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Evaluation of the thalamus volume and cortical thickness in patients with epilepsy and determining the relationship of these measurements with the clinical variables of the disease

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Abstract

Background & Objectives: The influence of cortical firing neurons and subcortical structures, especially thalamic networks, has a role in the formation and continuity of epileptic seizure activities. In our study, bilateral thalamus volume and cortex thickness from different regions (frontal, temporal, parietal, occipital) were measured in brain magnetic resonance imaging (MRI) of patients diagnosed with epilepsy (PWE)and compared with the healthy control (HC) group. The relationship between the obtained findings and clinical variables of PWEs is intended to be evaluated. *Methods:* Our study was designed as a retrospective cross-sectional study. Between January 2018 and December 2020, 62 PWE were diagnosed by specialist physicians in the neurology outpatient clinic, and 42HC groups were included in the study. Thalamus volume and cortical thickness of frontal, parietal, temporal, and occipital regions were measured by an experienced neuroradiologist and neurologist using a 1.5TMRI device from the 3-DT1sequence of brain MRI examinations of all participants. The measurements of MRI metrics in PWE and HC groups were compared. *Results:* The mean age of the PWE were35.7±12.162, and the mean age of the HC was35.7±11.0. The two groups were similar in age (p=0.842) and gender (p=0.812) distribution. Bilateral thalamus volumes (p<0.001) and cortical thickness (p<0.001) of PWE were found to be lower compared to the HC group. As the disease duration of PWE increased, there was a significant decrease in bilateral thalamus volüme (p<0.001) and temporal cortical thickness (p<0.001). In the group with high seizure frequency, there was a significant decrease in bilateral thalamus volüme (p<0.001) and a significant reduction in temporal cortical thickness (right temporal p=0.040; left temporal p=0.013). As MRImetrics were compared according to seizure type in the PWE group, right frontal cortex (p=0.043), bilateral parietal cortex (p=0.033, p=0.022), left occipital cortex thickness (p=0.031) were found to be lower in patients with focal seizures compared to patients with generalised seizures.
Conclusions: In this study, bilateral thalamus volume and cortical thickness were significantly lower in PWE than in the HC group.

Keywords: Epilepsy, cortex, thalamus, MRI metrics

INTRODUCTION

Epilepsy disease is a common chronic neurological disease characterised by spontaneous recurrent seizures.[1] It is thought epileptic seizures are triggered by cortical mechanisms, and cortical epileptic discharges spread to the thalamus with neuronal inputs and outputs.[2,3] The presence of firing neurons in the cortex and the effect of recurrent seizures on cortical and subcortical structures may cause neuronal degeneration in these structures.[4-6] The importance of the thalamus, one of the subcortical structures, in the pathogenesis of epilepsy can be explained

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by its anatomical and functional connection with many regions of the brain.[7,8] In addition, the thalamus is also involved in controlling seizure activity, regardless of the location of the epileptogenic focus. It is involved in the mechanism of seizure termination by inducing a stable hypersynchronization in the cortex.[9] This information makes it possible to evaluate the cortical thickness and thalamus volume during the disease process in different seizure types. It is important to elucidate the pathogenesis and evaluate the clinical follow-up and prognosis.

This study aimed to measure bilateral thalamus volume and cerebral cortex thickness from different regions (frontal, temporal, parietal, occipital) in patients with epilepsy (PWE) using magnetic resonance imaging (MRI), compare these measurements with those of the healthy control (HC) group, and determine the relationship between the obtained MRI metrics and clinical factors such as seizure type, seizure frequency, and disease duration.

METHODS

Our study was designed as a retrospective cross-sectional study. Approval for the study was obtained from the ethics committee of Health Sciences University Istanbul Training and Research Hospital dated 18.09.2020 with decision number 2521. Informed written consent was obtained from the participants after the nature of the transactions was fully explained. The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki".

