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A study on brain asymmetry in temporal lobe epilepsy

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ABSTRACT

Objective: Temporal lobe epilepsy (TLE) accompanied by hippocampal sclerosis (HS) is the most common type of focal epilepsies. Hemispheric asymmetry is a feature of brain organization in both invertebrates and vertebrates and may be the key to some neurodegenerative diseases. In this context, we aimed to investigate the volumetric asymmetry difference in cerebral structures between TLE patients and the healthy control group, based on magnetic resonance imaging (MRI) data that may be used as a new neuroimaging marker for TLE cases.

Patients and Methods: In this retrospective study the cranial MRIs of fourteen clinically manifesting, radiologically HS-identified, and diagnosed TLE patients and fourteen healthy individuals from the Radiology Department of Yeditepe University Hospital were evaluated. Volume measurements and asymmetry index (AI) calculations in the total brain, hippocampus, temporal lobe, amygdala, thalamus, nucleus accumbens (NAc), premotor cortex, primary and somatosensory cortices were performed using the medical NeuroQuant® software. A negative AI value represented asymmetry towards the right due to reduced left hemispheric volume; a positive AI value represented asymmetry towards the left due to reduced right hemispheric volume. Subsequently, differences in volume and asymmetric patterns were investigated among TLE subgroups (right and left-sided TLE) and controls.

Results: The left-sided TLE patients showed significant bilateral total brain volume reduction compared to the control group. Significant ipsilateral volumetric declines were also detected in the premotor cortex, the temporal lobe, and NAc with remarkable asymmetry to the right side. No significant changes were detected in right-sided TLE patients compared to the other groups.

Conclusion: Overall, findings suggest that TLE patients had volumetric alterations with symmetry changes beyond the mesial temporal structures. With further investigations, the asymmetry measures can provide additional knowledge for TLE diagnosis.

Keywords: Brain asymmetry, Temporal lobe epilepsy, Asymmetry index, Nucleus accumbens

1. INTRODUCTION

Epilepsy is one of the most common neurological diseases, accounting for over 0.5% of the global burden of disease affecting over 70 million people worldwide. It is characterized by abnormal electrical activity in the brain, causing seizures or unusual behavior, sensations, and loss of awareness [1]. The classification of epilepsy has an important role in evaluating individuals who have seizures. According to the International League Against Epilepsy (ILAE) classification tool, temporal lobe epilepsy (TLE) is a focal type of epilepsy with or impaired awareness both in adults and children with most of the cases being symptomatic [2]. The causes of TLE can vary with hippocampal sclerosis being the most common cause but extrahippocampal abnormalities are also frequently observed [3,4].

The clinical context, features of the seizure, and proper interpretation of the imaging are the keys to the diagnosis. Magnetic resonance imaging (MRI) has equal importance to the electroencephalogram (EEG) as a part of assessing epileptic patients. The challenge is to require optimized protocols suitable for epilepsy cases. MRI is critical in evaluating TLE, allowing characterization and detection of structural changes, especially hippocampal sclerosis. Imaging displays the anatomy and structural abnormalities of mesiotemporal structures including the hippocampus, amygdala [5], parahippocampal gyrus [6], entorhinal cortex [7], and temporal pole [8]. On T1-weighted images, the most common features associated with hippocampal sclerosis are hippocampal atrophy [9-12] and reduction of

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internal features of the hippocampus [13-15]. On T2-weighted images, the presence of increased signals from the hippocampus with atrophy can be detected [16, 17]. Several volumetric studies showed volume changes in the insula, thalamus, putamen, pallidum, and cortical thickness in TLE patients [18-23]. The diffusion tensor imaging (DTI) study focusing on the changes in grey and white matter showed alterations in the corpus callosum, corona radiata, cingulum, uncinate fasciculus, external and internal capsule in TLE patients [24].

