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Lateralizing Value of Artificial Intelligence-Based Segmentation Software in MRI-Negative Focal Epilepsy

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Background and Purpose: The magnetic resonance images (MRIs) ability of lesion detection in epilepsy is crucial for a diagnosis and surgical outcome. Using automated artificial intelligence (AI)-based tools for measuring cortical thickness and brain volume originally developed for dementia, we aimed to identify whether it could lateralize epilepsy with normal MRIs.

Methods: Non-lesional 3-Tesla MRIs of 428 patients diagnosed with focal epilepsy, based on semiology and electroencephalography findings, were analyzed. AI-based segmentation/volumetry software measured the cortical thickness and the hippocampal volume. The laterality index (LI) was calculated.

Results: We classified into temporal lobe epilepsy (TLE, n=294), frontal lobe epilepsy (FLE, n=86), occipital lobe epilepsy (OLE, n=29), and parietal lobe epilepsy (PLE, n=22). Onset age and MRI age were 24.0±16.6 (0-84) and 35.6±14.8 (16-84) years old. In FLE, the LI of frontal thickness was significantly different between the left and right FLE groups, with LIs of the right FLE group being right-shifted and those of the left FLE group being left-shifted, indicating that the lesion side was thinner than the non-lesion side (p=0.01). The discriminable group, which included the patients with left FLE and a LI lower than minus one standard deviation, as well as the patients with right FLE and a LI higher than one standard deviation, showed a longer duration of epilepsy than the non-discriminable group (12.7±9.9 vs. 8.3±7.7 years; p=0.03). Specifically, the LI of individual regions of interest showed that the rostral middle frontal cortex was significantly different in FLE. However, the TLE, PLE, OLE, and LIs were not significantly different.

Conclusions: AI-based brain segmentation software can be helpful to decide the laterality of non-lesional FLE especially with longer duration of disease. **(2024;14:59-65)**

Key words: MRI-negative epilepsy, Artificial intelligence, Asymmetry, Frontal lobe epilepsy

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Introduction

The identification of epilepsy-related lesions helps in the selection of antiseizure medication (ASM). Additionally, their presence is the crucial prognostic element for the surgical treatment of epilepsy[1] and successful withdrawal of ASM following surgery.[2] Therefore, various methods have been attempted to explore the epileptogenic focus in normal-looking magnetic resonance images (MRIs). Some of those are utilized as routing presurgical evaluation tools, such as single photon emission computed tomography or positron emission tomography, while some tools, such as arterial spin labeling[3] or post-processing[4] of MRI, are still under investigation.

Automated artificial intelligence (AI)-based tools for measuring cortical thickness and brain volume were developed mainly for dementia or neurodegenerative disease.[2,5] Unlike conventional structural analysis software, such as FreeSurfer version 5.3 (Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA, USA), AI-based software can analyze MRI much faster with highly correlated values with FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging) analysis. However, its clinical utility in the epi-

lepsy field has not been studied.

In this study, we aimed to identify the asymmetry of cortical thickness and hippocampal volume in various epilepsy patients with normal MRIs.

Methods

This study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Board of Seoul National University Hospital (No. 2005-012-1121). Informed consent was waived due to the retrospective design.

Study population

We searched for all lists of 3 Tesla MRIs with epilepsy protocols (6,233 MRIs in 4,408 patients) in the Seoul National University Hospital database. Among those, we selected 3,262 MRIs from 2,464 epilepsy patients. Then, 859 patients without discernable lesions were selected. Then, we excluded generalized epilepsy (n=79), nonlateralized electroencephalography (EEG) (n=85), normal EEG (n=258), and unavailable EEG (n=9). A total of 428 patients were finally analyzed (Fig. 1). There were seven types of MRI scanners, and the detailed parameters are described in Supplementary Table 1. Epilepsy classification was performed based on the semiology and electroencephalography results.

