이학석사 학위논문

Usefulness of Quantitative Voxel-based Morphometry of MRI and FDG-PET in detection of Focal Cortical Dysplasia

국소피질이형성증 병변 발견에서 정량적 복셀 기반 형태분석법을 사용한 MRI와 FDG-PET 유용성 연구

2017년 12월

서울대학교 대학원

뇌인지과학과 뇌인지과학전공

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ABSTRACT

Usefulness of Quantitative Voxel-based Morphometry of MRI and FDG-PET in detection of Focal Cortical Dysplasia

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It's important to detect the epileptogenic lesion in pre-surgical evaluation for refractory epilepsy surgery, since non-lesional epilepsy is known as a predictor of surgical failure. Focal Cortical Dysplasia (FCD) constitutes the most common non-lesional epilepsy. Voxel-based morphometry (VBM) of MRI has been useful in enhancing visualization of FCD compared to the conventional visual analysis. However, previous studies were based on qualitative methods to localize the lesion prone to subjectivity, depending on person. Thus, we investigated the usefulness of applying thresholds

quantitatively through VBM of MR T1 and T2-weighted image in objective way rather than subjective method. Also, T1-weighted image and T2-weighted image are known to be sensitive to different structural information, since they have different relaxation time and echo time. Moreover, FDG-PET detects the metabolic abnormality of FCD as a hypometabolic lesion, while MRI detects FCD structural abnormality. As different modalities have different sensitivities of various FCD characteristics, multimodal analysis in diagnosis may improve detection sensitivity of neuronal disease. As a result, we investigated additive values of combining quantitative voxel-based analysis of T1-weighted image, T2-weighted image and FDG-PET in FCD detection.

55 patients who underwent epilepsy surgery and histologically proven as FCD between 2004 and 2016 (30 female, mean age at MRI 29.5 years, range 16-55 years) at Seoul National University Hospital were retrospectively recruited. Preoperative T1, T2 MRIs and FDG-PET were analyzed with voxel-based methods in SPM 12, Matlab. The gray-white matter junction of each patient was extracted and compared to those from healthy controls (26 subjects including 14 female, mean age at MRI 33 years, range 23-45 years). Thereafter, the junction image was made to highlight the blurred gray-white matter. Two observers chose potential lesion in each junction image, which made the blurred region stand out. For quantitative analysis, we applied threshold and among the

over-threshold clusters, the 3 clusters with maximum size of voxels were selected as candidates of the lesion.

FDG-PET data were compared to those in 50 normal controls (37.8 years), using two sample t-test ($p<0.001$). Among the clusters over the threshold, the area with maximum standard deviation was selected as a candidate lesion. The area chosen in MRI and PET analysis was compared with the area surgically resected on post-operative MRIs, taking the surgical outcome into account.

Out of 46 patients whose seizure control after the surgery showed improvement, visual assessment alone in MRIs detected FCD in 16 patients. However, by voxel-based analysis, the FCD lesions were found in 21 patients. Furthermore, when conventional method and voxel-based method were combined, FCD lesions were detected in 26 patients with MRI T1 and T2-weighted image.

Consideration of MRI and PET images together detected 30 patients' lesion correctly, while MRI alone detected 26 patients' lesion with combination of conventional visual analysis and voxel-based morphometric method. Furthermore, the more concordant suspected lesion in between the modalities, the better the surgical outcome presented. There were no significant differences in sensitivity concerning the gender, age at surgery and scanner's difference respectively.

Our results suggest that voxel based analysis based on the blurring of gray and white matter junction not only helps visualization qualitatively, but also can be used quantitatively additional to the conventional visual analysis ($p<0.000$). Also, consideration of both MRI and PET leads better detection of FCD with good surgical outcome.

Key words: Focal cortical dysplasia (FCD), Voxel based morphometry (VBM), Magnetic resonance imaging (MRI), FDG-PET

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CONTENTS

1. Introduction

Post-operative outcome is better in lesional epilepsy than non-lesional epilepsy [1, 2]. Focal cortical dysplasia (FCD), malformation of cortical development, is one of the most common cause of refractory epilepsy, the detection of which may be difficult in MRI [3, 4]. Voxel-based morphometric method (VBM) has remarkably increased the sensitivity of FCD by enhancing visualization, focusing on blurring between white matter and gray matter in MRI [5-8].

However, the FCD detection using VBM has to be proved and confirmed by the observers manually. This means, even with VBM, the detection of FCD needed to be assessed in a subjective way. As VBM of MRI makes the lesion stand out and enhance lesion visualization, we believe that using threshold may provide an objective way to find FCD lesion in brain imaging. Furthermore, as T1-weighted image and T2-weighted image has different relaxation time, it has different sensitivities to various characteristics of pathologies [9, 10]. The previous study showed that blurring of grey and white matter was shown more clearly in T2-weighted VBM image than T1-weighted VBM image [8]. The studies of VBM to find FCD have been improved while there has been lack of studies on multimodal using VBM in detection of FCD.

As a result, we expect that detection sensitivity of FCD increases with the VBM T1 and T2-weighted image and FDG PET, which has complementary information in respect of showing structural and functional characteristics of the lesion.

In this study, our goal was to evaluate the usefulness of quantitative multimodality in detection of FCD. We adopted the voxel-based morphometry in MR- T1 and T2-weighted image- and threshold to get the lesion candidates in each image including FDG-PET.

2. Methods

2.1. Patients and normal database acquisition

Patients who underwent epilepsy surgery and histologically confirmed as FCD between 2004 and 2016 at Seoul National University Hospital were retrospectively recruited. Among them, patients who have pre-operative MR T1-weighted image and T2-weighted image with post-operative MRI available were included in the study. The MRI was taken in five various scanners with different tesla (1.0 T Magnetom Expert scanner (Siemens), 1.5 T Sonata (Siemens), Signa Excite (Siemens), 3T Signa Excite (GE), and Verio (Siemens)). The following sequences were used in each patient : magnetization-prepared rapid-acquisition gradient echo (MPRAGE) sequence (TR/TE = 1720/3.05ms, field of view = 250 x 250mm, flip angle 15°, voxel size =1.0 × 1.0 × 1.0 mm^3) or fast spoiled gradient recalled echo (FSPGR) sequence (TR/TE = 10.944/5.092ms, field of view = 250 x 250mm, flip angle 20°, voxel size =0.5 × 0.5 × 0.5 mm^3) for 3D T1-weighted image, FSE T2-weighted image (TR/TE = 7033.33/106.216ms, flip angle 90°, slice thickness 2mm axial). PET images were acquired using an ECAT Exact PET scanner (CTI-Siemens, Knoxville, USA). Axial resolution was 2.574 mm.