From an evolutionary aspect, even though both the left and right hemispheres of the brain develop symmetrically, the subsequent existence of structural and functional differences between the two hemispheres indicates asymmetry in both humans and animals. For many years, brain asymmetry and lateralization have been investigated, and correlated with handedness [25], and associated with some neurodegenerative diseases [26-28]. Some studies support the critical role of brain asymmetry with schizophrenia [29]. In Alzheimer's disease, a relationship was found between hippocampal asymmetry and the severity of the diagnosis [30]. Epileptic resting-state functional MRI (rs-fMRI) studies showed functional asymmetry in the hippocampus and amygdala which is evident in the hemisphere ipsilateral to the lesion in mesial temporal lobe patients [31, 32].

Due to the importance of the asymmetric characteristics of the human brain, we focused on the structural asymmetry patterns of epileptic brains. Therefore, in this retrospective study, we evaluated the MRI of healthy controls and TLE patients to define the changes in volume and symmetry patterns of the groups. The comparison was not only between the patient and control groups but also considering the side of the epileptic focus, hemispheric comparisons were made in the right and left-sided TLE patients.

2. PATIENTS and METHODS

Patient selection

In this retrospective study, patients who were followed at the Neurology Clinic of the Yeditepe University Hospital underwent cranial MRI in the Radiology Department between 2017-2021 and were diagnosed with TLE by an experienced neurologist, according to the criteria defined by the ILAE [33] were included. Patients with the following criteria were excluded: a significant medical history of acute encephalitis or ischemic encephalopathy, meningitis, severe head trauma, or any suspicious epileptogenic lesions like tumors, or dysplasia.

Healthy individuals who consulted the Neurology department due to headaches, and had a cranial MRI that was "normal" were included in the study as the control group. Individuals in the control group are included based on the following criteria: no history of neurological or psychiatric diseases; and no medication of central nervous system agents.

All patients and controls underwent a comprehensive clinical evaluation including interviews, neurological examination, neuropsychological assessment, and neurophysiological monitoring. All individuals were right-handed. Participant consent and ethical permissions were obtained. The study was approved by Marmara University's Clinical Research Ethics Committee on 05.03.2021 with the protocol number 09.2021.322.

Effect size and alpha error probability were taken as 1.1 and 0.05, respectively. 14 individuals in each group were evaluated and the power of the study (1-β error prob.) was planned to be 0.80. Totally fourteen patients were diagnosed by a specialist with unilateral TLE, (male/female, 5:9; right / left-sided TLE patients, 8:6), and fourteen age – and sex-matched controls (male/female, 8:6) were included in this study. There was no statistically significant difference in gender or mean age (Control/right and left-sided TLE; 35.86 ± 15.58: 35.75 ± 9.55: 36.33 ± 1308; p=0.99) between subjects.

MRI data acquisition

We obtained MRI data from all individuals. Scanning details were as follows: The MRI was performed on a 3.0-T MR system (GE DISCOVERY MR750w 3.0-T MR scanner. GE HealthCare Technologies, Inc., Chicago, Illinois.) with 16-channel head and neck coils.

Routine MRI examination with the following protocols was made: three-dimensional (3D) sagittal T1-weighted magnetization [TR/TE: 8.6/3.2 ms; matrix 230 × 230, 23 × 23 cm FOV; thickness 1.0 mm with – 0.5 mm gap; 310-330 slices; acquisition time 4:30 sec] and 3D CUBE fluid-attenuated inversion recovery (FLAIR) images [TR/TE 6000/113.5 ms; inversion time 1749 ms; matrix 224 × 224, 23 × 23 cm FOV; thickness 1.4 mm with – 0.7 mm gap; 220-230 slices; acquisition time 5:30 sec].

Images were transferred to FDA-cleared "NeuroQuant®" medical software tool (https://www.cortechs.ai/products/neuroquant/) to assess the volumes and asymmetry index values based on the 3D T1-weighted images for all groups. Automated volumetric analysis and asymmetry calculation of the brain regions for both groups were performed. The brain regions of interest that were executed and evaluated were the total brain, hippocampus, temporal lobe, amygdala, thalamus, nucleus accumbens (NAc), premotor cortex, primary were somatosensory cortices.

Evaluation of the asymmetry index values

An asymmetry index (*AI*) quantifies the differences between the right and left hemispheres. In the literature, cerebral asymmetry is generally reported by a "laterality index" measure. A commonly used formula is the R – L difference in ROI sizes divided by the sum of R + L ROI sizes [34]. Additionally, another "asymmetry index" formula often used in fMRI studies is mentioned in the literature [35].