Volumetry analysis

We applied segmentation/volumetry software (Atroscan, Seoul, Korea), which had been developed using a deep learning technique, to automatically measure the cortical thickness of 62 regions of interest (ROIs) from the Desikan-Killiany atlas and the volume of the hippocampus, entorhinal cortex, and amygdala following a developed algorithm. The principles, workflow, and architecture of this software were described in the previous paper.[2] It operates by uploading three dimensional T1 images of patients. The whole process takes approximately 15 minutes to complete. From the values, we calculated the laterality index (LI, [left-right]/[left+right]×100) and analyzed it according to the epileptic syndromes. Thirty-one ROIs in each hemisphere are as follows: caudal anterior cingulate, caudal middle frontal, cuneus, entorhinal, fusiform, inferior parietal, inferior temporal, isthmus cingulate, lateral occipital, lateral orbitofrontal, lingual, medial orbitofrontal, middle temporal, parahippocampal, paracentral, pars opercularis, pars orbitalis, pars triangularis, pericalcarine, postcentral, posterior cingulate, precentral, precuneus, rostral anterior cingulate, rostral middle frontal, superior frontal, superior parietal, superior temporal, supramarginal, transverse temporal, insula, and hippocampus.

In addition, we also used FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging) to quantify cortical thickness and hippocampal/medial temporal volume. The raw images were transformed to neuroimaging informatics technology initiative (NIFTI) file format using MRIcron (https://www.nitrc.org/projects/mricron), followed by automatic FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging) processes including skull stripping, normalization, transformation, registration, and parcellation.[6] Volumes were adjusted by the estimated total intracranial volume.

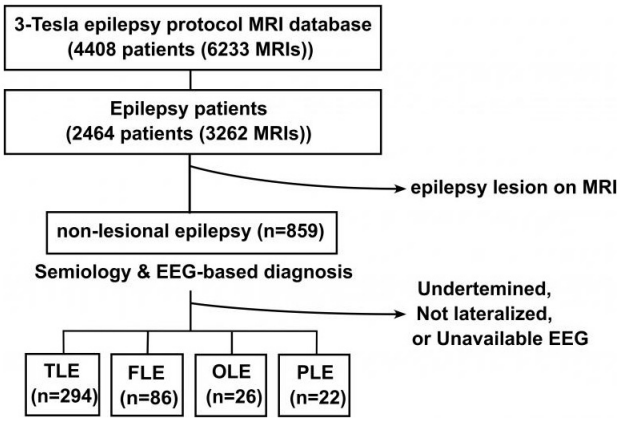

Figure 1. Study population. MRI, magnetic resonance image; EEG, electroencephalography; TLE, temporal lobe epilepsy; FLE, frontal lobe epilepsy; OLE, occipital lobe epilepsy; PLE, parietal lobe epilepsy.

Statistical analysis and machine learning

The numerical values are presented as the mean±standard deviation (SD). Student's *t*-test was performed for continuous variables. The statistical significance was set as a two-tailed *p*-value <0.05. For analysis of inter-lobar difference and sub-regions of interest within the lobe, multiple comparison was performed using the Holm-Bonferroni method with <0.05 of family-wise error rate i. SPSS version 25 (IBM, Chicago, IL, USA) or GraphPad Prism version 9 (Dotmatics, San Diego, CA, USA) was utilized. Support vector machine (SVM) was utilized through Python scripts using the Anaconda prompt, with a fivefold cross-validation to classify laterality.

Results

Study population

A total of 428 patients (230 females; 53.7%) were analyzed, ex-

cluding patients with normal, not-lateralized, and unavailable EEG. The first one was chosen if MRIs were repeated in the same patients. Temporal lobe epilepsy (TLE), frontal lobe epilepsy (FLE), occipital lobe epilepsy (OLE), and parietal lobe epilepsy (PLE) were 294 (right:left=118:176), 86 (right:left=50:36), 26 (right:left=12:14), and 22 (right:left=9:13), respectively.

