Alterations of structural connectivity and structural co-variance network in focal cortical dysplasia

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Abstract

Background

The aim of this study was to investigate alterations in structural connectivity and structural co-variance network in patients with focal cortical dysplasia (FCD).

Methods

We enrolled 37 patients with FCD and 35 healthy controls. All subjects underwent brain MRI with the same scanner and with the same protocol, which included diffusion tensor imaging (DTI) and T1-weighted imaging. We analyzed the structural connectivity based on DTI, and structural co-variance network based on the structural volume with T1-weighted imaging. We created a connectivity matrix and obtained network measures from the matrix using the graph theory. We tested the difference in network measure between patients with FCD and healthy controls.

Results

In the structural connectivity analysis, we found that the local efficiency in patients with FCD was significantly lower than in healthy controls (2.390 vs. 2.578, p = 0.031). Structural co-variance network analysis revealed that the mean clustering coefficient, global efficiency, local efficiency, and transitivity were significantly decreased in patients with FCD compared to those in healthy controls (0.527 vs. 0.635, p = 0.036; 0.545 vs. 0.648, p = 0.026; 2.699 vs. 3.801, p = 0.019; 0.791 vs. 0.954, p = 0.026, respectively).

Conclusion

We demonstrate that there are significant alterations in structural connectivity, based on DTI, and structural co-variance network, based on the structural volume, in patients with FCD compared to healthy controls. These findings suggest that focal lesions with FCD could affect the whole-brain network and that FCD is a network disease.

1. Introduction

Focal cortical dysplasia (FCD) belongs to the spectrum of malformations of cortical development, characterized by deranged neurons in the white matter, dyslamination, and abnormal balloon cells, first described by Taylor et al. in 1971.[1, 2] Although the pathomechanism underlying FCD has not been defined, environmental factors, such as perinatal injury or viral infections, and genetic factors are believed to disrupt formation of cortex in utero, which results in FCD.[1] Multiple studies support the hypothesis that post-migrational insult to the developing cerebral cortex results in FCD type I.[1] The histopathological features of FCD type II and its association with mutations in genes of the mammalian...
target of rapamycin (mTOR) pathway suggest that circumscribed, early abnormality in cell proliferation is the underlying pathomechanism.\[1, 3\]

FCD is one of the most common major congenital malformations in patients with epilepsy, with a prevalence of 48%.\[4\] In addition, it is one of the most common causes of drug-resistant focal epilepsy.\[5\] Although 25–33% of patients with FCD respond well to anti-seizure medications (ASMs), treatment is predominantly surgical and depends on the identification of structural and functional lesions.\[6\] The complicated interaction between neurons, and imbalance in inhibitory and excitatory neurotransmitters are known mechanisms of epileptogenesis in FCD; with overexpression of AMPA and NMDA receptor subunits and loss of GABAergic neurons.\[7, 8\]

Many studies have recently suggested that focal epilepsy is not a limited to a specific lesion, but results in alterations of the whole-brain network, due to the characteristic feature of the brain as a complex and interconnected system.\[9, 10\] However, little is known about the structural connectivity or network in patients with FCD. Graph theory is a branch of mathematics that represents a network as elements and their pairwise interconnections, also called nodes and edges.\[11\] Graph theory can summarize a complex network in the simplest form, as a connection matrix. This can offer important new insights into the structure of the networked brain systems.\[11\] Structural connectivity can be constructed by using diffusion tensor imaging (DTI), in which the fiber count obtained by accessing fibers connecting each possible pair of region of interests (ROIs) can be presented as a weighted matrix, the structural connectome.\[11, 12\] Structural connectivity is highly predictive and places constraints on the functional interactions across the brain network.\[13\] The study of structural connectivity is complemented by assessment of structural co-variance network, based on the regional structural volume or thickness. Structural co-variance network analysis can detect manifestation of persistent functional-trophic crosstalk, maturational changes, and common developmental and pathological influences.\[10\]

In this study, we investigated the alterations in structural connectivity based on DTI and structural co-variance network based on the structural volume, using graph theory, in patients with FCD, compared to healthy controls. We hypothesized that focal lesions with FCD could affect and cause many changes in the whole-brain network.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Board of our center. Thirty-seven patients with FCD were retrospectively recruited at an epilepsy center in a tertiary hospital between March 2010 and December 2020. All patients presented with seizures and were diagnosed with epilepsy. The clinical diagnosis of FCD was based on the concordance between seizure semiology, electroencephalography (EEG), brain magnetic resonance imaging (MRI) findings, recurrent stereotyped seizures, and focal interictal or ictal EEG epileptiform discharges that coincided with an FCD-concordant lesion on MRI. The
relevant brain MRI features included abnormal gyral pattern, increased cortical thickness, transmantle sign, and blurring of the gray matter-white matter interface (Fig. 1).[5, 14, 15] None of the patients had any other structural lesions on brain MRI, except FCD. We investigated the clinical characteristics of patients with FCD at the time of MRI, such as age, sex, age at seizure onset, duration of epilepsy, and ASM load (calculated by the defined daily dose of the World Health Organization (WHO).[16]

In addition, we enrolled 35 age- and sex-matched healthy controls, who had no history of medical, neurological, or psychiatric problems. The subjects in the control group showed normal brain MRI findings.