In order to compare to healthy control, the normal control group for each modality was enrolled. T1-weighted image normal database of 26 healthy subjects who were diagnosed as normal (14 female, mean age at MRI 33 years,

range 23-45 years) were acquired on a research-dedicated 3T MAGNETOM Trio Tim Syngo (Siemens, Erlangen, Germany) using a 32-channel head coil. T1-weighted images were obtained with 3D TFL sequence (TR = 1670 ms, TE = 1.89 ms, field of view = 250 × 250 mm, flip angle = 9°, voxel size = 1.0 × 1.0 × 1.0 mm^3). The healthy control of T2-weighted image had 75 normal subjects (25 female, mean age at MRI 30.3 years, range 18-35 years) with 1.5T Signa HDxt (GE) FSE T2-weighted image (TR/TE = 4666.67/127.14ms, flip angle 90°, slice thickness 5mm axial).

FDG-PET control group consists of 50 controls (22 female, mean age at FDG-PET 37.8 years, range 17-55 years) with FDG-PET acquired using an ECAT Exact PET scanner (CTI-Siemens, Knoxville, USA). Axial and in-plane resolutions were 4.3 and 6.1 mm, respectively.

All the controls in this study were healthy subjects without current or past neurological or psychiatric disease and found to be free of structural and functional abnormalities. This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number: C-1612-089-815)

2.2. MRI post processing

Preoperative 3D MRI data were normalized to the Montreal Neurological Institute (MNI) space. The normalized image was segmented into gray matter and white matter and corrected for intensity inhomogeneities at the same time. To focus on the blur of junction between gray and white matter, the voxels which have intensity value between the gray and white matter were extracted. The mean and standard deviations of the gray matter voxels and white matter voxels were used to set the individual's upper and lower thresholds. The lower intensity threshold was determined as the mean of gray matter voxels' intensities + 0.5 * standard deviation of gray matter and the upper threshold was determined as the mean of white matter voxels' intensities – 0.5* standard deviation of white matter.

Through this process, the normalized and intensity corrected image was converted to the binary image which has information of the junction of gray and white matter. The image only included cerebral cortex. The other region like cerebellum, brain stem and basal ganglia were masked out using a predefined mask. Then, the binary image was smoothed by a 5mm 3D kernel.

In order to compare to T1-weighted image of patients, the normal database of T1-weighted images had undergone the same process of normalization, segmentation, intensity correction, extraction of blur region and convolution as the patients' images. The mean normal group image was used to compare with the individual patient's image.

By subtracting individual patients' convolved image from the normal database, which had gone through the same protocol as the patient image, the blur region is highlighted. If the lesion has abnormal gyration or penetration of the white matter, it may stand out as darkened area. However, normal brain areas may be highlighted too if their signal intensities exist within the thresholds and differ from the normal database in this view. The process is briefly shown in figure 1 and the process is referred from the Huppertz's method [6-8].

T2-weighted image and healthy control of T2 had the same post-processing. As T2-weighted image has the higher signal in gray matter and lower intensity in white matter different from the T1-weighted image, the thresholds were changed. The gray matter intensity was used to calculate the upper thresholds while the white matter intensity was used for the lower thresholds [8]. As the T1-weighted image, the normal mean image was subtracted from each patient's image to highlight the abnormal blurred area in T2-weighted images.

Two observers blinded to the patient's information chose one region as the suspected lesion which has abnormal signal comparing to the other brain regions. The PET scan was not seen by subjective way as the hospital uses the additional morphometric method as routine in diagnosis.

2.3. Quantification using threshold

In order to get the candidate lesion area fully automatically, the processed junction image was converted to the binary image using threshold. The lower threshold was determined considering inclusion of resection area and not to exceed 1% of whole brain image empirically, as mean intensity of the junction image – 8*standard deviation of the junction image. The upper threshold was determined as the mean intensity of the junction image + 8*standard deviation of the junction image. The voxels which have intensity over the thresholds were converted to '1' while the others converted to '0'. To reduce the false positives, among the clusters over the threshold, the three clusters with the maximum numbers of voxels were chosen as the candidates of the lesion area.

The PET data were compared to normal controls using two sample t-test ($p < 0.001$, uncorrected). The cluster with the maximum standard deviation was selected as the candidate of the lesion among the clusters over the threshold.

Morphometric MRI and PET analysis was performed using a fully automated MATLAB script and SPM12 (statistical parametric mapping, Wellcome Dpt. Of Imaging Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm).

The lesion localization by analysis was confirmed by comparison with the post-operative MRI and surgical outcome.

The gold standard of sensitivity rate was determined by surgical outcome. The

patients with Engel class I-III's surgical area was concerned to be detected while Engel class IV patient's surgical area was not the lesion. Thus, the sensitivity rate was calculated only with patients who had Engel Class I – III, as they were assumed to have certain FCD lesion as surgical area. For the Engel Class IV patients, we compared suspected lesion with quantitative VBM and other pre-surgical modalities. The above process is described in figure 2.

2.4. Statistical analysis

Statistical analysis was performed using the SPSS Statistical software program for Windows, version 24.0 (SPSS, Inc., Chicago, IL, USA). Fisher's exact test and chi square test were used for the categorical variables. For comparisons of paired categorical data, a McNemar's test was used. The sensitivity, specificity, positive predictive value and negative predictive value of each method – CVA, VBM, T1 and T2-weighted image- was simply calculated by SPSS. Values of $P < 0.05$ were considered statistically significant. Percentage, mean and standard deviation were calculated using MATLAB (R2016b, Math-Works, Natick, MA, USA).

3. Results

3.1. Demographics of patients

55 patients underwent resective surgery for pharmacoresistant epilepsy between 2004 and 2016 (30 female, mean age at MRI 29.5 years, range 16-55 years) were included in the study. All the patients had the histopathological diagnosis of FCD. 43 patients had FCD type I and 12 patients were diagnosed as FCD II.

According to Engel's post-operative outcome classification followed up at least for 2 years, 24 (43.6%) had Engel I, 10 patients (18.2%) were classified as Engel II, 12 patients were III (21.8%) and 9 patients (16.4%) were IV.