The total follow-up duration, which means the duration between the first and last visit to the clinic, was 78.4±75.5 months (0-301), and the onset age of epilepsy was 24.0±16.6 years old (0-84). Age at MRI was 35.6±14.8 (16-84). The total duration of ASM usage was 5.1±8.4 years. The epilepsy duration was 11.0±11.4 years. Daily seizures were present in 7.4% of patients. More than one seizure in 1 month was experienced in 49.5% of patients at the time of MRI.

Table 1. Demographics of patients

	Value
Surgical intervention	
None	488 (92.6)
Resective	37 (7.0)
Vagal nerve stimulation	2 (0.4)
Follow-up duration (months)	78.4±75.5
Age at onset (years)	24.0±16.6
Age at MRI (years)	35.6±14.8
Seizure frequency	
≥1/day	39 (7.4)
1/week-1/day	75 (14.2)
1/month-1/week	147 (27.9)
1/6 month-1/month	69 (13.1)
1/year-1/6 months	56 (10.6)
≤1/year	98 (18.6)
Seizure-free	26 (5.0)
N.A	17 (3.2)
Duration of ASM usage (years)*	5.1±8.4
Number of ASMs at MRI	
0	180 (34.2)
1	119 (22.6)
2	115 (21.8)
3	66 (12.5)
4	23 (4.4)
5	12 (2.3)
6	4 (0.8)
N.A	8 (1.5)
Epilepsy duration (years)†	11.0±11.4

Values are presented as number (%) or mean±standard deviation or number.
MRI, magnetic resonance image; N.A, not available; ASM, antiseizure medication.
*Not available data in 63 patients.
†Not available data in 5 patients.

The clinical parameters are described in Table 1.

Laterality index analysis

We downloaded the data on the cortical thickness of 62 ROIs and averaged the thickness values of regions corresponding to each lobe. Comparing left TLE with right TLE, the LI of temporal cortical thickness showed no significant difference (p=0.91), nor did the LI of adjusted hippocampal volumes (p=0.29). We also compared LI values of the volume of the medial temporal area, which encompasses the amygdala, hippocampus, and entorhinal cortex, indicating no significant difference (p=0.15). FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging) analysis also did not show significant group differences in the LI of temporal thickness, hippocampal volume, and medial temporal volume (p-value=0.15, 0.12, and 0.22; respectively) (Supplementary Fig. 1).

In FLE, the LI difference in frontal cortical thickness was significant (p=0.01; -1.29±1.11 in the left FLE vs. -0.69±1.05 in the right FLE). The LI of frontal cortical thickness in the left FLE was lower than that of the right FLE indicating potential thinning of the frontal cortex on the side presumed to be the focus of epilepsy, despite a normal-looking MRI. In the right FLE group, the mean thickness of frontal lobe was 3.22±0.13 mm on the right side and 3.18±0.13 mm on the left side. In the left FLE group, the mean thickness of frontal lobe was 3.20±0.14 mm on the right side and 3.12±0.14 mm on the left side. However, the mean thickness was 3.22±0.13 in the right and 3.18±0.13 in the left the LI of cortical thickness was not significantly different in PLE (p=0.90) and OLE (p=0.30) (Fig. 2).

Among the 15 FLE patients with a LI higher than one SD, we observed that 14 patients were right FLE, while only one was left FLE. Conversely, the majority laterality was left in the case of a LI lower than minus one SD (eight left vs. four right) (Fig. 3). To investigate the cause of this LI difference, we divided the patients into two groups: the "discriminable" and "non-discriminable" groups. The "discriminable" group was defined as the patients with left FLE and a LI lower than minus one SD, as well as the patients with right FLE and a LI higher than one SD. This group was deemed to be relevant in terms of demonstrating AI's potential for laterality determination. The discriminable group consisted of 22 cases. The "non-discriminable" group included all the other patients. We compared various factors between the two groups, including the onset age of epilepsy, the number of ASMs, the age at which the MRI was conducted, the duration of ASM, seizure frequency and epilepsy duration. We found that the discriminable group had a significantly longer duration of epilepsy than the non-discriminable group (12.7±9.9 vs. 8.3±7.7 years; p=0.03) (Table 2).