In our study, the calculation was made by the Neuroquant® software. Our reference formula for AI is 200*(Left-Right volumes)/(Left+Right volumes). The formula divides the hemispheric volume difference by the mean hemisphere volume and reports the percentage. The interpretation of AI is shown in Table I with an example. Negative AI represents the volume decrease in the left hemisphere, interpreted as symmetric changes in the right hemisphere; positive AI value represents the volume decrease in the right hemisphere, interpreted as symmetric changes in the left hemisphere.

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Table I. *Asymmetry Index (AI) and volumetric measurments*

Group and Region	Hippocampus Right Volume	Hippocampus Left Volume	AI	Interpretation according to: AI = 200*(Left – Right)/(Left+Right)
Healthy Control	3.99	3.60	-10.22	Negative AI indicates asymmetry to the right
Right-sided TLE patient	3.12	4.14	28.07	Positive AI indicates asymmetry to the left
Left-sided TLE patient	4.14	3.38	-20.09	Negative AI indicates asymmetry to the right

TLE: Temporal lobe epilepsy, AI: Asymmetry index

Statistical Analysis

Statistical analyses of MR images among the groups were performed using GraphPad Prism 8 software. The variables were investigated by using the Shapiro-Wilk test to determine whether they were normally distributed or not. Descriptive analyses were presented using means and standard deviations for normally distributed volume and asymmetry index measures. The one-way analysis of variance (ANOVA) test was performed to compare the volumes and the asymmetry index values among three groups (control, right-sided TLE, and left-sided TLE). In binary comparison, the unpaired t-test was used. A p-value <0.05 was considered to indicate a significant difference. Pairwise posthoc tests were performed using Tukey's test when significance was observed.

3. RESULTS

This study compared the volumetric measurements and AI values of the brain regions between the TLE patient and the control groups. AI values were compared to define brain asymmetry patterns in groups. Our results showed diverse patterns of structural asymmetries in TLE patients compared to the control group.
In the first step, descriptive analysis (mean and standard deviation calculations) of the AI values and volumetric measurements of the total brain, hippocampus, temporal lobe, amygdala, thalamus, NAc, premotor cortex, primary and somatosensory cortices for each group (right and left-sided TLE and control) were conducted.

Table II. *Mean ± SD total volumes of the brain regions among the three groups (healthy; right-sided TLE and left-sided TLE)*

Structure and Group	Healthy Controls (n=14)	TLE Patients (n=14)		
		Right TLE (n=8)	Left TLE (n=6)	
	Mean ± SD	Mean ± SD	Mean ± SD	p-val.
Amygdala	*3.70* ± 0.68	3.78 ± 0.62	3.46 ± *0.71*	Ns (0.65)
Hippocampus	8.77 ± 0.91	8.44 ± 1.22	8.22 ± 1.14	Ns (0.54)
Nucleus Accumbens	1.45 ± *0.31*	1.47 ± *0.34*	1.18 ± *0.13*	Ns (0.15)
Premotor Cortex	13.71 ± *2.50*	13.07 ± 2.06	11.22 ± 1.24	Ns (0.08)
Primary Motor Cortex	28.46 ± 5.73	25.49 ± 4.41	25.09 ± 4.50	Ns (0.28)
Somatosensory Cortex	22.79 ± *5.26*	21.03 ± *4.35*	20.43 ± 4.29	Ns (0.53)
Temporal Lobe	136.5 ± 20.53	135.4 ± 12.52	119.6 ± *13.62*	Ns (0.13)
Thalamus	16.47 ± 2.83	15.54 ± *1.89*	14.17 ± *1.47*	Ns (0.15)
Total Brain	1262 ± *142.5*	1205 ± 86.02	1085 ± 87.96	**0.0486***

*Bold font denotes the significance of the analysis. * p<0.05 by post hoc comparisons. Ns=not significant*

Volume interpretation: As shown in Table II, the left-sided TLE patients showed significant total brain volume reduction compared to the control group but not with the right-sided TLE group. For other brain regions not mentioned, no significant difference was found between the study groups based on total volume comparisons.