Clinical data of the study group are presented in Table 1. FCDs were located in the temporal lobe (n=30), frontal lobe (n=17), parietal (n = 4) and occipital lobe (n= 4).

There were no significant differences in sensitivity concerning the gender, age at surgery and scanner's difference respectively.

3.2. Evaluation of Qualitative Voxel-based morphometry

The processed junction image of T1 and T2-weighted MRI were visually assessed by two observers, blinded to the subject's clinical data. The sensitivity was calculated with 46 patients whose seizure control got better after the surgery, Engel Class I-III. The sensitivity increased significantly with junction images, compared to the raw image. The conventional visual analysis by neuroradiologists detected 30.4% of the FCD patients in T1 and 10.9% patients in T2-weighted image. With the junction image, two observers detected 45.7%, 56.5% in T1 and 30.4%, 50% in T2-weighted images. (Fig. 3) The kappa indexes between two observers of qualitative VBM analysis were 0.269 and 0.087 in T1-wieghted image and T2-weighted image, respectively.

3.3. Evaluation of Quantitative Voxel-based morphometry

Using threshold, quantitative voxel-based morphometry detected 15 FCD patients in T1-wieghted image (30.4%) and 13 (28.3%) in T2-weighted image. In both T1 and T2-weighted image, quantitative VBM detected more FCD patients than conventional visual analysis (CVA) (30.4% versus 32.6% in T1-weighted image) (28.3% versus 10.9% in T2-weighted image). Combination of both methods, CVA and quantitative VBM, presented sensitivity of 50% and 32.6% in T1 and T2-weighed image, respectively, which showed statistically significant increase than using only CVA (p=0.004, 0.002) (Fig. 4).

3.4. Evaluation of Multimodality

T1-weighted image and T2-weighted image detected 50% and 32.6% of FCDs by CVA + quantitative VBM, respectively. Combination of T1-weighted image and T2-weighted image showed 56.5% of sensitivity rate, which was the highest value, compared to using one modality in CVA, VBM and CVA+VBM. Addition of FDG-PET, CVA detected 25 FCD patients, and CVA+ quantitative VBM detected 30 FCD patients. The addition of the FDG-PET scan increased the sensitivity compared to the T1-weighted image, T2-weighted image and T1+T2-weighted image in CVA and VBM and CVA+VBM (Fig. 4).

3.5. Concordance of Multimodality as a Prognosis factor in quantitative method

Comparing with the resection region and candidate lesion by each modality only with quantitative method, we scored concordance of each modality to the resection site. If they match in every modality- T1, T2-wieghted image and FDG-PET, the score was 3, if they have two modalities indicating the resection region- T1+/T2-/FDG-PET+ or T1-/T2+/FDG-PET+ or T1+/T2+/FDG-PET-, the score was 2. With this progress, the result showed the relation between surgical outcome and concordance score.

As more modalities showed the concordance in candidate of lesion to the resection site, the surgical outcome got better. (P =0.002, Fig. 6)

3.6. Pathology type in respect of method sensitivity rate

43 out of 55 patients had FCD type I and the other 12 were diagnosed as type II. In FCD I, CVA detected more than quantitative VBM in T1-weighted image (10 versus 8), while quantitative VBM detected FCD regions significantly better than CVA in T2-weighted image (7 versus 4, p=0.008) and combination of T1 and T2-weighted image (14 versus 10). There was no significant difference CVA and quantitative VBM sensitivity rate in T1-weighted image by FCD pathology type. In FCD II, CVA detected 4 FCD in each T1 and T2-weighted image, while quantitative VBM detected 7 and 3 FCD patients with T1 and T2-weighted image, respectively. Sensitivity rate of FDG-PET image showed more in FCD type II (8 out of 12) than FCD type I (14 out of 43) slightly (p = 0.047). The results are shown in figure 7.

3.7. Sensitivity, Specificity, positive predictive value and negative predictive value in each method and modality

We calculated sensitivity and specificity in CVA, VBM and CVA+VBM. It is described in table 2. The sensitivity of quantitative VBM was higher than CVA in T1-weighted image and T2-weighted image (0.33 versus 0.3, 0.28 versus 0.11). Also, CVA+VBM showed the highest sensitivity in T1, T2-weighted image and multimodalities. However, the specificity of VBM in T1-weighted image was 1, while CVA showed 0.89. In other modalities, the specificity showed slight decrease in VBM, compare to CVA. The positive predictive value in T1 and T2-weighted image didn't show any prone with small difference between the methods. However, the negative predictive value was higher in quantitative VBM than CVA. Furthermore, it showed highest result by CVA+VBM in every modality.

4. Discussion

4.1. Evaluation of Qualitative and Quantitative VBM analysis

The detection sensitivity rate by the observers – qualitative voxel-based morphometry - presented much higher than the conventional visual analysis with the raw image. However, the kappa index between two observers was 0.269 and 0.087 in T1 and T2-weighted images, which indicate slight agreement. This means that qualitative inspection even with the voxel-based morphometry can't be free of subjectivity.

Using a threshold to delineate the lesion has been widely used in clinical imaging like cancer [11]. Unlike cancer, focal cortical dysplasia shows subtle abnormality in MR images, so it was hard to apply the threshold method to the pathology. However, the voxel-based morphometry suggested by Huppertz enables the abnormality of FCD to stand out than other region in brain, so we suggested that the threshold could delineate the lesion well with VBM.

As a result, quantitative voxel-based morphometry + conventional visual analysis increased the sensitivity with statistically significance than CVA. This was shown not only in T1-weighted image, but also in T2-weighted image.

4.2. Evaluation of Multimodality

Multimodality showed the highest sensitivity of all in every method – CVA, VBM and CVA+VBM. Combination of T1 and T2-weighted images detected 26 FCDs, while T1-weighted image detected 23 and T2-weighted image detected 15 each in quantitative VBM + CVA. The T1-positive/T2-negative cases were 11 and T1-/T2+ cases were 3 in quantitative VBM + CVA (Fig.5.d, e). MR-/PET+ cases were 9 (Fig. 5.f). The addition of FDG-PET made a great increase showing statistically significant p value in either only CVA or only VBM, but did not show statistical significance in CVA+ quantitative VBM. Thus, these results mean that each modality has sensitivities in different information, and they work as complementary information.