Participants

Between January 2018 and December 2020, 62 PWEs diagnosed by specialist physicians in the neurology outpatient clinic and 42 HC groups were included in the study. The socio-demographic characteristics of all participants were recorded. The seizure types of PWE were made according to the ILAE 2017 classification[10], but due to the insufficient number of patients, they were evaluated by dividing them into two separate groups as focal and generalised in terms of statistical significance. Duration of illness and age at onset of a seizure, seizure frequency (at least once a year, less than once a year), anti-seizure medications used, and electroencephalography (EEG) results were recorded. Inclusion criteria: between the ages of 18-65, diagnosed with epilepsy by specialist doctors and had regular follow-ups. Epilepsy syndromes such as parietal lobe or occipital lobe epilepsies were not included in the study because of their limited number. Also, patients with structural lesions such as mesial temporal lobe epilepsy were not included. Our exclusion criteria are epileptic seizures caused by ischemic stroke, space-occupying mass, demyelinating disease, etc.; the presence of additional neurological, neurodegenerative, and autoimmune diseases; and the presence of structural lesions that will affect MRI measurements.

MRI acquisition and data processing

The thalamus volume and cortical thickness of the frontal, parietal, temporal and occipital regions were measured by an experienced neuroradiologist and neurologist using a 1.5 T MAGNETOM Aera (Siemens, Erlangen, Germany) MRI device from the 3D T1 sequence taken in the Epilepsy Protocol of all patients.

While measuring the thalamus volume, In each axial section where the thalamus is visible, the thalamus is segmented by drawing its borders around it. The workstation automatically marked the coronal and sagittal sections according to the axial sections we marked in the MRI. Lastly, each section was checked, and the workstation performed the volume calculation automatically.

Cortical thickness measurements were measured from the superior frontal gyrus, postcentral gyrus, hippocampus, and cuneus level behind the parietooccipital fissure in the same sections for each patient (Figure 1).

Statistical analysis

SPSS 27.0 program was used in the analysis. In the descriptive statistics of the data, mean, standard deviation, median minimum, maximum, frequency and ratio values were used. The distribution of the data was analysed using the Kolmogorov-Smirnov test. An independent sample T-test and Mann-Whitney U test were used to analyse the quantitative independent data. Chi-square test was used in the analysis of qualitative independent data. Relationships between measurements were made using the Pearson correlation coefficient and multiple regression analysis. The statistical significance level was accepted as $p<0.05$.

Intraclass Correlation Coefficient (ICC) value was measured to compare the measurements of two people in thalamus volume measurements and to determine the reliability. The ICC value was calculated as 0.942 for the right thalamus and 0.940 for the left thalamus. The two measurements

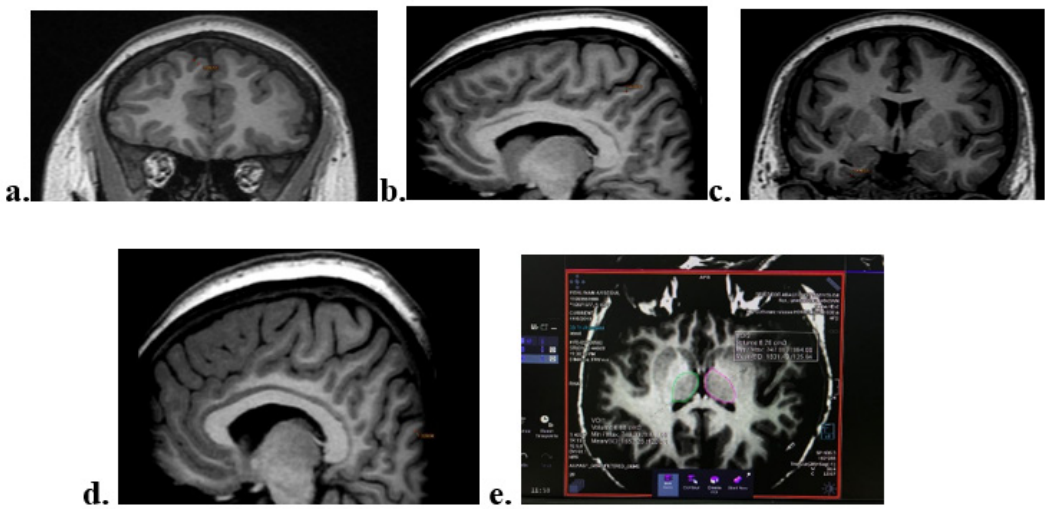

Figure 1. **a.** Superior frontal gyrus cortical thickness measurement **b.** Postcentral gyrus parietal cortical thickness measurement **c.** Hippocampal gyrus temporal cortical thickness measurement **d.** Occipital cortical thickness measurement from the cuneus level **e.** Thalamus volume measurement

