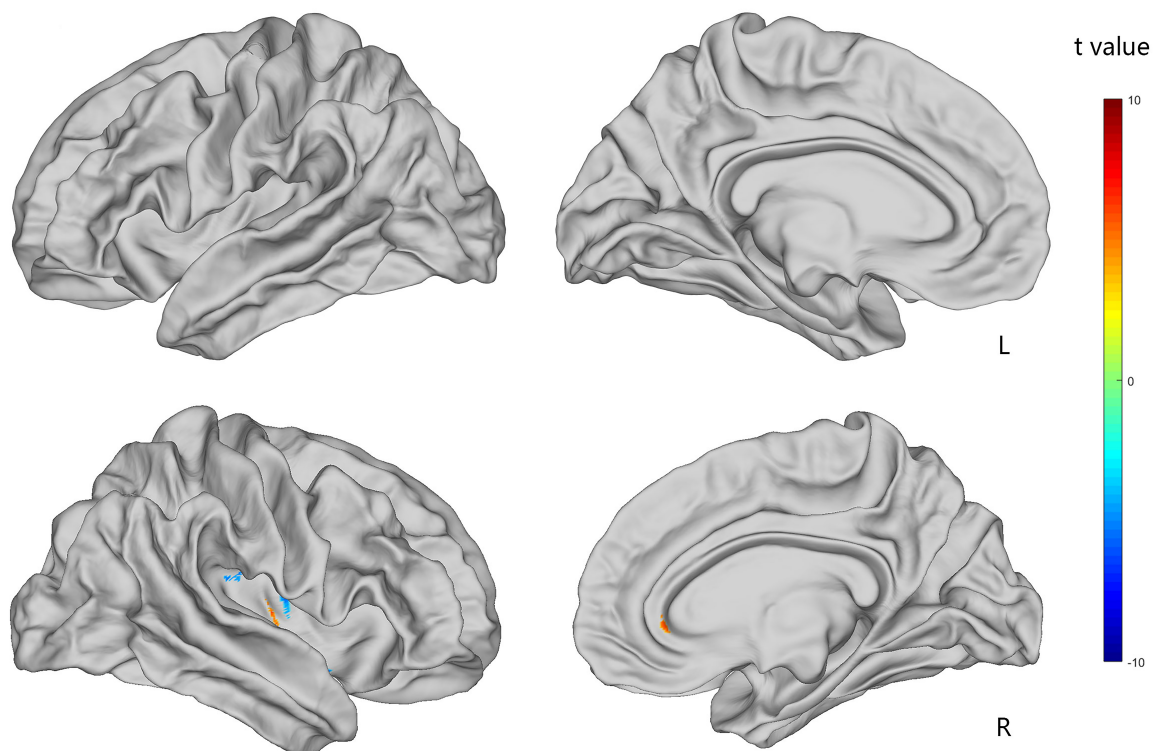


Fig. 2. Comparison of cortical curvature between HC group and TLE-N group. According to SBM analysis, the red area indicates an increase in cortical curvature compared to the HC group, while the blue area indicates a decrease in cortical curvature compared to the HC group.

Table 3. Group differences in cortical curvature between case and control groups.

Location	HCP	Cluster size (mm ²)	MNI coordinate			<i>t</i> value
			X	Y	Z	
Right Piriform Cortex	110	139	35.84	6.12	-14.35	-6.23
Right Insular Granular Complex	168	75	34.39	-8.16	11.50	-6.20

HCP, Human Connectome Project; MNI, Montreal Neurological Institute. $p < 0.025$.