4.3. Concordance between modalities and surgical outcome

As more modalities showed the concordance in candidate of lesion to the resection site, the surgical outcome got better. ($p = 0.002$, fig. 6) This result indicates that multimodalities concordance may function as prognosis factor of epilepsy surgery. Multimodal concordance as a prognosis factor was suggested in previous studies [12, 13]. However, the lesion detection in this study was acquired by solely automatic way, while previous studies depended on subjective method as conventional visual analysis.

4.4. Sensitivity and Specificity in each method and modality

As the sensitivity and negative predictive value of each modality showed the highest value in CVA+VBM, we assert that quantitative VBM's usefulness in diagnosis of FCD. However, the specificity was increased in T1-weighted image with VBM than CVA (1 versus 0.89), while it was decreased in T2-weighted image with VBM. For the specificity, we investigated the Engel Class IV patients suspecting the region, excluding the resection area.

As all the patients in this study were histopathologically proven as FCD, the Engel class IV patients regarded to have multifocal epilepsy, which have lesion other than resection site. Thus, we inspected patients with Engel class IV (n=9) whether they have concordance between modalities, indicating other region than resection site. Among them, one patient showed concordance of lesion candidates in T1 and T2-weighted image by quantitative VBM in the right frontal lobe, in precentral gyrus. The lesion candidate by FDG-PET scan did not indicate the same region by the method which only showed the maximum cluster over threshold p-value of 0.001. However, it showed hypo metabolism in right frontal lobe with significance ($p = 0.005$). It did not match strictly to the suspected region as in MRI, but it was shown in very close to the region, existed as an extension to the gyrus. Furthermore, magnetoencephalography(MEG), which indicates the brain region with abnormal functional activity, of the patient showed multifocal lesions, including right frontal region. Other pre-surgical evaluations indicated left temporal region as an epileptogenic location, the resected site. However, as all

modalities showed concordance and patients with score of 3 (n=5), which all modalities showed concordance to the resection site all showed good surgical outcome (Fig. 6). Thus, we strongly suggest that the right precentral gyrus region of the patient as the FCD lesion and surgery of the region enable the patient's surgical outcome better. The multimodal images are shown in figure 8.

4.5. Relation between pathology type and VBM

According to Blumcke's classification, cortical dysplasia type I presents as abnormal cortical lamination either in radial or tangential. FCD type II is defined as specific cytological abnormalities, dysmorphic neurons (FCD IIa) and balloon cells (FCD IIb) [14].

In figure 7, we analyzed the sensitivity of modalities with different methods used in the study in relation to the type of FCD. T1-weighted image and FCD I did not show any differences or relations between pathology types and imaging sequences, respectively. However, T2-weighted image detected FCD I significantly better with CVA+VBM and VBM than using only CVA (n= 10, 12 versus 2). A possible reason for the superiority of FCD type I in T2-weighted quantitative VBM could be the T2-weighted image's higher sensitivity to the subtle white matter alterations. Due to a better measure of water content, T2-weighted images are more sensitive to subtle signal of demyelination or inflammation, which can be found in FCD I, which has mild dyslamination, compare to FCD II [16]. Thus, the result means that subtle signal of FCD type I which is hard to detect by human, can be detected by VBM in automatic way.

There were 9 cases which were detected by visual inspection with T1-weighted image while VBM couldn't (Fig. 7.a). However, among them, 4 cases' lesion were found in VBM, which were over the threshold, but couldn't be included in the maximum 3 clusters. Also, the 5 patients out of 9 was diagnosed as FCD by size abnormality in CVA. Size atrophy can't be detected by VBM we used in the study, because it only focused on blurring of grey and white

matter. Moreover, 2 patients had severe structural abnormality like dilation of ventricles (fig.5.c) which couldn't be corrected by normalization process of SPM12. However, it showed the lesion over the threshold, not included in maximum 3 clusters.

FDG-PET scans showed less sensitivity for type I compared with type II CD, as in previous studies on FCD and FDG-PET scans. [12, 17-20]

There was no relation between epileptogenic location and FDG-PET or T1-weighted image's sensitivity, while T2-weighted image of quantitative VBM method showed relation (p=0.010). Quantitative VBM of T2 –weighted image detected temporal and occipital lobe much better than frontal or parietal lobe. This can be explained by the relation between pathology type and the epileptogenic location. In this study, most of temporal lobe and occipital lobe patients had FCD type I, which was detected by quantitative VBM in T2-weighted image better than type II.

4.6. Limitations

As this study is retrospective, the normal database of each modality was different and the scanners of the patients were various and this may cause

the normalization or signal inhomogeneity's error. Besides, the period of the study was long (2004-2016), there's change in clinical issues and techniques. Though this problem was solved by statistical analysis that showed it has no effect on sensitivity of scanners and periods in the study. However, we expect that the unity of scanners, normal database and clinical setting would allow more precise results.

However, in the clinical setting, the experienced neuroradiologist did the conventional visual analysis, who has been involved in the pre-surgical evaluations, while the post-processing in the study was applied by the non-radiologist. Thus, the diagnostic value assumed to be higher in VBM than CVA presented in this study.

5. Conclusion

In this study, we showed that morphometric MRI analysis applied in addition to CVA significantly increases the diagnostic sensitivity not only in

qualitative way but also in quantitative way of using threshold for the first time. Furthermore, multimodality – MRI T1-weighted image, T2-weighted image and FDG-PET- helps to detect the FCD lesion better than single modality and it can be function as a prognostic factor of epilepsy surgery. As a consequence, the quantitative multimodality method appears to be a promising additional diagnostic tool in the evaluation of patients with pharmacoresistant epilepsy.

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LIST OF TABLES

	All	FCD I	FCD II
N (male)	55 (25)	43	12
Age at surgery	29.5(16-55)		
Outcome			
Engel I, n (%)	24 (43.6)	15	9
Engel II, n (%)	10 (18.2)	9	1
Engel III, n (%)	12 (21.8)	11	1
Engel IV, n (%)	9 (16.4)	8	1

Table 1. Clinical and postoperative outcome data of the study group.

a)

T1-weighted Image	Sensitivity	Specificity
CVA	0.30	0.89
VBM	0.33	1
CVA+VBM	**0.5**	**0.89**

T1-weighted Image	Positive predictive value	Negative predictive value
CVA	0.93	0.2
VBM	1	0.23
CVA+VBM	**0.96**	**0.26**

b)

T2-weighted Image	Sensitivity	Specificity
CVA	0.11	1
VBM	0.28	0.89
CVA+VBM	**0.33**	**0.89**

T2-weighted Image	Positive predictive value	Negative predictive value
CVA	1	0.18
VBM	0.93	0.20
CVA+VBM	**0.94**	**0.21**

c)