were found to be similar, and these values showed that our measurements were reliable. In cortical thickness measurements, almost all values were calculated the same by two measurers, and neuroradiologist measurements were used in the analysis.

RESULTS

Sixty two PWE (31 females, 31 males) and 42 HC (22 females, 20 males) were included in the study. The mean age of the patient group was 35.7±12.1 years, and the mean age of the HC group was 35.7±11.0 years. There were similar characteristics in terms of age and gender distribution between the PWE and HC groups ($p > 0.05$). Considering the distribution of seizure types, there were 35 patients (18 females, 17 males) in the generalised group and 27 patients (13 females, 14 males) in the focal group. Half of our patients (50%) were used one anti-seizure medication (ASM) (Table 1).

Bilateral thalamus volumetric values were found to be significantly lower in the PWE group than in the HC ($p<0.001$). Similarly, in the PWE group, bilateral temporal ($p=0.009$, $p<0.001$), bilateral frontal ($p<0.001$, $p<0.001$), bilateral parietal ($p=0.001$, $p=0.006$) and bilateral occipital ($p=0.002$, $p=0.014$) cortex thickness values were found to be significantly lower than the HC group (Table 2).

A significant negative correlation was observed between disease duration and, bilateral thalamus volume and bilateral temporal cortex thickness ($p<0.001$). As the duration of the disease increased, both thalamus volumes and bilateral temporal cortex thickness were found to decrease. No significant correlation was observed between disease duration and bilateral frontal, parietal and occipital cortex thickness measurements ($p> 0.05$). (Table 3)

Considering the seizure types, no significant difference was observed in the bilateral thalamus volume, bilateral temporal cortex and right occipital cortex thicknesses in the generalised and focal seizure groups ($p> 0.05$). Right frontal cortex, bilateral parietal and left occipital cortex thickness values were found to be significantly lower in the focal seizure group than in the generalised seizure group ($p< 0.05$). (Table 4)

When the patients were divided into two groups in terms of seizure frequency; one or more seizures per year and less than one seizure per year; there was a significant decrease in bilateral thalamus volume ($p<0.001$) and a significant thinning in bilateral temporal thickness (right temporal $p=0.040$; left temporal $p=0.013$) in the group with high seizure frequency (Table 5).

When the patients were divided into two groups in terms of anti-seizure medication use, one ASM and multi ASM users, there was a significant thinning in left temporal cortex thickness ($p=0.024$) in the multi ASM group. There was no significant difference in bilateral thalamus volume and other cortical thicknesses according to anti-seizure medication use. (Table 6)

Table 1: Demographic, clinical and MRI data of PWE and HC

Sex			
• **Female**	**%51(n=53)**		
• **Male**	**%49(n=51)**		
Seizure Type			
• **Generalized onset tonic-clonic seizure**	%56.5 (n=35)		
• **Focal onset aware seizure**	%43.5 (n=27)		
ASM			
• **ONE ASM**	%50 (n=31)		
• **MULTİ ASM**	%50 (n=31)		
	Min-Max	**Median**	**Mean ± SD/%**
Age	18.0 – 65.0	34.5	35.7 ± 11.6
Duration of Epilepsy (Year)	1.0 – 51.0	12.0	14.6 ± 10.8
Thalamus Right	2.8 – 7.7	5.5	5.6 ± 1.0
Thalamus Left	3.3 – 7.9	5.7	5.7 ± 1.0
T. Cortex Right	2.0 – 3.6	2.9	2.9 ± 0.3
T. Cortex Left	2.1 – 4.1	3.1	3.1 ± 0.4
F. Cortex Right	1.3 – 4.0	2.6	2.7 ± 0.5
F. Cortex Left	1.7 – 3.9	2.8	2.9 ± 0.5
P. Cortex Right	2.0 – 3.8	2.7	2.7 ± 0.4
P. Cortex Left	2.0 – 3.9	2.8	2.8 ± 0.4
O. Cortex Right	1.6 – 3.0	2.3	2.3 ± 0.3
O. Cortex Left	1.6 – 3.2	2.4	2.4 ± 0.3