2.2. MRI scans

All subjects, patients with FCD as well as healthy controls, underwent brain MRI with the same scanner and protocols. MRI scans were performed using a 3.0T MRI scanner (AchievaTx, Phillips Healthcare, Best, The Netherlands) equipped with a 32-channel head coil. All subjects underwent brain MRI, as follows: 3-dimensional (3D) fluid-attenuated inversion recovery (FLAIR), coronal T2-weighted imaging, 3D T1-weighted imaging, and DTI. 3D T1-weighted images were obtained using a turbo-field echo sequence (TI = 1300 ms, repetition time/echo time [TR/TE] = 8.6/3.96 ms, flip angle = 8°, and 1 mm³ isotropic voxel size). DTI was performed using spin-echo single-shot echo-planar pulse sequences in 32 different diffusion directions (TR/TE = 8620/85 ms, fractional anisotropy = 90°, slice thickness = 2.25 mm, acquisition matrix = 120 × 120, field of view = 240 × 240 mm², and b-value = 1,000 s/mm²).

2.3. Structural connectivity and structural co-variance network analysis using graph theory

We analyzed the structural connectivity with DTI in patients with FCD and healthy controls using a DSI studio program (Fig. 2A). The analysis method has been described in detail in previous studies.[17, 18] Briefly, we opened the source images and reconstructed them. We subsequently tracked the fibers and created a connectivity matrix. Finally, we extracted the network measures from the matrix, such as the mean clustering coefficient, characteristic path length, global efficiency, local efficiency, small-worldness index, transitivity, radius of graph, diameter of graph, and assortative coefficient, using graph theory.[11, 19]

We calculated the structural co-variance network based on structural volume with 3D T1-weighted imaging using FreeSurfer and BRAPH programs (Fig. 2B).[19] The analysis method has been described in detail in our earlier studies.[20, 21] Briefly, we obtained the structural volume of 81 ROIs using a FreeSurfer cortical reconstruction process. We used the order of “recon-all”. We then created an undirectional weighted connectivity matrix, in which the node was defined as the volume of the ROIs, and the edge was defined as the partial correlation among the volume of ROIs corrected for age and sex. Finally, we extracted the network measures from the matrix using graph theory.

2.4. Statistical analysis
We tested the statistical significance of the differences in structural connectivity between patients with FCD and healthy controls using independent Student’s t-test (with a MedCalc program, version 19.6.4). Furthermore, we tested the statistical significance of the differences in structural co-variance network using a nonparametric permutation test (with a BRAPH program) between the two groups[22] because we could obtain the network measures at the group level. Statistical significance was set at p < 0.05.

Categorical variables are presented as number and percentile, and continuous variables as mean value and standard deviation (with normal distribution) or median value with interquartile range (without normal distribution).

3. Results

3.1. Clinical characteristics

The mean age of patients with FCD was 28 years, and approximately half of them were male (54%). The most common FCD location was the frontal lobe. Table 1 shows the clinical characteristics of the patients with FCD and healthy controls. Age and sex were not significantly different between patients with FCD and healthy controls.

Table 1

|                                    | Patients with focal cortical dysplasia (N = 37) | Healthy controls (N = 35) | p-value |
|------------------------------------|-----------------------------|-----------------------------|---------|
| Age, years (± SD)                  | 28.0 (± 9.8)                | 25.5 (± 2.6)                | 0.137   |
| Male, n (%)                        | 20 (54.0)                   | 21 (60.0)                   | 0.613   |
| Age of seizure onset, years        | 14 (11–23)                  |                             |         |
| (interquartile range)              |                             |                             |         |
| Duration of epilepsy, months       | 78 (12–180)                 |                             |         |
| (interquartile range)              |                             |                             |         |
| ASM load (interquartile range)     | 1.4 (0.6–2.5)               |                             |         |
| FCD Location                       |                             |                             |         |
| Frontal lobe, n (%)                | 16 (43.2)                   |                             |         |
| Temporal lobe, n (%)               | 15 (40.5)                   |                             |         |
| Parietal lobe, n (%)               | 3 (8.1)                     |                             |         |
| Occipital lobe, n (%)              | 3 (8.1)                     |                             |         |

SD, standard deviation; ASM, anti-seizure medication; FCD, focal cortical dysplasia.