T1+T2	Sensitivity	Specificity
CVA	0.35	1
VBM	0.46	0.89
CVA+VBM	**0.57**	**0.89**

T1+T2	Positive predictive value	Negative predictive value
CVA	0.94	0.20
VBM	0.95	0.24
CVA+VBM	**0.96**	**0.29**

d)

T1+T2+PET	Sensitivity	Specificity
CVA	0.54	0.78
VBM	0.63	0.78
CVA+VBM	**0.65**	**0.78**

T1+T2+PET	Positive predictive value	Negative predictive value
CVA	0.93	0.25
VBM	0.94	0.29
CVA+VBM	**0.94**	**0.30**

Table 2. Sensitivity, specificity, positive predictive value and negative predictive value of each method used in the study.

a) shows the sensitivity, specificity, positive predictive value and negative predictive value of CVA(Conventional Visual Analysis), VBM(quantitative VBM) and combination of CVA and VBM in T1-weighted image. b), c), d) shows T2-weighted image, combination of T1 and T2 weighted image and combined all modalities – T1, T2 and FDG-PET scan respectively.

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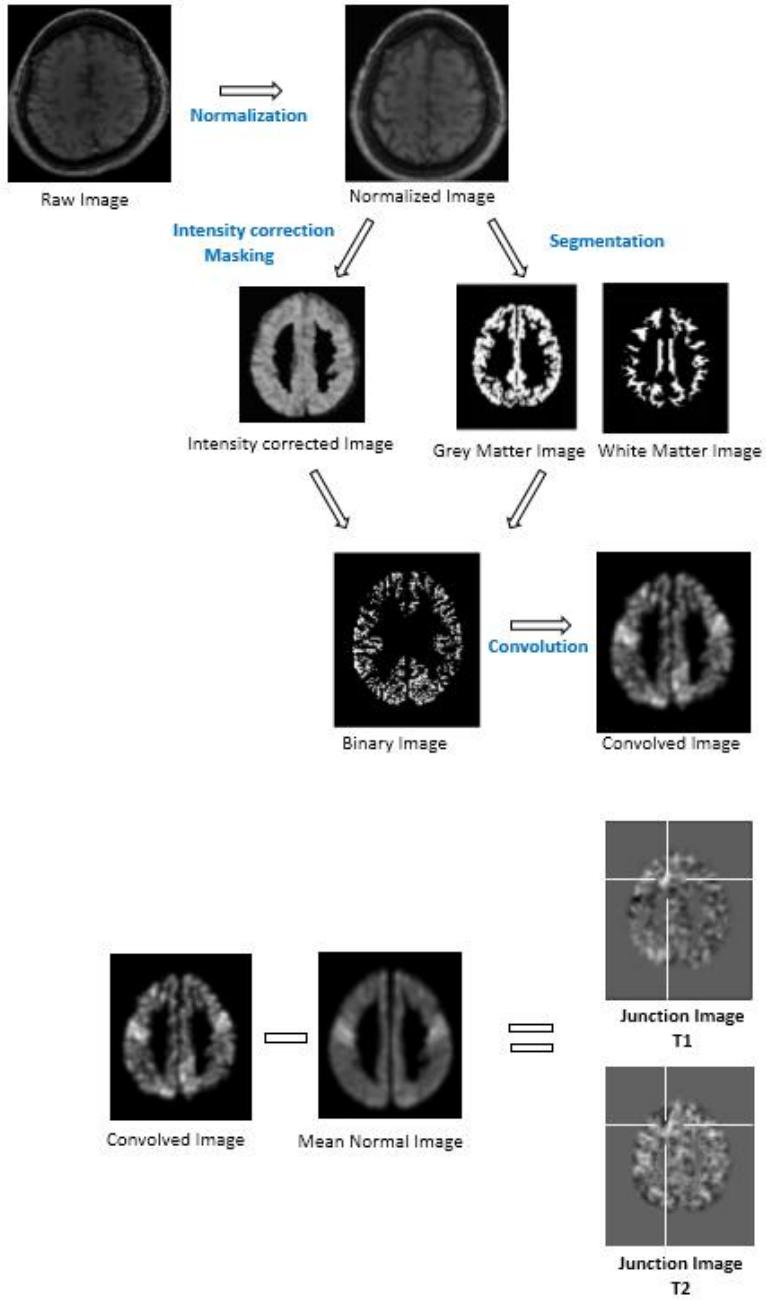

Figure 1. Overview of the MRI post-processing steps making junction image. Overview of the image processing steps to get the junction image of T1-weighted image and T2-weighted image, respectively.

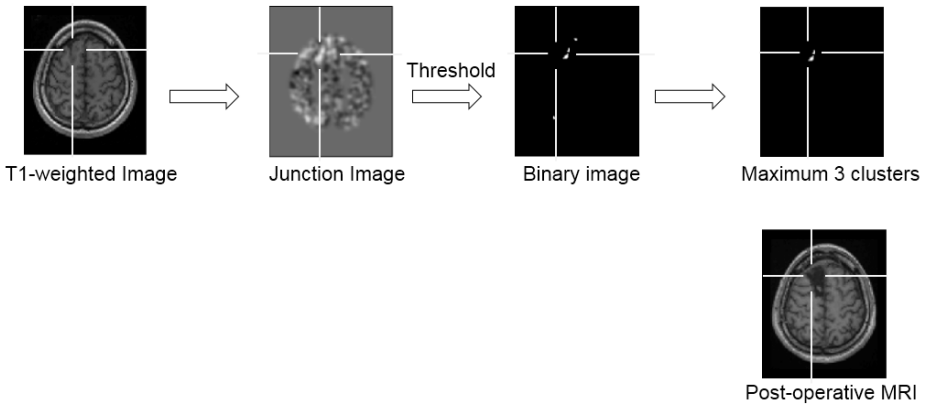

Figure 2. Quantification of MR junction image. Adjusting the threshold to each junction image, only supra-threshold areas are left in the binary image. Among them, 3 clusters with the maximum voxel size are left. Those 3 clusters are the candidates of the FCD lesion. This process is the same for the T2-weighted image.