The comparisons of the hemispheric volumes in control and patient groups are presented in Table III. In the left-sided TLE group, remarkable right and left hemispheric volume reductions were observed, consistent with total brain atrophy compared to the controls (Figure 1). Significant volume decreases in the left temporal lobe, left NAc, and left premotor cortex were detected in the left-sided TLE group compared to the controls (Figure 2). However, no significant difference in volume was revealed in the right-sided TLE patient group compared to other groups.

Table III. *Mean ± SD hemispheric volumes of the regions, control vs left-sided TLE patient group*

Structure	Group		p val.
	Healthy (n=14)	Left TLE (n=6)	
Left Amygdala	1.86 ± 0.39	1.69 ± 0.32	Ns
Left Hippocampus	4.23 ± 0.6	3.73 ± 0.80	Ns
Left Nucleus Accumbens	0.76 ± 0.15	0.57 ± 0.071	**0.0126***
Left Premotor Cortex	7.02 ± 1.47	5.34 ± 0.75	**0.0176***
Left Primary Motor Cortex	14.06 ± 2.85	12.57 ± 3.24	Ns
Left Somatosensory Cortex	11.64 ± 2.78	10.54 ± 3.35	Ns
Left Temporal Lobe	66.85 ± 9.83	57.19 ± 7.54	**0.0465***
Left Thalamus	8.10 ± 1.41	6.99 ± 0.81	Ns
Left Hemisphere	614.3 ± 77.63	534,2 ± 45.88	**0.0312***
Right Amygdala	1.84 ± 0.35	1.76 ± 0.4	Ns
Right Hippocampus	4.53 ± 0.47	4.48 ± 0.46	Ns
Right Nucleus Accumbens	0.68 ± 0.17	0.6 ± 0.07	Ns
Right Premotor Cortex	6.68 ± 1.31	5.86 ± 0.78	Ns
Right Primary Motor Cortex	14.40 ± 3.32	12.51 ± 1.52	Ns
Right Somatosensory Cortex	11.16 ± 2.77	9.89 ± 1.13	Ns
Right Temporal Lobe	69.61 ± 10.85	62.44 ± 6.88	Ns
Right Thalamus	8,36 ± 1.5	7.17 ± 0.74	Ns
Right Hemisphere	627.4 ± 79.3	551.1 ± 42.78	**0.0411***

*Bold font denotes the significance of the analysis. * p<0.05 by post hoc comparisons. Ns=not significant*

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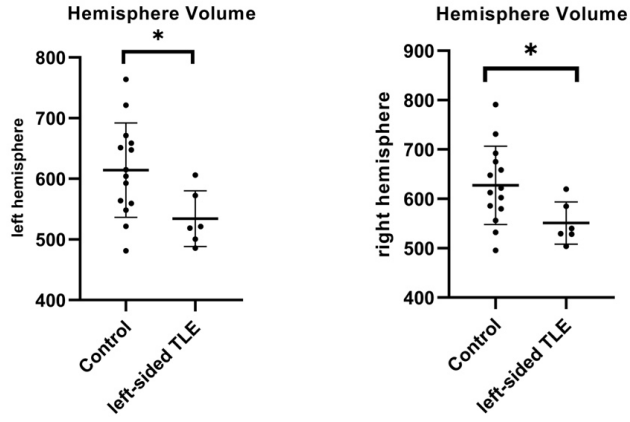

Figure 1. *Significant hemispheric volume reduction in the left-sided TLE group compared to the control group*

