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Abstract

The purpose of this study was to reveal differences in connectivity from spike-free waking electroencephalogram (EEG) of benign epilepsy with centrotemporal spikes (BECTS) patients, which is considered normal in visual analysis. Thirty BECTS patients and 30 disease-free, age- and gender-matched controls were included. Only patients with serial EEGs and sufficient follow-up period to confirm the benign EEG and seizure outcomes were included. Only the EEGs to confirm quiet wakefulness and free of artifacts were included for analysis. Eight-second EEG epochs without artifacts were sampled and bandpass filtered to delta, theta, lower alpha, upper alpha and beta band for network matrix construction. Weighted phase lag index (wPLI) was used as an association measure for EEG signals. Band specific connectivity, which is a matrix of wPLI values of all edges were compared for analysis of connectivity itself. Network topology measures for comparison were node strength, characteristic path length (CPL), and mean clustering coefficient (CC). Spike-free waking EEGs showed a significant difference in connectivity and network topology compared to otherwise same normal waking EEGs of disease-free controls. For delta and theta band connectivity, a mixture of increased and decreased wPLI values was noted. However, for lower alpha and beta bands, edges that showed significant difference had consistently lower wPLI values compared to the controls. Node strength was significantly lower in patients for specific nodes in alpha and beta band connectivity. The mean global wPLI was significantly smaller and the CPL was significantly longer for BECTS patients

in the lower alpha band connectivity. Overall, the resting state functional connectivity of BECTS showed a decrease integration and low efficiency compared to disease-free controls. There was a significant difference in connectivity that was not identified from visual analysis, and these connectivity aberrations can further be studied and used as a candidate for disease activity marker.

Key words: Functional connectivity, Network, Resting stage, Benign Epilepsy with Centrotemporal Spikes, Electroencephalography

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List of Abbreviations and Symbols

EEG - Electroencephalogram, electroencephalography

BECTS - Benign Epilepsy with Centrotemporal Spikes

wPLI - Weighted Phase Lag Index

CPL - Characteristic Path Length

CC - Clustering Coefficient

IED - Interictal Epileptiform Discharge

MEG - Magnetoencephalography

PSD - Power Spectral Density

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Introduction

Epilepsy is a disorder of recurrent spontaneous seizures, and the hallmarks of electrophysiological abnormalities are cerebral hyperexcitability and hypersynchrony. Interictal epileptiform discharges (IEDs) in routine electroencephalogram (EEG) represent this hallmark. Interictal epileptiform discharges play a critical role in the diagnosis of specific epilepsy. Its presence or absence during serial EEGs is an essential laboratory marker for decision making in treatment withdrawal.[1] So the primary focus in analyzing routine EEG of an epilepsy patient was detecting IEDs and background abnormalities. Although there have been well-designed studies on signal analysis using paper EEGs, the number of EEG studies using signal processing and digital analysis is rapidly increasing. Digitalization of EEGs and increasing computing power has enabled EEG connectivity studies in the field of basic science and electronic engineering.[2]

Network science has developed in the field of social science based on the phase mathematics through simplifying the network structure to understand a complex system.[3,4] Recent advances in diagnostic technology, such as digital EEG, magnetoencephalography (MEG), and brain magnetic resonance imaging (MRI) have provided big data regarding brain anatomy and function. Moreover, tremendously increased computing power by advances in computer engineering has enabled scientists to perform very complex calculations handling these huge-size datasets in medicine.[3] Using graph theory to understand the human

brain has produced a field of connectivity analysis of the brain.[5-8] The number of connectivity analysis in epilepsy has also increased, and the results of this analysis provided novel insights to the normal brain network,[9] epilepsy,[10-13] and medication-refractory epilepsy.[14]

Benign epilepsy with centrotemporal spikes (BECTS) is a very typical age-related epilepsy syndrome with excellent seizure and EEG outcomes.[15] Its benign course has been explicitly recognized and the new terminology of 'SLECT' (self-limited epilepsy with centrotemporal spikes) has newly appeared.[16] A Majority of patients reveal normal waking EEGs unless there is a centrotemporal spike on waking state. So there is no abnormality to call in their waking EEG on a routine visual EEG analysis. However, it is well known that centrotemporal spikes persist longer than their Rolandic seizures and IEDs usually last until adolescence.[17] For cases where anticonvulsants are initiated on BECTS patients, waiting for IEDs to disappear could take longer due to its natural course. We need additional information regarding connectivity in otherwise normal waking background EEG in BECTS.