T=Temporal, F=Frontal, P=Parietal, O=Occipital, ASM: anti-seizure medication

Table 2: Comparison of demographic and MRI metrics of PWE and HC

		HC				**PWE**				**p**	
		Mean ±SD /n-%			Median	Mean ±SD /n-%			Median		
Age		35.7	±	11.0	36.0	35.7	±	12.1	33.5	0.842	*
Sex	Female	22		52.4%		31		50,0%		0.812	**
	male	20		47.6%		31		50,0%			
Thalamus Right		6.2	±	0.8	6.2	5.2	±	1.0	5.1	***0.000***	***
Thalamus Left		6.3	±	0.9	6.3	5.3	±	0.9	5.3	***0.000***	***
T. Cortex Right		3.0	±	0.3	3.0	2.8	±	0.4	2.9	***0.009***	*
T. Cortex Left		3.2	±	0.3	3.2	2.9	±	0.4	3.0	***0.000***	*
F. Cortex Right		2.9	±	0.4	3.0	2.5	±	0.5	2.5	***0.000***	*
F. Cortex Left		3.1	±	0.4	3.1	2.7	±	0.5	2.7	***0.000***	*
P. Cortex Right		2.8	±	0.4	2.9	2.6	±	0.4	2.5	***0.001***	*
P. Cortex Left		3.0	±	0.3	3.0	2.8	±	0.5	2.7	***0.006***	*
O. Cortex Right		2.4	±	0.2	2.4	2.2	±	0.3	2.2	***0.002***	*
O. Cortex Left		2.5	±	0.3	2.5	2.3	±	0.3	2.3	***0.014***	*

T=Temporal, F=Frontal, P=Parietal, O=Occipital, *Mann-Whitney U test ** Ki-kare test ***Independent T-test, HC: Healthy Control, PWE: Patients with Epilepsy

Table 3: Correlation of disease duration with thalamus volume and cortical thickness measurements

		Thalamus Right	Thalamus Left	T. Cortex Right	T. Cortex Left	F. Cortex Right
Duration	r	-0.501	-0.535	-0.449	-0.449	-0.028
	p	***0.000*** *	***0.000*** *	***0.000*** *	***0.000*** *	0.826 *
		F. Cortex Left	**P. Cortex Right**	**P. Cortex Left**	**O. Cortex Right**	**O. Cortex Left**
Duration	r	-0.033	-0.008	0.126	-0.087	-0.138
	p	0.797	0.952	0.329	0.500	0.286
Spearman Korelasyon		*	*	*	*	*

Table 4: Thalamus volume and cortical thickness measurements in generalised and focal epilepsy groups

	Generalized		Focal		p	
	Mean±SD	Median	Mean±SD	Median		
Thalamus Right	5.2 ± 0.9	5.1	5.2 ± 1.0	5.0	0.862	t
Thalamus Left	5.3 ± 0.9	5.4	5.2 ± 1.0	5.2	0.419	t
T. Cortex Right	2.9 ± 0.4	2.9	2.8 ± 0.4	2.9	0.327	t
T. Cortex Left	3.0 ± 0.4	2.9	2.9 ± 0.4	3.0	0.060	t
F. Cortex Right	2.6 ± 0.5	2.6	2.4 ± 0.4	2.3	***0.043***	m
F. Cortex Left	2.8 ± 0.5	2.8	2.6 ± 0.4	2.6	0.258	m
P. Cortex Right	2.7 ± 0.5	2.7	2.5 ± 0.3	2.5	***0.033***	m
P. Cortex Left	2.9 ± 0.5	2.8	2.6 ± 0.3	2.6	***0.022***	m
O. Cortex Right	2.3 ± 0.3	2.2	2.2 ± 0.3	2.1	0.203	m
O. Cortex Left	2.4 ± 0.4	2.4	2.2 ± 0.3	2.3	***0.031***	m