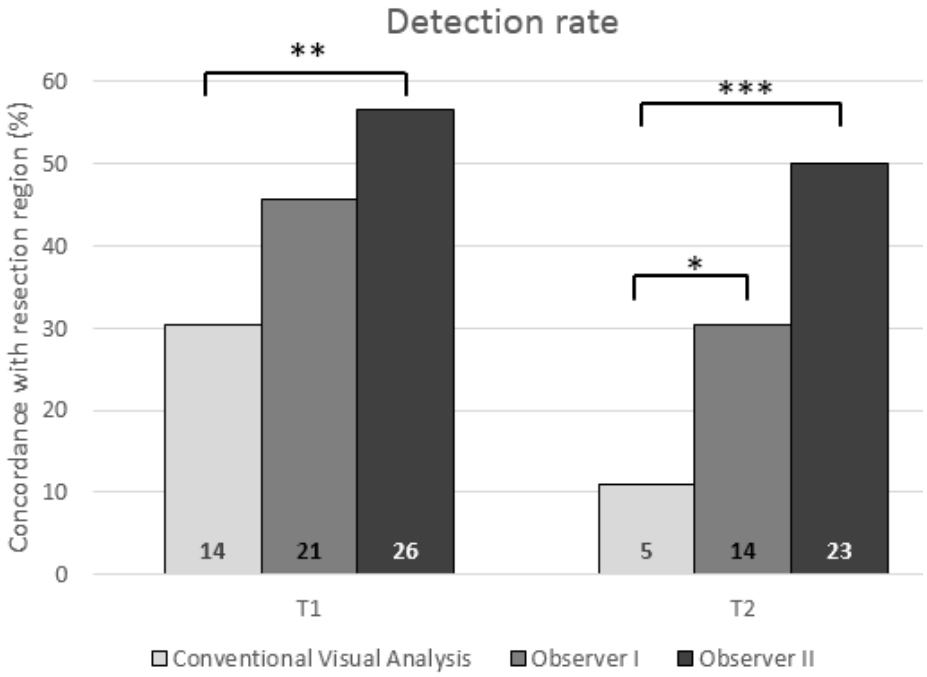

Figure 3. Sensitivity rate of qualitative VBM. Sensitivity rate of the raw image and junction image investigation by two observers. Numbers above the bars represent sensitivity rate in each group. *P≤0.05; **P≤0.01; ***P≤0.001.

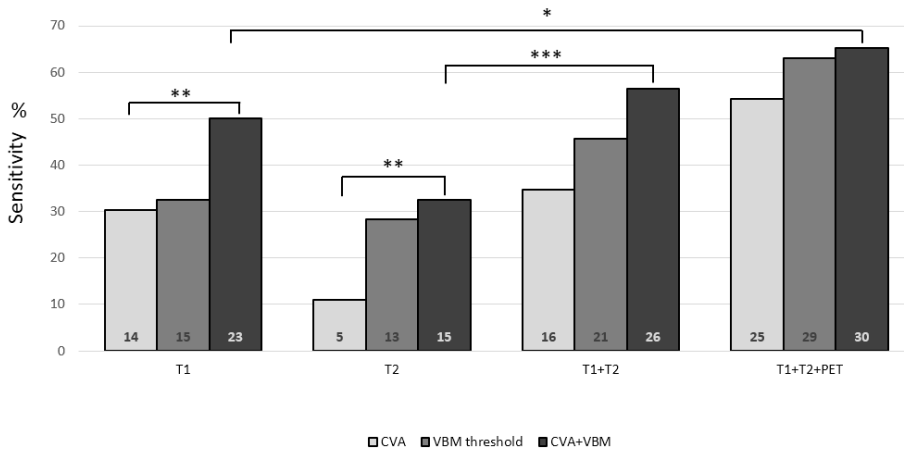

Figure 4. Comparison of Sensitivity rate between CVA and quantitative VBM. Sensitivity rate of CVA, quantitative VBM and CVA + quantitative VBM in each modality (T1-weighted image, T2-weighted image and FDG-PET) and multimodality. CVA+VBM means detection sensitivity of overall methods, combination of conventional visual analysis and quantitative VBM. Numbers below the bars represent number of patients in each group. *P≤0.05; **P≤0.01; ***P≤0.001.