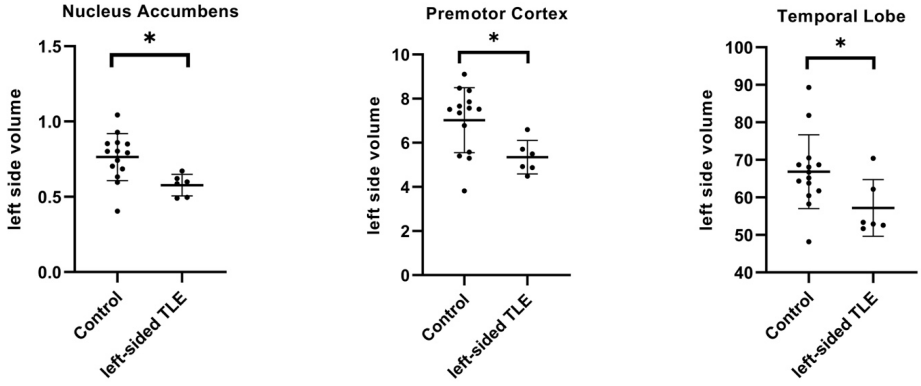

Figure 2. *Significant regional (nucleus accumbens, premotor cortex, and temporal lobe) ipsilateral volume reduction in the left-sided TLE group compared to the control group*

Asymmetry interpretation*:* Comparisons of AI values among the control group, right-sided TLE, and left-sided TLE patients are shown in Table IV. Following the comparisons, there were no significant symmetry differences for the total brain, amygdala, hippocampus, premotor, primary and somatosensory cortices, temporal lobe, and thalamus among the groups. Conversely, the left-sided TLE patients showed significant right asymmetry (contralateral to the lesion side) with negative AI value in the NAc compared to the controls (Figure 3). There were no symmetry changes in the right-sided TLE group compared to other groups. Besides, significant symmetry differences in the amygdala (p=0.0091), hippocampus (p=0.0173), and temporal lobe (p=0.0208) were observed between the patient groups.

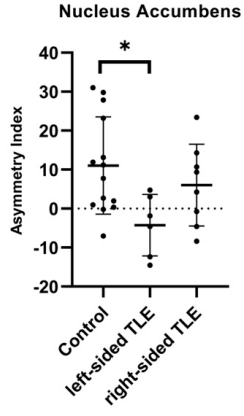

Figure 3. *Significance in asymmetry index value changes of the nucleus accumbens in the left-sided TLE patient group compared to the right-sided TLE and control groups*

Table IV. *Mean ± SD asymmetry index values of the brain regions among the three groups (healthy and subgroups of the patients)*

Structure and Group	Healthy Controls (n=14)	TLE Patients (n=14) Right TLE (n=8)		Left TLE (n=6)	
	Mean ± SD	Mean ± SD	p-val.	Mean ± SD	p-val.
Amygdala AI	0.94 ± 17.30	14.53 ± 10.15	0.1061	-3.16 ± 11.08	0.8309
Hippocampus AI	-7.03 ± 14.10	10.49 ± 22.1	0.0744	-19.35 ± 16.66	0.3230
Nucleus Accumbens AI	11.05 ± 12.46	6.03 ± 10.52	0.5746	-4.25 ± 7.89	**0.0245***
Premotor Cortex AI	4.30 ± 18.71	-2.16 ± 19.36	0.7075	-9.25 ± 15.40	0.2992
Primary Motor Cortex AI	-1.91 ± 15.52	0.18 ± 9.62	0.9408	-1.41 ± 16.04	0.9972
Somatosensory Cortex AI	4.50 ± 16.65	4.46 ± 14.42	>0.9999	3.18 ± 19.77	0.9858
Temporal Lobe AI	-3.84 ± 4.22	0.12 ± 4.22	0.2296	-8.91 ± 8.37	0.1457
Thalamus AI	-3.01 ± 9.17	1.84 ± 8.03	0.4254	-2.65 ± 7.95	0.9961
Total Brain AI	-2.11 ± 1.37	-0.62 ± 2.24	0.1874	-3.16 ± 2.28	0.4861

*Bold font denotes the significance of the analysis. * p<0.05 by post hoc comparisons.*

4. DISCUSSION

Temporal lobe epilepsy is the most common and well-defined localized epilepsy type with HS characterized by neuronal loss as primary pathological evidence. MRI has been one of the most valuable neuroimaging techniques to identify structural changes and epileptogenic foci in epileptic patients. In this study, we aimed to compare the findings of TLE patients versus healthy individuals on changes in volume and symmetry patterns of the total brain, hippocampus, temporal lobe, amygdala, thalamus, NAc, premotor, primary, and somatosensory cortices.