3.2. Structural connectivity
Table 2 shows the differences in the structural connectivity between patients with FCD and healthy controls. There was a significant difference in structural connectivity between them. The local efficiency in patients with FCD was significantly lower than the healthy controls (2.390 vs. 2.578, \( p = 0.031 \)). However, other network measures of structural connectivity, such as mean clustering coefficient, characteristic path length, global efficiency, small-worldness index, transitivity, radius of graph, diameter of graph, and assortative coefficient, were not different between patients with FCD and healthy controls.

Table 2
Differences in the structural connectivity using diffusion tensor imaging between patients with focal cortical dysplasia and healthy controls

| Network measures                  | Patients with focal cortical dysplasia | Healthy controls | Difference | \( p \)-value |
|-----------------------------------|----------------------------------------|------------------|------------|--------------|
| Mean clustering coefficient       | 0.218 ± 0.077                          | 0.221 ± 0.098    | 0.003      | 0.872        |
| Characteristic path length        | 4.419 ± 0.485                          | 4.380 ± 0.416    | -0.039     | 0.719        |
| Global efficiency                 | 1.524 ± 0.178                          | 1.573 ± 0.154    | 0.049      | 0.221        |
| Local efficiency                  | 2.390 ± 0.348                          | 2.578 ± 0.376    | 0.187      | 0.031        |
| Small-worldness index             | 0.237 ± 0.098                          | 0.248 ± 0.119    | 0.010      | 0.685        |
| Transitivity                      | 0.259 ± 0.093                          | 0.251 ± 0.109    | -0.008     | 0.742        |
| Radius of graph                   | 1.712 ± 0.318                          | 1.656 ± 0.236    | -0.056     | 0.399        |
| Diameter of graph                 | 3.227 ± 0.605                          | 3.097 ± 0.407    | -0.130     | 0.293        |
| Assortative coefficient           | 0.167 ± 0.100                          | 0.139 ± 0.122    | -0.027     | 0.299        |

SD: standard deviation

3.3. Structural co-variance network

Table 3 presents the differences in the structural co-variance network based on the volume between patients with FCD and healthy controls. There were significant differences in the structural co-variance network between them. The mean clustering coefficient, global efficiency, local efficiency, and transitivity in patients with FCD were significantly lower than in the healthy controls (0.527 vs. 0.635, \( p = 0.036 \); 0.545 vs. 0.648, \( p = 0.026 \); 2.699 vs. 3.801, \( p = 0.019 \); 0.791 vs. 0.954, \( p = 0.026 \), respectively). However, the other network measures of structural co-variance network, such as characteristic path length, small-worldness index, radius of graph, diameter of graph, and assortative coefficient, did not differ between patients with FCD and healthy controls.
Table 3
Differences in the structural co-variance network based on the volume between patients with focal cortical dysplasia and healthy controls

| Network measures                  | Patients with focal cortical dysplasia | Healthy controls | Difference | CI lower | CI upper | p-value |
|----------------------------------|----------------------------------------|------------------|------------|----------|----------|---------|
| Mean clustering coefficient      | 0.527                                  | 0.635            | 0.108      | -0.105   | 0.100    | 0.036   |
| Characteristic path length       | 1.968                                  | 1.651            | -0.317     | -0.323   | 0.286    | 0.051   |
| Global efficiency                | 0.545                                  | 0.648            | 0.102      | -0.083   | 0.092    | 0.026   |
| Local efficiency                 | 2.699                                  | 3.801            | 1.102      | -0.893   | 0.894    | 0.019   |
| small-worldness index            | 0.984                                  | 0.984            | -0.001     | -0.019   | 0.018    | 0.481   |
| Transitivity                     | 0.791                                  | 0.954            | 0.163      | -0.144   | 0.135    | 0.026   |
| Radius of graph                  | 2.539                                  | 2.632            | 0.093      | -1.034   | 1.117    | 0.479   |
| Diameter of graph                | 4.059                                  | 4.386            | 0.327      | -1.779   | 1.804    | 0.367   |
| Assortative coefficient          | -0.013                                 | -0.014           | -0.001     | -0.012   | 0.010    | 0.424   |

CI: 95% confidence interval of difference between the groups

4. Discussion

In this study, we found that there were significant alterations in structural connectivity and structural co-variance network in patients with FCD compared to healthy controls. These findings suggest that focal lesions in FCD can produce alterations in the whole-brain network.