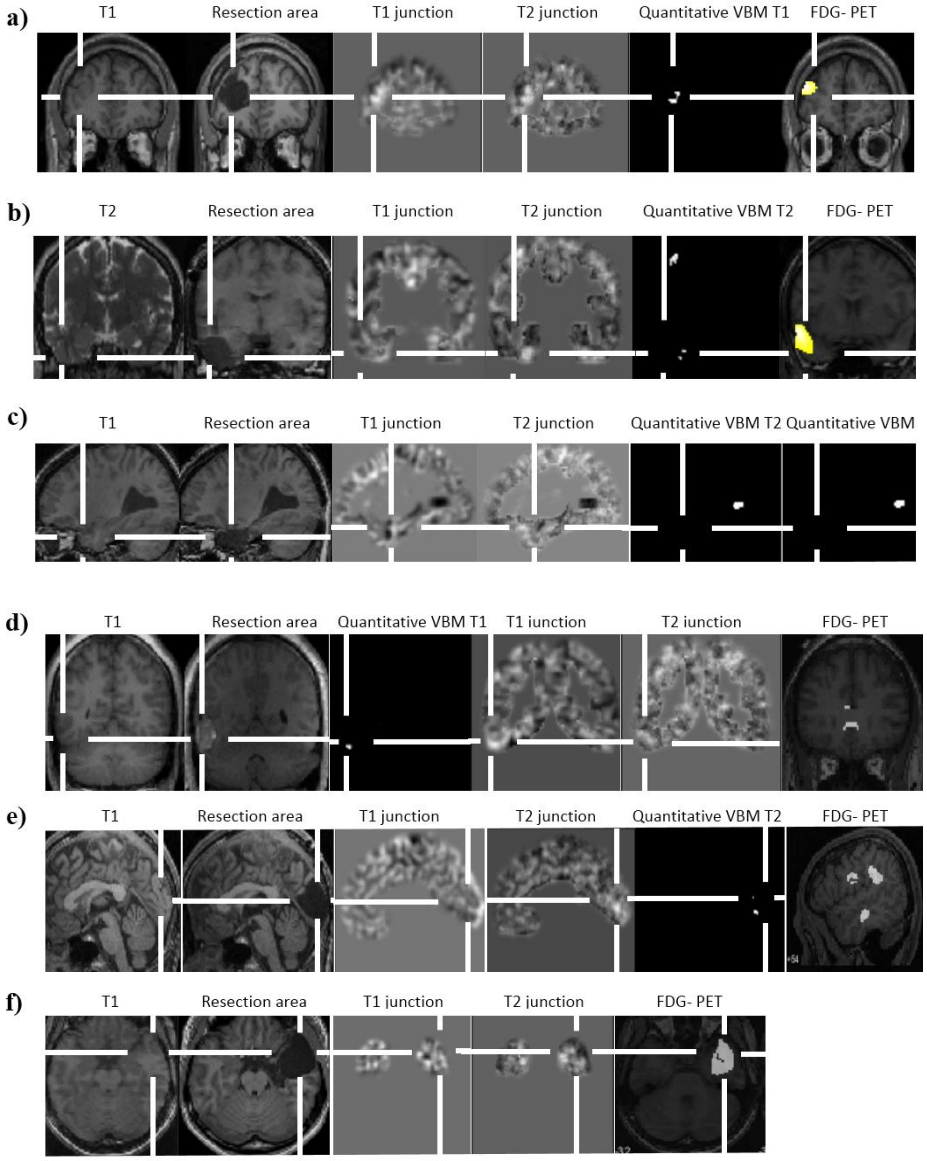

Figure 5. Examples of FCD lesions that were either T1-weighted quantitative VBM+ or T2-weighted quantitative VBM+. (a) presents a patient with FCD Ib in left temporal lobe and CVA+, VBM+, PET+ (EC I) (b) shows a CVA-, VBM+ case who had an over-threshold cluster at the left temporal lobe, matched with the resection site. (EC I) (c) presents a FCD IA in right medial temporal lobe epilepsy, which was detected in CVA, but not in VBM. The patient has a hypoplasia of corpus callosum and focal dilatation of

the right lateral ventricle. This case did not have FDG-PET scan. (EC I) (d) shows a patient positive in quantitative VBM of T1-weighted image and CVA-. It had FCD Ib in the left temporal region. (EC III) (e) indicates FCD Ia with CVA-,VBM+ (only in T2-weighted image) and Engel class I. (f) shows FCD Ia which had a result of negative in conventional visual analysis of MR and quantitative VBM of MR, but positive only in FDG-PET scan analysis.

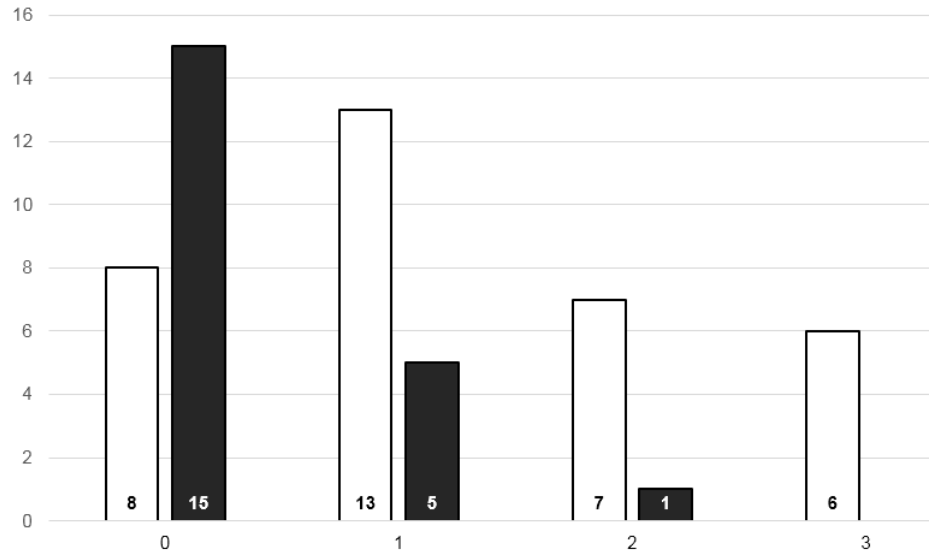

Figure 6. Surgical outcome according to concordance of modalities. The white bar presents good surgical outcome (Engel class I-II) and the black bar presents poor surgical outcome (Engel class III-IV). The number below the bar means number of patients in each group. (p=0.002, Fisher's exact test)

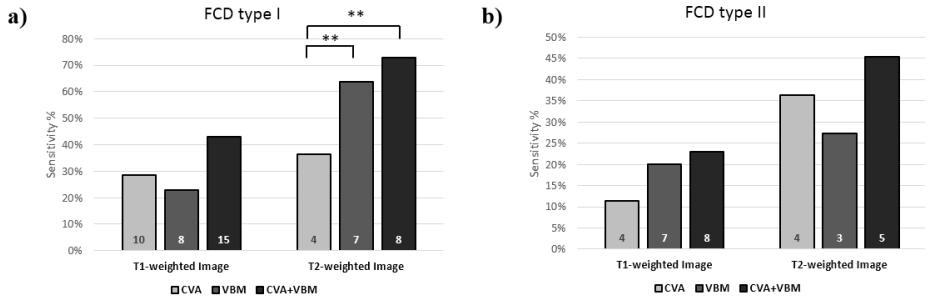

Figure 7. Sensitivity rate in relation to pathology types of FCD. The graph shows detection sensitivity rate of each method introduced in the study in relation to FCD I and II. (a) presents the sensitivity rate in T1-weighted image, and (b) shows the sensitivity rate in T2-weighted image. The number below the bar means number of patients in each group. *P≤0.05; **P≤0.01

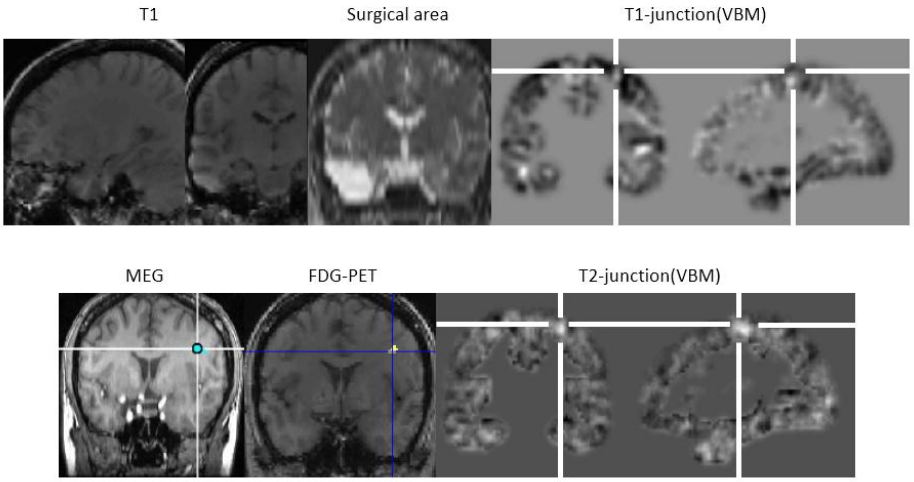

Figure 8. Multimodal images of Engel class IV patient. The figure shows pre-operative T1-weighted image, surgical area, T1-junction image, MEG, FDG-PET scan and T2-junction image of Engel class IV patient. The crosshair indicates the suspected region from quantitative VBM T1 and T2-weighted image, FDG-PET($p<0.005$) and MEG, which all point out right precentral gyrus.