Furthermore, we explored which regions in the frontal lobe are specifically different in FLE patients. Among 10 sub-regions, including the caudal middle frontal, lateral orbitofrontal, medial orbitofrontal, paracentral, pars opercularis, pars orbitalis, par triangularis, precentral, rostral middle frontal, and superior frontal gyri, the LI of cortical thickness in the lateral orbitofrontal and rostral middle frontal gyrus were significantly different (p=0.019 and 0.022) (Table 3). Multiple comparison analysis showed that the rostral middle frontal gyrus is the only region showing different thickness in non-lesional frontal lobe epilepsy. With a cutoff of two standard deviations, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for left FLE were 0.22, 0.92, 0.67, and 0.62, respectively. For right FLE, the corresponding values were 0.27, 0.97, 0.93, and 0.49. Using a cutoff of 1.5 standard deviations, the sensitivity, specificity, PPV, and NPV for left FLE were 0.11, 1, 1, and 0.61, respectively. For right FLE, the values were 0.10, 0.97, 0.83, and 0.44. Furthermore, with a cutoff of one standard deviation, the sensitivity, specificity, PPV, and NPV for left FLE were 0.08, 1, 1, and 0.6, respectively. For right FLE, the corresponding values were 0.02, 1, 1, and 0.43.

To predict the laterality using LI and clinical variables including ASM number/duration, seizure frequency, sex, epilepsy onset age, and duration of epilepsy, SVM analysis was performed with a 5-fold cross-validation, yielding that accuracy, precision, recall, and F1-score are 0.59, 0.57, 0.98, and 0.72.

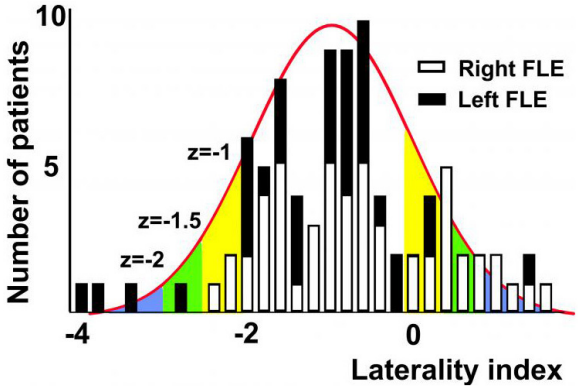

Figure 3. Distribution of laterality index in frontal lobe epilepsy (FLE). Black bars indicate the left FLE and white bars do the right FLE.

