Investigation of Subcortical Gray Matter in Patients with Non-lesional Neocortical Focal Epilepsy

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Abstract-

Purpose: To investigate whether there is any change in the subcortical gray matter of patients with neocortical focal epilepsy without visible magnetic resonance imaging (MRI) abnormalities.

Methods: MRI morphometric parameter data from 24 patients and 29 neurologically normal controls were analyzed. All of the MRI scans were reported to have no any anomaly. Differences were evaluated by vertex-wise shape analysis.

Results: A shape analysis showed significant surface reductions at the anterior-ventral and the posterior-dorsal aspects of the bilateral thalami, the global left caudate nucleus, part of the bilateral dorsal putamen and the left hippocampus.

Conclusion: Patients with focal seizures and secondary generalization had smaller volumes and microstructural anomalies in subcortical gray matter regions.

Key Words: Focal neocortical epilepsy, Subcortical structures, Vertex analysis.

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INTRODUCTION

Recent studies have demonstrated the importance of cortical-subcortical network interactions in seizure generation and propagation[1,2]. Emerging magnetic resonance imaging (MRI) and image processing techniques have attracted investigators to explore the structural subcortical gray matter abnormalities. The thalamus and basal ganglia often have structural alterations in patients with idiopathic generalized epilepsies (IGE)[3-10]. In an important epilepsy syndrome, temporal lobe epilepsy (TLE), nearly all the subcortical nuclei show different degrees of alteration[11-16].

Voxel-based MRI analysis is widely used to compare the size difference of the regions of interest[6,7]. Complementary to volumetric analysis, vertex-wise shape analysis is an automated method that provides useful detailed information about the location and pattern of

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morphological changes[3,5,17]. Unlike for IGEs or TLE, few neuroimaging studies have addressed abnormalities in the deep brain structure of patients with neocortical focal epilepsy. This study aimed to characterize the abnormalities of subcortical structures in this patient group. We estimated the volumes of seven subcortical regions: the hippocampus, caudate nucleus, putamen, globus pallidus, nucleus accumbens, thalamus and amygdale (Figure 1). We then investigated changes in the shape of each structure via group comparisons.

METHODS

Subjects. Twenty-four patients (mean age of 25.6 ± 12.9 years) with focal neocortical epilepsy were recruited from the Epilepsy Center at Buddhist Tzu-Chi General Hospital, Hualian, Taiwan. All patients had undergone clinical brain structural MRI and long-term video-EEG recording. None of the patients exhibited any radiologic abnormalities. The seizure focus/foci of the individual patient was/were determined by ictal video EEG. All patients were categorized as having neocortical epilepsy and secondary generalization based on the clinical presentations, the findings of long-term EEG and the conventional MRI analysis. We excluded patients that showed space-occupying lesions in their brain scan, including neoplasms, traumatic lesions, vascular anomalies, well-defined developmental abnormalities or hippocampal atrophy. Patients with maximal ictal or interictal epileptiform discharges at T3, T4 or sphenoid electrodes were also excluded (Table 1). Twenty night age-matched healthy volunteers with structural MRI scans consisting of 14 females and 15 males with a mean age of 27.5 ± 4.2 years were recruited as the control group. Informed consent for the study was obtained from each participant and/or his/her parents and approved by the Ethics Committee.

MRI acquisition. All subjects were scanned in a 3T MRI scanner (General Electric, Waukesha, Milwaukee, WI). Anatomic T1-weighted images were acquired using a high-resolution, axial three-dimensional, T1-weighted, fast spoiled gradient recalled echo (3D T1-FSPGR) sequence. Congruent slices with a thickness of 1 mm were generated with a repetition time (TR) of 11.812 ms, echo time (TE) of 5.036 ms, field of view (FOV) of 22 cm^2, flip angle of 15 degrees and a 512 × 512 matrix.

