Voxel Based Morphometry and Manual Volumetric Analysis of the Cingulate Gyrus in Patients with Juvenile Myoclonic Epilepsy and Frontal Lobe Epilepsy Compared to Normal Controls

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Purpose

It has been known that patients with Juvenile Myoclonic Epilepsy (JME) and Frontal Lobe Epilepsy (FLE) subjects have deficits in working memory [1]. High resolution MRI has found increasing number of neuronal dysplastic regions in the so-called "cryptogenic" (unknown) origin group in FLE subjects. The subjects with FLE show neuro-cognitive deficits in the frontal domain, whether or not a clear structural lesion is seen, leading to the hypothesis that it is the seizures, not the structure abnormalities that cause the cognitive dysfunction. Many neuroimaging studies have been performed for JME, and the findings include a lack of increased prefrontal glucose uptake during an activation paradigm [2], increased grey matter in the medial frontal region [3], possible decreased NAA in the cingulate [4], increased myoinositol in the prefrontal cortex [1], and abnormal texture of the thalamus [5]. Fewer studies were available for FLE. In this study we compared the brain morphology in patients with FLE to patients with JME and normal age-matched controls. The manual volumetric analysis was performed to measure the volume of cingulate gyrus, also the voxel-based morphometry (VBM) analysis was performed to assess the differences across the whole brain.

Methods

Twenty-eight subjects, 10 JME (30 ± 9 years old, 4M, 6F), 9 FLE (36 ±15 years old, 5 M, 4 F) and 9 controls (32 ± 13 years old, 5M, 4F) were included in this study. Diagnosis of epilepsy was confirmed by findings of myoclonic jerks, generalized tonic clonic seizures, and generalized fast polyspike wave complexes on EEG. MRI was performed on a 1.5 T Philips Eclipse scanner. The seizure focus was localized on the left in all FLE subjects. The 3D high resolution T1 weighted images were acquired using TR=20 ms, TE=4.47 ms, flip angle=20º, slice thickness= 1.5 mm, FOV=25.6 cm, matrix= 256x256. For manual volumetric analysis, ROI were drawn using an in-house Matlab based program (ROITOOL). The images from three orthogonal views were displayed together, and the outlined structures referenced to internal landmarks on 3 planes could be clearly seen. After tracing the volume was automatically calculated. The left and right cingulate volumes (LC, RC) were separately analyzed and the ratio to the whole brain volumes (LC, RC/TBV*100) were compared across the three groups. A one-tailed test was used to test the hypothesis that FLE cingulate is smaller than controls; a 2-tailed test was used to compare between FLE and JME. For the Voxel-based Morphometry (VBM) analysis, all individual scans were used to create the template and the GM, WM, and CSF probability maps using the technique describe in [6]. The template and the probability maps were smoothed with 8 mm FWHM Gaussian kernel. Next, all original scans were normalized to this template then segmented. The resultant GM and WM maps were smoothed with 12 mm FWHM Gaussian kernel. Statistical inferences were made using an analysis of covariance ($p < 0.001$) with TBV, age, and gender as nuisance variables. The differences in GM volume between FLE and control groups, and between FLE and JME were investigated.

Results

The comparisons of regional ROI-based MRI volumes between 3 groups are presented in table 1. There were no significant differences in total brain volumes. The FLE cingulate volume was smaller compared to both controls and JME, especially in the left side. Voxel-based Morphometry (VBM) analysis showed the same pattern: the FLE group had less gray matter in the cingulate regions, especially in the left compared to the control group (Figure 1). The cingulate GM in FLE is also smaller than in JME group. Moreover, the VBM analysis also demonstrated that the FLE group has less gray matter than the control group in the superior frontal gyrus region, middle temporal gyrus, insula and the parahippocampus region. The VBM was also performed to compare JME and control, which showed less gray matter in the insula, middle temporal gyrus, and the parahippocampus region, but not in the cingulate gyrus.

Table 1: Comparison of cingulate volumes in FLE to JME and controls

	FLE	JME	NC	P_{F-C}	P_{F-J}
TBV	1484±105	1397±138	1452±107	0.24	0.05
LC/TBV%	0.5± 0.1	0.7± 0.1	0.6± 0.1	0.06	<0.001
RC/TBV%	0.5 ±0.1	0.7± 0.1	0.6± 0.2	0.02	<0.001

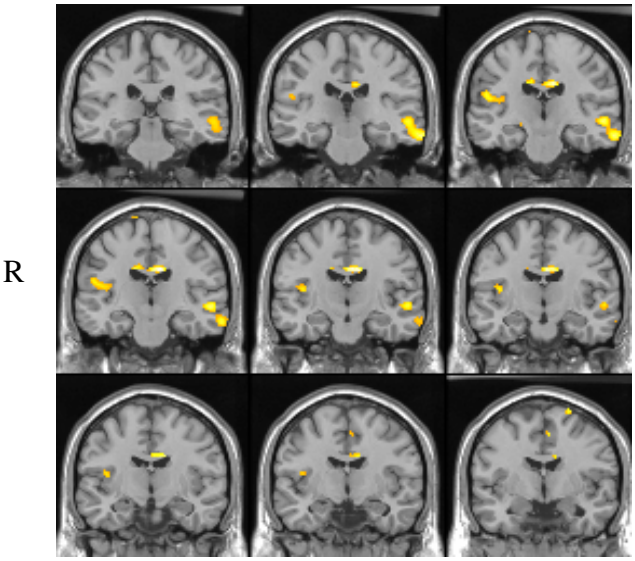

Figure1. VBM analysis of regions where the FLE group have less gray matter than the control group, summarized in Table 2.

Table 2: Regions showing difference between FLE and Control in VBM

Region	Cluster size k	Voxel T	Z score
Cingulate Gyrus	2450	5.44	3.86
Middle Temporal Gyrus	2486	4.90	3.42
Insula	5558	7.10	4.15
Parahippocampal Gyrus	1102	4.35	3.19

Discussion

Our volumetric analysis data support the hypothesis that the cingulate gyrus in FLE is smaller than in control or in JME. Results from VBM analysis also agree with volumetric analysis findings. While manual analysis is more accurate, it is very time consuming and is dependent on the reliability of the operator. Our results indicate that VBM can be applied to investigate cingulate atrophy without performing manual analysis, which may be in part due to that the cingulate is a relatively large and anatomically well-defined region. VBM analysis also reveals that both FLE and JME had smaller GM in middle temporal gyrus, insula and the parahippocampal gyrus compared to the control group. Therefore, it may be possible to differentiate FLE from JME based on the cingulate atrophy. The finding that parahippocampal gyrus is involved is also interesting, which may be related to memory deficit to some extent.

References [1] Swartz et al. J Epilepsy 1994, 7(3): 232-241. [2] Swartz et al. Neurology 1996, 47(5): 1203-1212. [3] Woehrmann et al. Brain 1999: 2101-8. [4] Savic et al. Epilepsia 2000, 41(3): 290-296. [5] Betting et al. Neurology 64(S1): A152; 2005. [6] Good et al. NeuroImage 2000, 14(1): 21-36.

Acknowledgement This study was supported in part by a grant from the Veteran's Administration No. 821/103.