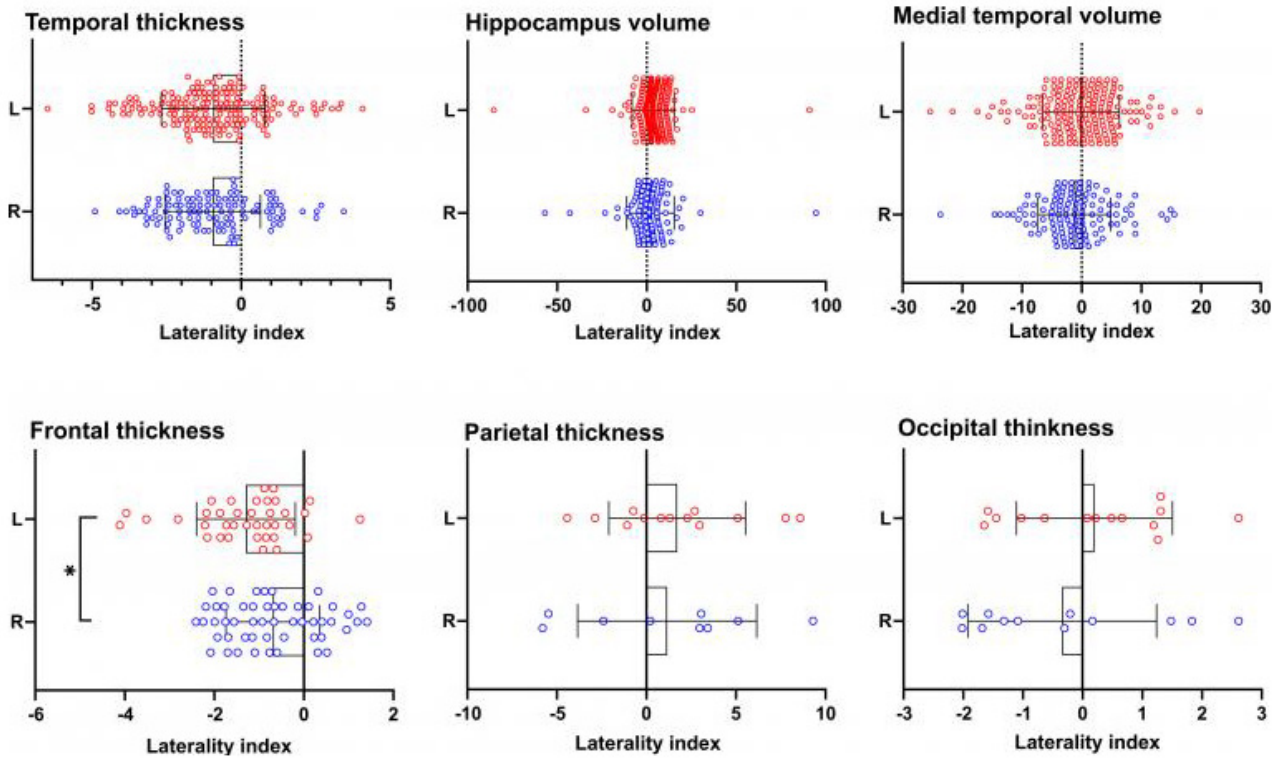

Figure 2. The distribution of the laterality index of cortical thickness and hippocampal/medial temporal volume. The laterality index of cortical thickness is different only in frontal lobe epilepsy. L, left; R, right. *p-value <0.05.

Table 2. The difference of clinical variables between discriminable and non-discriminable group

	Discriminable vs. non-discriminable	*p*-value
Duration of follow-up	71.0±56.6 vs. 80.6±76.3	0.59
Epilepsy onset age	18.0±12.7 vs. 21.2±12.2	0.28
Age at MRI (years)	30.5±12.8 vs. 29.6±10.8	0.73
Number of ASM	1.4±1.3 vs. 1.6±1.4	0.53
ASM duration (years)	4.5±6.9 vs. 2.6±4.9	0.28
Seizure frequency (months)	6.9±16.0 vs. 13.2±34.1	0.41
Epilepsy duration (years)	12.7±9.9 vs. 8.3±7.7	0.03

Values are presented as mean±standard deviation.
MRI, magnetic resonance image; ASM, antiseizure medication.

Table 3. The laterality index of individual regions of interest in frontal lobe epilepsy

	Mean, laterality index		95% confidence interval	*p*-value*
	Right FLE	Left FLE		
Caudal middle frontal	-2.387	-2.527	-1.489 to 1.208	0.84
Lateral orbitofrontal	-0.015	-1.283	-2.322 to -0.215	0.02
Medial orbitofrontal	3.145	2.665	-1.627 to 0.668	0.41
Paracentral	-0.171	-1.233	-2.472 to 0.348	0.14
Pars opercularis	-2.190	-1.935	-1.291 to 1.802	0.74
Pars orbitalis	-1.136	-1.785	-2.657 to 1.358	0.52
Pars triangularis	-0.112	-0.834	-2.267 to 0.823	0.36
Precentral	-2.406	-2.739	-1.111 to 0.444	0.40
Rostral middle frontal	-2.188	-3.516	-2.462 to -0.194	0.02
Superior frontal	0.251	0.083	-0.819 to 0.481	0.61

FLE, frontal lobe epilepsy.
**p*-value non-adjusted.