T=Temporal, F=Frontal, P=Parietal, O=Occipital, [m] Mann-Whitney U test [t] Independent T-test

Table 5: Thalamus volume and cortical thickness measurements in seizure frequency (one or more seizures per year and less than one seizure per year)

	One or more seizures per year (n=32) Mean ± SD	Less than one seizure per year (n=32) Mean ± SD	p
Thalamus Right	4.6±0.8	5.9±0.7	**<0.001** *
Thalamus Left	4.7±0.8	5.8±0.8	**<0.001** *
T. Cortex Right	2.7±0.4	2.9±0.3	**0.040** *
T. Cortex Left	2.8±0.4	2.9±0.4	**0.013** *
F. Cortex Right	2.4±0.4	3.0±0.3	*0.097* * *
F. Cortex Left	2.6±0.4	2.6±0.4	0.219 * *
P. Cortex Right	2.6±0.4	2.6±0.4	*0.910* * *
P. Cortex Left	2.8±0.5	2.7±0.4	*0.562* * *
O. Cortex Right	2.2±0.3	2.2±0.3	0.651 * *
O. Cortex Left	2.3±0.4	2.3±0.4	*0.871* * *

T=Temporal, F=Frontal, P=Parietal, O=Occipital, *Independent T-test * *Mann-Whitney U test

Table 6: Thalamus volume and cortical thickness measurements in anti-seizure medication (single ASM or multi ASM)

	Single anti-seizure medication (n=32) Mean ± SD	Multi anti-seizure medication (n=32) Mean ± SD	P
Thalamus Right	5.3±0.9	4.9±0.9	0.105 *
Thalamus Left	5.3±0.8	5.1±0.9	0.363 *
T. Cortex Right	2.8±0.3	2.8±0.4	0.308 *
T. Cortex Left	3.0±0.1	2.8±0.4	**0.024** *
F. Cortex Right	2.5±0.5	2.6±0.5	*0.452* *
F. Cortex Left	2.7±0.4	2.7±0.5	0.849 *
P. Cortex Right	2.7±0.4	2.6±0.4	*0.560* *
P. Cortex Left	2.8±0.5	2.8±0.5	*0.911**
O. Cortex Right	2.2±0.3	2.2±0.3	0.842 * *
O. Cortex Left	2.3±0.4	2.3±0.3	*0.823**

T=Temporal, F=Frontal, P=Parietal, O=Occipital, *Independent T-test * *Mann-Whitney U test

DISCUSSION

In our study, in which the MRI metrics obtained by measuring the thalamus volume and cortical thickness from the brain MRIs of the patients followed up with the diagnosis of epilepsy were compared with the HC group, it was found that the thalamus volume was significantly lower in the PWE group, and the bilateral frontal, parietal, temporal and occipital cortex thicknesses were significantly lower. Significant data were also obtained in the comparison of clinical variables of the PWE group with MRI metrics. While there was a negative correlation between the prolongation of the disease duration and the thalamus volume and temporal cortex thickness, it was found that the thalamus volume and temporal cortex thickness were significantly lower in the group with high seizure frequency.