Stam et al. introduced the phase lag index (PLI) to quantify a statistical sense in the phase synchronization of two signals.[18] The PLI performed better than previous methodologies such as imaginary part of coherence in detecting true changes in phase-synchronization. However, PLI is sensitive to noise and volume conduction. Furthermore, Vinck et al. introduced a new member to the family of phase-synchronization, the weighted phase lag index (wPLI), to reduce the influence of common noise sources and to reduce the influence of changes in

the phase of the coherency.[19] Among many association measures used in connectivity analysis of EEG and MEG signals, wPLI is a good candidate to reveal synchronization.

The purpose of this study is to reveal the difference of resting state connectivity from visually normal EEG of BECTS patients at the time of diagnosis and before treatment. Resting state connectivity and network topology measures will be compared to normal controls.

Materials and Methods

1. Patients and Controls

Patients, who were diagnosed with BECTS from Seoul National University Bundang Hospital (SNUBH) between June 2003 and February 2016, were identified using the clinical data warehouse (CDW) program. The diagnosis of BECTS was made at the clinic and was reassessed for this research according to ILAE criteria.[20] Inclusion and exclusion criteria were applied to include only the patients showing typical benign and self-limiting course of BECTS.[16,21] Patients with short follow-up duration or lost to follow-up, and the evidence of atypical progression[22,23] were excluded. Only patients with serial routine (sleep with or without waking) EEGs from onset to remission and sufficient medical records were included to confirm the typical benign nature of seizures and EEG outcomes. Patients with only sleep EEG recordings at the diagnosis were excluded. Patients with EEG recordings with an excess amount of artifacts that hinder connectivity analysis were also excluded. Gender and age-matched control EEGs were obtained from patients who underwent EEG examination for the evaluation of syncope or seizure-like events. Only patients with normal neurological condition and free of a central nervous system (CNS) disorder such as a headache, developmental delay, and epilepsy were included as the control group.

2. EEG Examination

EEG was performed using a 32-channel digital EEG (Grass Telefactor Inc.), and electrodes were placed according to the international 10–20 system. The sampling rate was 200 Hz. If needed, patients were sedated with chloral hydrate (50 mg/kg; maximum, 1 g). Only the EEGs with sufficient length were used for analysis. Medication naïve EEGs at the diagnosis of BECTS were analyzed to exclude the medication effect on functional connectivity.

3. EEG Preprocessing and Epoch Selection

Since the purpose of this study was to find the difference in functional connectivity from visually interpreted normal waking EEG of patients, epochs for analysis were selected from artifact free parts of waking EEGs. Quiet wakefulness was evaluated by the quality of posterior rhythm, overall EEG background, and artifacts. All the EEGs were reformatted to average reference montage to minimize confounding effects of specific brain activities and to achieve reference cancellation effects.[24] Raw EEG files were transformed to European Data Format (EDF) files using band pass (0.5 – 70 Hz) and 60 Hz-notch filter. Eight-second epoch selection and data transformation to ASCII files were performed using BESA (Brain Electrical Source Analysis) Research 6.0 software (BESA GmbH, Grafelfing Germany). Epoch length was set to 1600 data points (8 seconds, 200 Hz) based on the reference paper and subsequent research that assessed minimum length for wPLI analysis.[25]

4. Band Separation

For the off-line analysis on MATLAB platform, the recordings were converted to ASCII files with 200 Hz of the sampling rate. Epochs were band-pass filtered for the commonly used frequency bands: delta (0.5 - 4 Hz), theta (4 - 8 Hz), lower alpha (8 - 10 Hz), upper alpha (10 - 13) and beta (13 - 30 Hz), and all further analyses were performed for these bands separately.

5. Measures of Functional Connectivity via Weighted Phase Lag Index

The weighted PLI (wPLI)[19] was used as measures of functional connectivity, which is an extension of the PLI. The PLI is an index of the asymmetry in the distribution of phase differences calculated from the instantaneous phases of two time-series. The instantaneous phases were determined by the Hilbert transformation, applying a Hanning window on the concurrent fast Fourier transform. By letting Δϕ is phase differences, PLI is defined as:

$$\mathrm{PLI} \equiv |E\{\mathrm{sgn}(\Delta\phi)\}|,$$

where E is a function that computes a mean value, and sgn is a function that extracts the sign of a real number.

wPLI can be derived by weighting each phase difference according to the magnitude of the lag as below:

$$\mathrm{WPLI} \equiv \frac{|E\{\Delta\phi\}|}{E\{\Delta\phi\}} = \frac{|E\{|\Delta\phi|\mathrm{sgn}(\Delta\phi)\}|}{E\{|\Delta\phi|\}}.$$

This weighting prevents the risk of a true signal being easily affected by small noise perturbations. Uncorrelated noise sources increase the signal power, but the wPLI is calculated based only on the imaginary component, thus robustness to noise can be obtained.