Discussion

We applied AI-based quantification software to non-lesional focal epilepsy to identify laterality. This software, developed using a 3D U-Net algorithm based on FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging) ground truth, showed a high correlation with FreeSurfer's (Athinoula A. Martinos Center for Biomedical Imaging) results (r=0.9623) in previous studies.[2]

In TLE, this software could not show the difference in the asymmetry of the temporal neocortex and medial temporal structures, including the hippocampus. Possible reasons include false EEG and clinical-based localization due to contralateral propagation of epileptiform discharges.[7] Another consideration is the normal asymmetry.[8] This volumetry software could not recognize the signal or internal structure of the hippocampus. A previous large-scale study conducted by the epilepsy workgroup of the enhancing neuro imaging genetics through meta analysis (ENIGMA) consortium demonstrated the asymmetry of cortical thickness in TLE using FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging).[9] Our negative results, however, likely stem from differences in our MRI-negative population rather than the analysis method. This is supported by the negative result obtained by FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging) in our population.

We observed the asymmetry of the cortical thickness only in FLE, particularly in the rostral middle frontal. In epilepsy patients, two plausible situations of cortical thickness alteration exist. One is a migration disorder, such as focal cortical dysplasia, and the other is regional degenerative change. Our results showed that LI was left-shifted in the left FLE and relatively right-shifted in the right FLE, indicating regional thinning of the cortex on the lesion side.[10] The location of cortical thinning might not necessarily indicate the epilepsy focus but could reflect the cortico-cortical connections within the frontal lobe network.[11]

We classified patients with LI values exceeding 1 SD as the "discriminable" group, where right-shifted LI values corresponded to right FLE and left-shifted LI values corresponded to left FLE. This group was correctly lateralized by the software. We compared the clinical variables of this discriminable group with those of patients not correctly lateralized by the software. The discriminable group had longer epilepsy duration, indicating localized degeneration over time, consistent with conventional volumetry data.[9,12,13]

A previous study with 53 patients with generalized tonic-clonic seizures demonstrated cortical thinning in the lateral orbitofrontal, medial orbitofrontal, frontal pole, superior frontal, rostral middle frontal, caudal middle frontal, and precentral gyrus,[12] which is partly similar to our findings. Cortical thinning in the frontal lobe is common, and the altered thalamocortical network[13] and hypoperfusion[14] in repeated seizures were suggested as plausible mechanisms.

In recent years, there has been a significant effort to develop tools to improve the detection of lesions in MRI-negative epilepsy cases. Notably, Fischl[15] conducted a point-wise morphometric analysis, comparing the affected hippocampus of patients with hippocampal sclerosis-medial TLE to healthy subjects. They reported significantly lower thickness in the presubiculum, subiculum, CA1, and the medial regions of CA2/3. However, when comparing MRI-negative medial TLE with healthy subjects, no significantly different clusters were observed, which aligns with our negative result for differentiating laterality in MRI-negative TLE.

Another study using the MRI post-processing method demonstrated promising performance in MRI-negative epilepsy cases, achieving a positive rate of up to 43%.[16] Previously, we also evaluated pathologically confirmed focal cortical dysplasia (FCD) patients with a similar method and found a relatively small increase of only 3.4% in detection rate compared to previous studies.[4]

The performance of lesion detection appears to depend on the definition of MRI-negative focal epilepsy within the study population, which has been reported to range widely from 0% to 100% in various studies.[17] The expertise of epileptologists and radiologists and their multidisciplinary approach play a significant role in reducing the proportion of MRI-negative epilepsy cases, which can, in turn, decrease the difference in detection rate between new technologies and conventional reporting systems. A previous study collected multicenter data to develop the AI-assisted algorithm. Interestingly, many cases initially categorized as "normal" or "unspecific abnormality" were ultimately found to have FCD upon final in-house diagnosis.[18] This finding supports the notion that the definition of "normal" MRI can be ambiguous. Although that study reported a sensitivity of 81.0% and specificity of 84.2%, strictly speaking, those cases were not MRI-negative.