Group analyses of vertex-based morphometry. The algorithm FIRST (FMRIB's Integrated Registration and Segmentation Tool) was applied. The FIRST can create a surface mesh that consists of individual corresponding vertices of each subcortical structure (Figure 1). We then investigated the significance of localized shape abnormalities by examining individual and group differences using F-statistics. The statistical threshold was set at $p < 0.05$. The false discovery rate (FDR) was used to correct the statistical threshold for multiple comparisons of vertex analysis.

Table 1. Clinical data on 24 patients with focal neocortical epilepsy

ID	Gender	Age	Age at onset	Disease duration	Seizure focus/foci
1	F	21	12	10	Undetermined
2	F	42	36	7	R F, T
3	M	15	14	2	L F
4	F	25	8	18	L T
5	M	42	12	31	R T
6	F	24	2	23	R O
7	F	16	1	16	R F, T, O
8	M	30	2	29	L O
9	M	18	5	14	R F
10	F	22	6	17	L T
11	F	11	5	7	R and L F
12	M	15	3	13	Undetermined
13	F	31	2	30	R F
14	F	12	9	4	Undetermined
15	M	63	10	54	R F
16	F	14	14	1	R't T
17	M	21	Unclear	Unclear	L O
18	F	40	Unclear	Unclear	L F
19	F	16	16	1	Undetermined
20	M	45	31	15	L T
21	F	32	16	17	L F
22	M	18	6	13	R F, T
23	F	25	22	4	L F
24	F	17	17	1	R F

F = Frontal; T = Temporal; O = Occipital; R = Right hemisphere and L = Left hemisphere; Undetermined = seizure activity arising on the EEG in bilateral frontal regions or diffuse epileptiform discharge with asymmetric body posturing at seizure onset.

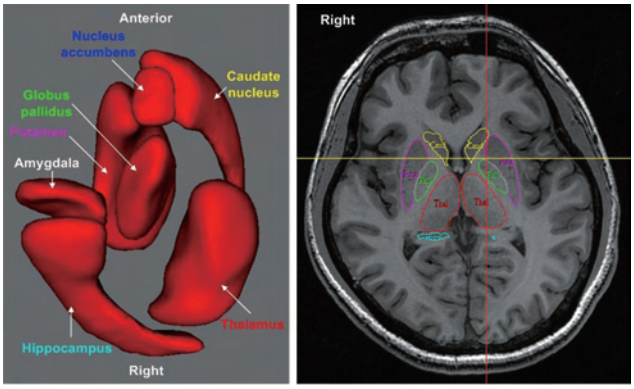
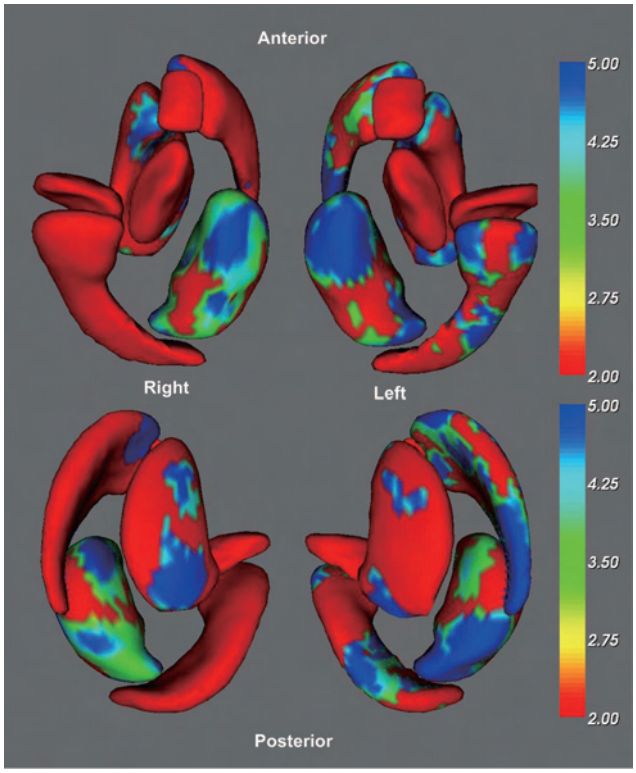


Figure 1. The seven segmented subcortical regions demonstrated in axial and 3D views.