Reduction in total brain volume was observed in left-sided TLE patients compared to the control group in our study. These results are compatible with the meta-analysis that states widespread grey matter volume reduction in unilateral TLE patients [36]. Additionally, the results from our study revealed hemispheric volume reductions in both ipsilateral and contralateral to the lesion in the left-sided TLE group.

The comprehensive surface-based analysis of mesiotemporal and neocortical morphology study displayed marked ipsilateral mesiotemporal atrophy as cortical thinning that was bilateral in the TLE patients versus the controls [37]. Similarly, our results revealed significant volume reduction in the ipsilateral temporal lobe, NAc, and premotor cortex in the left-sided TLE group.

No significant difference was observed in the right-sided TLE patient group in any region compared to other left-sided TLE and control groups. This result is not congruent with the study that detected more expressed structural abnormalities in the right-sided TLE subgroup [38]. Our findings suggest that these results may be consistent with the dominant side of the brain but require more comprehensive research with detailed clinical findings.

The volume reduction of the left temporal lobe in the left-sided TLE group in our results is compatible with voxel-base morphological studies showing atrophy in the temporal regions predominantly ipsilateral to the seizure focus in TLE patients [21, 22, 39-41]. Our findings are also supported by an MRI study showing an asymmetric reduction in cortical surface area in the ipsilateral mesial and anterior temporal lobe subregions in mesial TLE patients [42].

The premotor cortex is highly connected to other brain parts and the elementary motor signs especially arise from precentral and premotor regions in frontal lobe epilepsy patients [43], for temporal region-originated epilepsies the premotor cortex is understudied. The volume reduction in the premotor cortex in our study may provide a new contribution to the literature.

The NAc, an extension of the ventral striatum, is the key nucleus in mediating emotional and motivational processes. Recent studies have shown that NAc participates in the process of epileptic seizures of patients and animal models with TLE thus NAc has been suggested as a target for the treatment in some epilepsy cases [28, 44, 45]. Evidence from both human and animal studies showed that detecting NAc volume reduction can provide valuable data for further investigations on TLE cases.

Hemispheric asymmetry is an important feature of the healthy human brain and reflects the structural and functional differences in the right and left hemispheres. The meta-analysis of the ENIGMA consortium revealed widespread asymmetries at both hemispheric and regional levels in healthy individuals predominantly in the left hemisphere [46]. As shown in previous studies, altered brain asymmetry has also been linked to psychiatric diseases and substance dependence [47, 48].

In our study, we discussed asymmetry patterns concerning TLE and investigated asymmetrical changes in epileptic patients using asymmetry index data calculated by the volumetric measures from the NeuroQuant® software. We detected significant volume asymmetry in the nucleus accumbens with a negative asymmetry index value in left-sided TLE patients compared to the control group. Interestingly, the prior study indicated remarkable whole-brain volumetric asymmetry and blood perfusion in TLE with high AI values [49], the difference between this study and our results was mainly methodological.

Ipsilateral volume decrease and contralateral symmetry deviation of the NAc in the left-sided TLE group could be related to an anatomical injury such as neuronal damage or degeneration in the lesion side. Functional connection changes

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of the NAc subregions have been studied by using the DTI connectivity-based parcellation method and detected the distinct structural connectivity patterns that provide anatomical evidence to support the role of NAc subregions in seizures [50]. The latest study using rs-fMRI pointed out the decrease in functional connectivity between NAc and other brain regions in left-sided TLE patients suggesting that NAc plays an important role in mesial TLE [51]. The small sample size of our study may limit the evaluation of the NAc changes and their relation in TLE patient brains and should be verified in future studies.

In conclusion, researchers have focused on neuroimaging findings in TLE for a long time. Despite the small study group size, the results can provide insight into the morphological changes in TLE patients and symmetry deviation related to the side of the seizure focus. Since the relationship between epileptogenic focus and functional lateralization has been a matter of curiosity recently, asymmetry index results with volume alterations can be considered and implicated in the diagnosis protocols and it may shed light on the correct intervention to the epileptogenic focus treatment like resective surgery for TLE cases.

Compliance with Ethical Standards

Ethical approval: The study was approved by Marmara University, School of Medicine, Clinical Research Ethics Committee on 05.03.2021 with the protocol number 09.2021.322. Participant consent and ethical permissions were obtained.

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