Focusing on AI methodologies, Walger et al.[17] reviewed recently developed three AI-based algorithms: the multi-centre Epilepsy lesion detection (MELD),[19] deep fine-grained change detector (deepFCD),[20] and morphometric analysis program (MAP18).[18] DeepFCD utilized a dataset of pathology-proven FCD cases and employed a patch-based difference approach using a convolutional neural network algorithm. This dataset comprised a 51% MRI-negative population, and the sensitivity in the external set was 83%. MAP18 utilized both radiological and pathological diagnoses of FCD and employed features from various image maps based on z-scores in each voxel. They utilized an artificial neural network (ANN) method and achieved a sensitivity of 87.4%. MELD employed a dataset of 618 radiologically and pathologically diagnosed FCD patients, including pediatric cases. They utilized an ANN with vertex-based features and achieved lesion detection in 62.9% of MRI-negative cases. All three tools mentioned above utilized manual segmentation for lesion localization, surpassing our results. It is important to note that our algorithm was primarily developed for cortical segmentation and quantification of cortical thickness in a 3D dimension to identify cortical thinning. Hence, the strength of our algorithm does not lie in its ability for lesion localization.

This study has the following limitations. Given that this cohort comprises normal MRIs, the localization of epilepsy solely depends on EEG and semiology, which are not the gold standard. To mitigate this limitation, we conducted the same task within a sub-population that had undergone the respective surgery (Supplementary Fig. 2). However, we did not obtain meaningful results due to the small number of cases. Additionally, most cases did not undergo extensive presurgical work-up. However, localization through a consensus among our experienced epileptologists could reduce false localization. This study demonstrated group differences in right-left asymmetry, and it does not mean that this tool is feasible for all patients of non-lesional FLE. This tool could provide helpful information about laterality in patients with a longer duration of epilepsy. In the future, determining the absolute LI value and appropriate cut-off to decide laterality will be essential for clinical applications on an individual basis. However, since the LI value of this software is not distributed symmetrically with respect to zero, it is necessary to perform some troubleshooting, such as accounting for slight tilting of the original image during scanning.

AI-based brain segmentation software could be feasible to detect

frontal lobe asymmetry only in FLE. A person-based quick analysis tool such as this software could offer additional information underpinning epileptogenic lesion detection and laterality. In addition, this result might become a consideration when assessing neurodegeneration in epilepsy patients using this software.

Conflict of Interest

None.