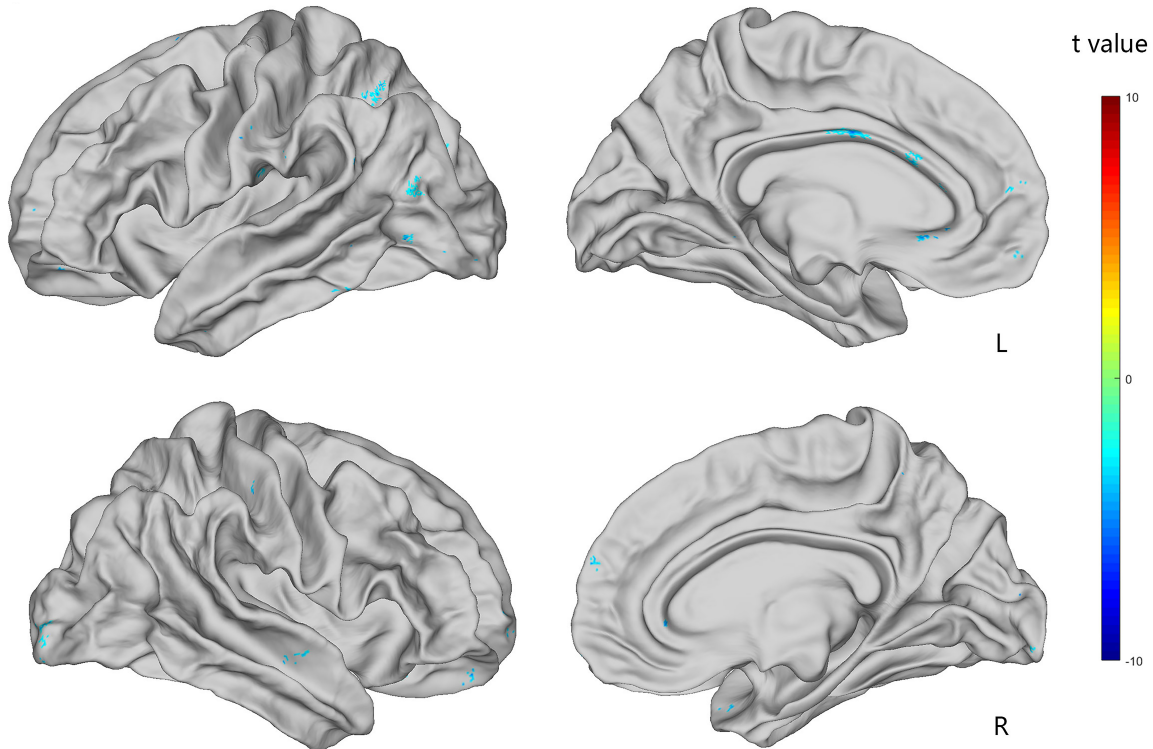


Fig. 3. Comparison of cortical volume between HC group and TLE-N group. According to SBM analysis, the blue area indicates a decrease in cortical volume compared to the HC group.

Table 4. Group differences in cortical volume between case and control groups.

Location	HCP	Cluster size (mm ²)	MNI coordinate			<i>t</i> value
			X	Y	Z	
Left OP1/SII	101	129	-6.31	-3.22	32.00	-6.03
Left Third Visual Area	5	60	-25.75	-59.08	45.80	-4.52

HCP, Human Connectome Project; MNI, Montreal Neurological Institute; OP1/SII, the secondary sensory cortex. $p < 0.025$.

TLE-N and healthy controls at baseline (cluster size = 0; $p > 0.025$, corrected by TFCE).

4. Discussion

This study investigated cortical morphological abnormalities in TLE-N patients. A preliminary analysis compared brain structures in TLE-N patients and healthy controls. The results indicated a decline in the piriform cortex (PC) cortical curvature in the right hemisphere and the cortical OP1/SII volume in the left hemisphere, and an enhancement in the insular cortex thickness in both hemispheres.

The thickness of the insular cortex in both cerebral hemispheres was greater in TLE-N patients than in healthy controls. This increased thickness represents possible functional alterations in the related area. The pathophysiological changes associated with epilepsy are dependent on the stage of the disease; initially, neuroinflammation causes an increase in cortical thickness. Early epilepsy is caused by these neuropathological alterations, which are followed by progressively worsening pathological processes that affect neural networks. Proinflammatory cytokines stimulate astrocytes in the early phases of epilepsy, causing them to proliferate and swell and thickening the cortical layer [25].

Current interventional study in rodent epilepsy models have confirmed that activating specific inflammatory pathways in brain cells can decrease neuronal excitability thresholds, thereby inducing seizures, which lead to neuroinflammation [26]. Koren *et al.* [27] observed that particular neurons within the insular cortex of the brain can record information concerning peripheral immune stress. The reactivation of these neurons can trigger an increase in bodily inflammatory levels. The insular lobe is intricately linked with the surrounding areas, including the amygdala, basal ganglia, and the entire cortex, except for the occipital lobe. From an anatomical perspective, the insular and temporal lobes form the closest fiber connections. Schmidbauer *et al.* [28] observed that TLE leads to asymmetric middle temporal lobe activation. Interestingly, the insula can compensate for the damaged middle temporal lobe structures in some TLE patients. Our results also support the close relationship between TLE and the insular lobe, with evidence indicating that TLE-N affects the insular cortex structure.

The PC is susceptible to epileptic stimulation and plays an essential role in seizures, serving as a critical site for seizure onset, propagation, and generalization [29]. This study showed that the cortical curvature of the PC region in TLE-N patients was lower than in healthy controls, which further establishes the close relationship between TLE-N and PC. Iqbal *et al.* [30] identified that the right PC is positioned more forward with a significantly larger volume than the left PC. However, there is no detailed and systematic research on the left-right asymmetry of the PC. Due to the observed asymmetry, the cortical curvature of the right PC can be more significant than that of the left PC. This could contribute to the positive study results focusing on the right PC. Various PC segmentation methods have been developed and refined to authentically identify the PC using neuroimaging techniques. Volumetric analysis has been performed to determine the reduction in PC volume in TLE patients [31]. This study also identified that the PC cortical curvature is reduced in TLE-N patients compared with healthy controls, which is a novel finding. The decreased cortical curvature suggests abnormal folding and cortical surface alterations in specific brain regions [32]. This could represent changes in cortical development or acquired changes due to epilepsy [33], providing a new perspective on studying PC in TLE.