The present findings are in agreement with previous studies that have investigated the brain network in FCD using various MRI modalities. Liu et al. investigated the functional connectivity using resting state functional MRI and graph theory, and they found disrupted interactions and dysconnectivity in a large-scale neural network in patients with FCD, compared to healthy controls.[23] Another study analyzed the functional connectivity using magnetoencephalography recordings and graph theory, and successfully demonstrated that the brain had increased functional connectivity in the beta and gamma frequency bands in resting state in patients with FCD compared to healthy controls.[24] In addition, a graph theoretical analysis of structural co-variance network using the cortical thickness of ROIs has indicated a consistent rearrangement characterized by inefficient global and excessive local connectivity in patients with FCD.[25] However, our study is the first to investigate the alterations in structural connectivity based
on DTI and structural co-variance network based on volume in patients with FCD and compare it to healthy controls, and successfully demonstrate significant changes in the whole-brain network.

In the structural connectivity analysis, we found that the local efficiency in patients with FCD was lower than in healthy controls. Structural co-variance network analysis revealed that the mean clustering coefficient, global efficiency, local efficiency, and transitivity were lower in patients with FCD than in healthy controls. The local efficiency was calculated as the inverse of the average shortest path connecting the given node with all other nodes, which provides a measure of the efficiency of a given node in communicating with the rest of the brain.[26] The mean clustering coefficient was calculated as the mean local clustering coefficient, averaged over all nodes in the network, which assesses the degree to which the regions cluster, providing a measure of local connectivity.[26] The global efficiency was calculated as the average of the inverse of the shortest path length in a network, which estimates the ability of the network for parallel information transfer.[26] Decreased local efficiency and mean clustering coefficient reflects a decrease of segregation in a network, and decreased global efficiency represents a decrease of integration in a network. Segregation is supported by densely connected network communities, whereas integration is promoted by network hubs that are rich in connections between the communities, referred to as the ‘rich club’, members of which have high graphical measures of node degree and betweenness.[27] Thus, decreased segregation and integration decreases small-worldness in a network, which plays a crucial role in complex dynamical processes such as information transmission, pattern recognition, or learning.[28] These findings suggest decreased connectivity of the whole-brain network in patients with FCD.

Both segregation and integration of a brain network are critical for cognitive function.[27, 29] Thus, their alteration can be related to cognitive dysfunction, behavioral issues, or developmental delay, which are the clinical presentations of patients with FCD.[14, 30] Furthermore, previous studies have indicated a high prevalence of autism spectrum disorders in patients with FCD.[31] In connectivity studies, it has been demonstrated that autism spectrum disorders are accompanied by abnormal functional and structural features in specific brain regions of the default mode network.[32] Thus, we can postulate that all these disorders lie in a continuum of network diseases.

Although we successfully demonstrate alterations in structural connectivity and structural co-variance network in patients with FCD, there were several limitations to this study. First, we included patients with FCD with a clinical presentation of seizures. Thus, we cannot exclude the possibility that alterations in structural connectivity and structural co-variance network in patients with FCD might have been caused by symptoms of seizures. However, it was difficult to enroll patients with FCD who had no neurological or psychiatric problems. Second, we only looked at the structural connectivity and structural co-variance network at the whole-brain network level, because the specific location of FCD was variable. Thus, we could not investigate whether decreased connectivity was related to the location of FCD lesion. Lastly, the diagnosis of most of the patients was not pathologically confirmed, but were diagnosed with FCD based on clinical and MRI findings. However, we exclusively enrolled patients with typical MRI findings,
compatible with FCD. Further studies with pathologically confirmed patients in a large sample size may be needed to confirm our findings.

5. Conclusion

We demonstrate that there are significant alterations in structural connectivity based on DTI and structural co-variance network based on volume in patients with FCD compared to healthy controls. These findings suggest that focal lesions with FCD could affect the whole-brain network, and additionally, that FCD is a network disease.

Declarations

Ethics approval and Consent

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Haeundae Paik hospital approved this study.

Consent for publication

None

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing of interest

Neither of the authors has any conflict of interest to disclose.

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Authors’ contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Dong Ah Lee, Ho-Joon Lee, Hyung Chan Kim and Kang Min Park. The first draft of the manuscript was written by Kang Min Park and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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**Figures**

**Figure 1**

An example of typical brain MRI findings compatible with a focal cortical dysplasia Fluid-attenuated inversion recovery (FLAIR) MRI of a patient showing focal cortical thickening with blurring of gray-white matter differentiation in the left frontal lobe (red arrow) (A). FLAIR MRI of another patient reveals focal increased signal intensity (blue arrow) with transmantle sign (red arrow) in the right frontal lobe (B).
Figure 2

The process of graph theoretical analysis of the structural connectivity based on diffusion tensor imaging (A) and the structural co-variance network based on the structural volume with T1-weighted imaging (B)