RESULTS

We enrolled 24 patients with neocortical epilepsy and without significant abnormalities in their brain MRI. Although more patients suffered from seizures in the forehead, the proportion of patients with frontal lobe seizures was equal between the right hemispheric epilepsy and left hemispheric epilepsy subgroups. All of the enrolled patients had seizure manifestations with the subsequent development of generalized convulsions.



The vertex analysis technique revealed regional atrophic alterations. Significant regional atrophy was demonstrated at the anterior-ventral and the posterior-dorsal aspects of bilateral thalami, at parts of the bilateral dorsal putamen and in the global left caudate nucleus when comparing the patient group and control group (Figure 2).

DISCUSSION

In this study, we identified the abnormality of subcortical structures underlying cortical original epilepsy, especially for patients without MRI lesions. The morphological characteristics of subcortical gray matter were demonstrated by using validated methods that can accurately and objectively evaluate changes in the volume and shape.

DeCarli firstly discussed volume asymmetry in the extratemporal structures of patients with complex partial seizures of left temporal origin. In addition to the corresponding hippocampus changes, the mean volumes of the left thalamic, left caudate, and bilateral lenticular nuclei were significantly reduced[19]. Consequently, the amygdala[15], putamen[10,12-14,16], caudate[11,14-16], globus pallidus[11] and hippocampus[11,13-15] were also found to show atrophy in patients with temporal lobe epilepsy with or without MRI-visible hippocampal lesions. Thereafter, patients with IGEs, including absence epilepsy, JME, and GTCs, were found to have a subcortical abnormality[3-10]. Here, we further demonstrated that the reduction in volume of subcortical gray matter in patients with frontal, lateral temporal, parietal, or occipital lobe seizures is

Figure 2. Vertex-wise morphometry comparison between patients and controls. Upper schemes show ventral view of subcortical structures. Lower schemes show dorsal view of subcortical structures. The color bars indicate the values of F-statistics: an increase from red to blue is going from a lower to higher statistical significance. Significant regional atrophy at the anterior-ventral and the posterior-dorsal aspects of bilateral thalami, parts of the bilateral dorsal putamen and the global left caudate nucleus was demonstrated. Tendency of the left hemisphere to predominate was also observed.

universal.

Currently, some studies have addressed the shape differences of subcortical structures between patients with generalized epilepsies and normal controls using FSL-FIRST, a vertex-based shape analysis method. Hanjuan et al. found significant regional atrophy in the left thalamus, left putamen, and bilateral globus pallidus in patients with GTCs[5]. Kim identified regional bilateral atrophy on the anterior-medial and posterior-dorsal aspects of the thalamus in 50 adult patients with IGE[17]. In patients with JME, Saini observed focal surface reductions in the medial and lateral aspects of the bilateral thalami[3]. These findings agree with the shape changes on the anterior and posterior portions of the bilateral thalami observed in our study.

Tendency of the left hemisphere to predominate observed in our study is also comparable with many neuroimaging studies either in patients with temporal epilepsy or IGEs. In a pilocarpine-induced epilepsy model study, Xia et al. measured further epileptiform discharges from left hemisphere[24]. Bonilha proposed two possibilities when they also observed extensive extra-hippocampal gray matter loss in their patients with left MTLE: seizures ipsilateral to the dominant hemisphere cause more excitotoxic damage and widespread connections of the dominant hemisphere with the rest of the brain[25]. In our another study in which we used voxel-based morphometry to evaluate tensor features of subcortical structures [26].

Patients with neocortical seizures and secondary generalization had smaller volumes and microstructural anomalies in subcortical gray matter regions. The correlations of the structural abnormalities with clinical variables need more investigations.

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