The SII area is closely connected to both the temporal limbic structure and the insular lobe [34]; projections originating from the OPI/SII area enter the temporal limbic structures through the insula. The SII could be involved in functions such as learning, memory, and object recognition. Cognitive dysfunction is observed in TLE patients [35]. Changes in structural connectivity in the brain may induce the collapse of excitation–inhibition balance and network reconstruction. This plays a crucial role in the cognitive process of TLE patients. Jiang *et al.* [36] observed that functional connectivity between the hippocampus and

the right insula was consistently higher among patients with subjective cognitive decline than healthy controls. Similarly, our study identified elevated thickness of the insular cortex in TLE-N patients. Therefore, cognitive dysfunction in these patients could be associated with structural and functional changes within the insular lobe. Since no cognitive investigations and analyses of TLE-N patients were conducted in this study, this aspect can be refined through future studies.

With the advancement of MRI technology, the neuroanatomical brain morphology phenotype has attracted more attention as one of the cornerstone methods to diagnose epilepsy [37]. Previous study has indicated that TLE is a very heterogeneous group [38]. Some studies have assessed cortical morphology of different temporal lobe epilepsy, such as medial temporal lobe epilepsy with hippocampal sclerosis (mTLE + HS) and drug-resistant temporal lobe epilepsy, etc., [39,40]. TLE-N involves complex interactions of different brain regions. Our findings of elevated insular cortical thickness, decreased cortical curvature in the PC region, and reduced cortical volume in the OPI/SII region in TLE-N patients differ from previous findings and confirm the heterogeneity of TLE. The number of TLE patient subtypes should be increased in future studies to explore its pathogenesis and pathophysiological significance.

Cortical surface area and thickness are affected by a combination of environmental and genetic factors that form gyri and sulci, thus impacting early brain development [41]. The SBM method used in our study helped to quantify various parameters, such as cortical thickness, area, curvature, and sulcal depth. In future studies, long-term follow-ups should be conducted to explore the pathophysiological mechanisms underlying TLE-N and the relationship between brain development, age, disease progression, and drug treatment effects. For instance, we could investigate whether the cortical curvature and sulcal depth of this region also change as the disease progresses based on the findings of our previous study, where changes in insular cortex thickness were observed in TLE-N patients. Furthermore, it would be interesting to investigate whether the structural abnormalities in the PC area during the early stages of TLE-N are reflected in MRI examinations performed during follow-up.

Limitations and Considerations

Our study has several limitations that must be considered. First, the small sample could limit the generalizability of the results. Due to the small sample size, patients with left and right TLE-N were combined into a single case group to enhance the statistical power of the study. However, alterations in cortical structure may vary depending on the epileptic side. The sample size was too small to consider different epilepsy subtypes. Previous study has indicated many similarities in the pathogenesis of partial and

generalized epilepsy with common neuroanatomical features between various epilepsy subtypes [14]. Second, no cognitive assessment was performed to investigate the association between structural changes in the brain and neurodevelopment. The SBM method helps to identify TLE-N or suspicious abnormal areas, and epileptic foci often show structural abnormalities. However, structural abnormalities in the epileptogenic zone do not necessarily represent the truth, but may also represent the epileptic discharge affect areas of the brain.

5. Conclusions

The current study used the SBM method to analyze brain structural MRI data of TLE-N patients. We observed increased cortical thickness in the insular cortex in TLE-N patients compared with the healthy controls. Moreover, the PC cortical curvature and the cortical OP1/SII area volume were reduced in such patients compared with the controls. Therefore, analyzing cortical morphology and microstructure has necessary pathophysiological and clinical significance for TLE-N patients.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

In the annals of scientific innovation, XC and YHe forged the blueprint for this groundbreaking experiment, their minds alight with visionary design. The intrepid trio of ZG, YHuang, and HZ meticulously amassed a trove of data, while CXue and DZ deftly deciphered its intricate tapestry. YHe, with eloquence unmatched, penned the saga that would become the manuscript. Guiding every facet with astute vigilance, CXiao and XH orchestrated the symphony of conception, analysis, design, and manuscript crafting. All authors lent their expertise to sculpting the manuscript's narrative, ensuring it resonated with intellectual harmony. Unanimously endorsing the final opus, each author stood steadfast in accountability for the work's entirety, their collective dedication echoing through the halls of scientific endeavor. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The studies involving human participants were approved by the Ethics Committee of the Affiliated Brain Hospital of Nanjing Medical University (Ethics Approval number is 2017-KY118-01) and written informed consent was obtained from patients or their families/legal guardians.

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Conflict of Interest

The authors declare no conflict of interest.

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