Funding

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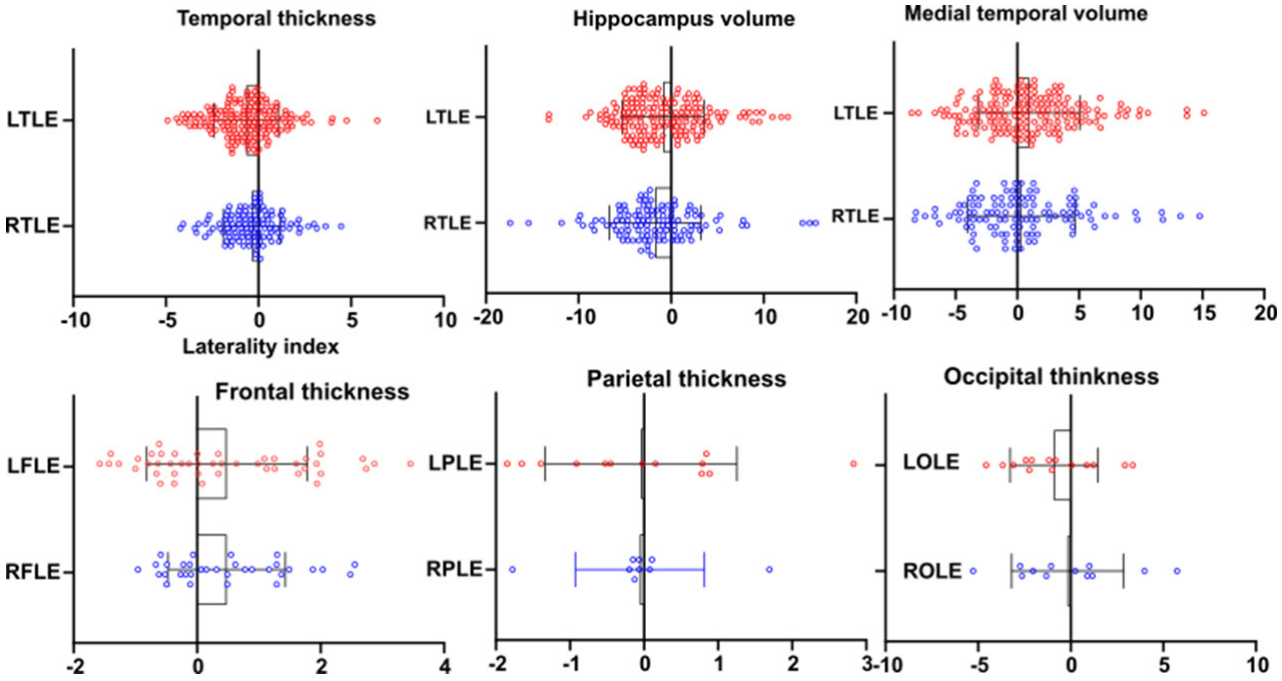
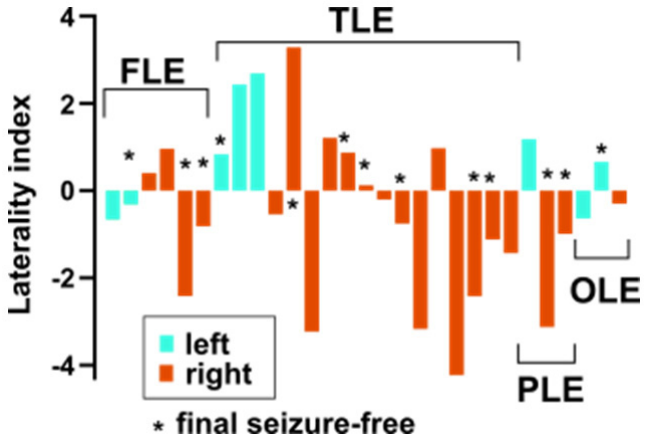
Supplementary Table 1. Detailed parameters of MRI scanners used in this study

	Tesla	TR	TE	Thickness	FA	FOV	NEX
GE Discovery MR750w	3T	8.5	3.2	1.0	12.0	256×256	0
Philips ingenia CX	3T	8.2	3.7	1.0	8.0	240×240	1
Philips ingenia 3T	3T	8.1	3.7	1.0	8.0	240×240	1
GE signa excite	3T	6.0	1.3	1.5	20.0	220×219	0
Siemens skyra	3T	1,600.0	2.8	1.0	9.0	242×250	1
Siemens magnetom trio	3T	1,600.0	2.8	1.0	9.0	250×250	1
Siemens verio	3T	1,500.0	1.9	1.0	9.0	250×250	1

MRI, magnetic resonance image; TR, repetition time; TE, echo time; FA, flip angle; FOV, field-of-view; NEX, number of excitations; GE, general electrics.



Supplementary Figure 1. Laterality index using FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA, USA). No significant difference exists in temporal/frontal/parietal/occipital thickness and hippocampal/medial temporal volume in each population of epilepsy (p=0.15, 0.93, 0.95, 0.56, 0.12, and 0.22). LTLE, left temporal lobe epilepsy; RTLE, right temporal lobe epilepsy; LFLE, left frontal lobe epilepsy; RFLE, right frontal lobe epilepsy; LPLE, left parietal lobe epilepsy; RPLE, right parietal lobe epilepsy; LOLE, left occipital lobe epilepsy; ROLE, right occipital lobe epilepsy.



Supplementary Figure 2. The laterality index in the surgical group. FLE, frontal lobe epilepsy; TLE, temporal lobe epilepsy; OLE, occipital lobe epilepsy; PLE, parietal lobe epilepsy. *Indicates final seizure freedom.