국문초록

국소피질이형성증 병변 발견에서 정량적 복셀 기반 형태분석법을 사용한 MRI와 FDG-PET 유용성 연구

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약물 난치성 뇌전증 환자들의 수술에 있어 수술 전 평가에서 발작유발 부위를 찾는 것은 매우 중요하다. 수술 전 평가에서 병소를 찾지 못한 뇌전증은 수술 후 발작 통제 실패의 예측 요소가 된다. 국소대뇌피질이형성증은 약물난치성 뇌전증의 큰 원인 중 하나로 꼽힌다. 복셀 기반 형태분석법을 이용한 연구들은 대뇌피질이형성증의 병변을 더욱 잘 보이도록 하여 기존의 이미지보다 훨씬 더 발견을 잘 하도록 발전해왔다. 그러나, 이전의 연구들은 복셀기반 형태분석법을 이용하였더라도 사람의 주관적 판단이 필요하였다.

그러므로, 우리는 역치를 세우고 정량적으로도 자기공명영상 – T1과 T2 강조 영상 – 복셀 기반 형태 분석법이 대뇌피질이형성증 병소 발견에 이용될 가치가 있는지를 분석해 보고자 한다. 또한, T1 강조영상과 T2 강조 영상은 서로 다른 이완 시간과 에코시간을 갖고 있으므로 뇌의 다른 구조적인 변화로 인한 특성에 민감도를 갖고 있다고 알려져 있다. 게다가 뇌자기공명영상은 구조적 변화를 감지하는데 반하여 FDG-PET은 대뇌피질이형성증의 비이상적 기능인 뇌대사 저하를 감지한다. 다른 영상기법들이 대뇌피질이형성증의 다양한 특징에 다른 민감도를 가지므로 다중영상기법을 이용하는 것이 진단 확률을 높이는 데 도움이 될 것이라고 예상한다. 결과적으로, 우리는 정량적 복셀기반 형태계측법을 통한 MRI와 FDG-PET을 함께 이용한 기법의 대뇌피질이형성증 병소를 발견하는 데 있어 유용성을 연구하였다.

서울대 병원에서 2004년부터 2016년까지 약물난치성 뇌전증을 앓아 뇌절제술을 받은 환자들 중, 병리학적으로 국소대뇌피질이형성증으로 진단을 받은 55명을 대상으로 후향적으로 진행 되었다. (30명 여성, MRI 찍을 때의 평균 나이 29.5세, 범위 16-55세) 수술 전 MRI T1, T2 강조영상과 FDG-PET 영상을 Matlab의 SPM12을 이용하여 복셀기반 형태계측법으로 분석하였다. MRI에서

는 각 환자의 회질과 백질의 경계 영상을 추출하였고 정상군의 회백질 경계 영상과 비교 하였다. 그리하여 회질과 백질의 경계가 불분명하고 흐트러진 부분이 더 잘 보이게 된 영상을 얻었다. 두 명의 관찰자가 환자의 회백질 경계가 불분명한 곳이 강조된 영상을 보고 병변으로 의심되는 부분을 골라 복셀기반 형태계측법을 이용한 정성적인 평가를 했다. 정량적인 평가를 위해, 역치값을 이용하여 특정 값 이상의 수치를 나타내는 무리만을 추출한 영상을 만들었다. 이 와중에 제일 많은 복셀들을 가진 무리 3개를 병변의 후보군으로 뽑게 되었다. FDG-PET 영상은 정상인 50명(평균 나이 37.8세)과 2-표본 t 검정을 이용하여 비교하였다 ($p<0.001$). 역치값 이상의 무리들 중, 가장 큰 표준편차를 가진 것을 병변 후보로 선택하였다.

이렇게 MRI와 FDG-PET 영상에서 국소피질이형성증의 후보군으로 뽑힌 곳은 수술 후 MRI 영상에서 확인되는 절제 부위와 수술 후 결과를 참고하여 비교하였다.

수술 후 발작 조절이 좋아진 46명의 환자 중에서, 기존의 방법처럼 MRI 영상을 보았을 때에는 16명의 병변을 발견할 수 있었다. 그러나 복셀기반 형태분석법을 통한 정량적 방법으로는 MRI에서 21명의 환자에서 병변을 발견하였다. 기존의 방법과 복셀 기반 형태분석법을 함께 보았을 때에는 총 26명의 환자에서 병소 발

견이 가능하였다. 기존의 방법과 복셀기반 형태분석법의 발견을 함께 보았을때, MRI에서는 26명, MRI와 FDG-PET을 함께 보았을 때에는 30명의 환자에서 병변 발견이 가능하였다. 게다가 더 많은 영상들의 병변 후보군이 일치할수록 수술 결과는 더 좋은 것으로 나타났다 (p=0.002). 병변 발견율에 있어 성별, 나이, 스캐너의 다양성은 영향을 끼치지 않았다.

이 연구의 결과는 국소피질이형성증의 큰 특징인 회백질의 경계가 흐릿해지는 것에 집중하여 복셀 기반 형태분석법을 이용하는 것이 병변 발견에 있어 정성적, 정량적으로 도움이 됨을 시사하고 있다. 그리고 MRI와 FDG-PET 모두 고려하였을 때 발작 조절에 있어 더 좋은 수술 결과를 나타낼 수 있음을 확인하였다. 이러한 방법을 통해 MRI와 FDG-PET을 수술 전 평가가 불분명한 환자에게 적용한다면, 기존의 방법보다 국소대뇌피질이형성증의 병변 발견과 수술 후 발작 조절에 있어 도움이 될 것이다.

주요어: 국소대뇌피질이형성증, 복셀기반 형태분석법, 자기공명영상, 양전자방출단층촬영

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