When the literature is examined in terms of similar studies, most of the studies are related to temporal lobe epilepsy (TLE). In their study showing ipsilateral thalamic atrophy in TLE patients with hippocampal sclerosis, Park *et al*. reported that thalamic atrophy is a result of cumulative damage due to the excitotoxic effects of recurrent seizures involving thalamo-limbic circuits.[11] Dongyan *et al*., on the other hand, showed that there are morphological changes not only on the side of Hippocampal Sclerosis (HS) but also in the bilateral thalamus and contralateral hippocampal region in Mesial Temporal Lobe Epilepsy (MTLE) patients.[12] When we look at the studies in the literature evaluating the thalamus volume in patients with generalised and focal epilepsy, similarly, Kim *et al*. found regional changes and atrophy in the thalamus, especially in the anterior-medial and posterior-dorsal parts, and also point out that it was negatively associated with the duration of the disease.[13] Ciumas *et al*., in their study of 19 patients with generalised tonic-clonic seizures, showed that grey matter atrophy was particularly evident in the thalamus, temporal, prefrontal, insular, and inferior parietal cortical areas.[14] In the ENIGMA study, which investigated structural brain abnormalities in generalised epilepsy, which included a very large patient group (2,149 epilepsy patients and 1,727 control groups) in 2018, cortical thickness and volumes of subcortical structures (including the thalamus) were analysed, and they found lower volumes in the right thalamus and reduced thickness in the precentral gyrus (bilateral) in all epilepsy groups.[15] In our study, similar to previous studies, bilateral thalamus volumes were found to be low in all patients with focal and generalised seizures when compared to the HC group. In addition, the fact that all of our patients had low measurements of all cortical structures is open to discussion. It can be thought that the reason for this is the long duration of the disease in the selected patient group and difficulties in seizure control.

There are studies showing that epilepsy may cause progressive cortical atrophy as the duration of epilepsy disease increases. (Galovic *et al*, 2019) In these studies, subcortical volume and cortical thickness measurements showed a strong correlation with the epilepsy disease process.[16] In our study, it was found that as the duration of

the disease increased, there was a decrease in the thalamus volume and a thinning in the cortical thickness.

While the amount of cortical thinning is 0.001-0.008 mm/year in the normal healthy population, this amount is reported as 0.02-0.05 mm/year in epilepsy patients, which is emphasised as a marker of neurodegeneration associated with neuronal loss.[17-19] In studies in which different cortical thickness measurements of patients with epilepsy, it was reported that progressive cortical thinning was observed in 76.8% of epilepsy patients, unlike that seen with normal aging.[20] It has been emphasised that cortical thinning rates are 2 times higher than normal ageing in epilepsy patients under 55 years of age and 4 times higher in patients over 55 years of age.[20] In the study of Huang *et al*. in patients with generalised tonic-clonic seizure, they emphasised that a significant decrease in grey matter volumes of the frontal lobe, insula and cerebellum as well as bilateral thalamus, epileptic seizures cause damage, especially in these brain regions, the thalamocortical pathway plays a fundamental role between the thalamus and frontal cortex in patients with generalised tonic-clonic seizures.[21] In the study of Galovic et al. in focal epilepsies, it was reported that atrophy seen in frontal lobe epilepsy is common in cortical areas, whereas in temporal lobe epilepsies, it is mostly seen in the medial temporal lobe.[20] In our study, a significant decrease was found in bilateral frontal, temporal, parietal and occipital cortical thicknesses in the entire patient group. These findings support the important role of thalamo-cortical and especially fronto-thalamic loops in both focal and generalised seizures, as shown in many studies.

Our study has some limitations. Due to the small number of participants, subgroup analysis could not be performed with all epileptic seizure types. Our study was cross-sectional and not longitudinal. The lack of serial imaging to evaluate disease progression is an important limitation. Cognitive functions could not be evaluated and the clinical effect of cortical thinning and thalamus volume reduction in PWE could not be determined. In addition, morphological evaluation was performed, but microstructure evaluation could not be performed.

In conclusion, in this study, bilateral thalamus volume and cortical thickness measurements from the frontal, parietal, temporal and occipital lobes were found to be significantly lower in PWE compared to the HC group. Our results suggest that MRI metrics may help the clinician predict the course of the disease, provide additional clinical findings and prognosis, determine treatment decisions, and determine the timing of surgery when necessary.

DISCLOSURE

Ethics: This study was approved by Istanbul Training and Research Hospital Ethics Committee. Approval for the study was obtained from the ethics committee of Health Sciences University Istanbul Training and Research Hospital dated 18.09.2020 with decision number 2521.

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Conflict of interest: None

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