6. Network (Connectivity) Construction

We constructed a weighted, undirected network by defining the 19 EEG electrodes ("Fp1", "F3", "C3", "P3", "O1", "Fp2", "F4", "C4", "P4", "O2", "F7", "T3", "T5", "F8", "T4", "T6", "Fz", "Cz", and "Pz") as the node of the network and the wPLI value between the electrodes as the edge. First, each single connectivity network is calculated for every epoch. To improve reliability, we computed representative connectivity network by averaging the computed single connectivity networks.[26]

7. Network Metrics

For network analysis, we calculated several metrics for the representative connectivity network per each subject. Global network metrics and Local network metrics were calculated using the brain connectivity tool (BCT).[26] The global network metric has one representative value per network. The mean clustering coefficient (CC) and the characteristic path length (CPL) were calculated from the network as the global metrics. First, the clustering coefficient (CC) is a measure of the degree to which nodes in a graph tend to

cluster together. The mean CC is calculated by averaging the CC values from each node. The higher mean CC value means that the network tends to create tightly knit groups characterized by a relatively high density of ties. Second, the CPL is calculated by averaging the shortest path length of every node pairs. The higher CPL implies network is almost in liner chain and the lower CPL implies the network is in the compact form. The local network metric has one value for each channel, allowing more detailed analysis in the connectivity network. The node strength (NS) was calculated as the local network metric. NS is the sum of weights of edges connected to the given node. The high NS value in the brain connectivity networks implies that the given node plays a major role by synchronizing other nodes.

8. Comparison between Patients and Controls

Overall frequency and amplitude distribution of the two groups were analyzed using power spectral density (PSD) plots. PSD plot of each epoch was generated and averaged for each subject. PSD plots of each subject were then averaged for group analysis. Resting stage EEG functional connectivity was compared between the two groups by comparing wPLI values of all edges. Mean global wPLI value which is an average of all 171 wPLI values of each edge was also compared. Network topology measures were compared to identify the differences in global and local network characteristics. Global measures were mean characteristic path length and mean clustering coefficient. Node strength of each node (electrode) was compared as local connectivity measure.

9. Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 22.0). Normality of wPLI values, CPL, CC, and global wPLI were checked using the Kolmogorov-Smirnov test. Since all the variables showed normal distribution, a paired t-test was performed to compare the mean of both groups. Analyses were performed with a two-sided alpha level of 0.05. P-values were corrected for 5 different frequency bands with the Bonferroni method. For the comparison of connectivity itself and node strengths, nominal p-value was used since this is the first study to show wPLI-based resting state EEG functional connectivity in BECTS. Significant channel pair identification within lower alpha band connectivity were performed using false discovery rate (FDR) correction and network based statistics (NBS).[27] When applying NBS one-sided t-test was used due to its technical limitation.

10. Ethical Issues

This study protocol was reviewed and approved by the institutional review board (IRB) of the Seoul National University Bundang Hospital (IRB No. B-1705-399/102). The IRB approved a waiver of informed consent, which was a retrospective review of medical records and EEG data.

Results

Among 132 patients that were diagnosed with BECTS in SNUBH, 30 patients (17 boys and 13 girls) with sufficient information and follow-up duration were included for analysis. Reasons for exclusion were: lost to follow-up (12 patients), short follow-up duration (63 patients), and raw EEG data loss due to data storage problems (12 patients), and poor EEG quality for analysis (15 patients). Mean age at onset was 8.5 years (range, 5.5 - 11.0 years) and mean age at EEG was 8.7 years (range, 5.5 - 12.1 years). Mean age at EEG of controls was 8.8 years (range, 5.8 - 12.4 years). Mean follow-up duration of the patients was 5.0 years after onset (range, 3.5 - 9.0 years). The mean number of epochs analyzed was 28.3 (range, 45 - 67) and 43.5 (range, 12 - 154) for patients and control, respectively (Table 1).

PSD graphs of absolute and relative power were compared between patient and control groups, and they were similar between the two groups (Figure 1).

Connectivity matrices that were constructed using wPLI between the two groups were compared for specific frequency bands. For delta and theta band frequency connectivity, wPLI values were mainly decreased for certain edges and increased in fewer accounts for the patient group. However, for the lower alpha and beta band connectivity, all the edges with statistically significant difference showed decreased wPLI values in patients. The wPLI values for 2 edges were significantly higher in the upper alpha band (Figure 2). This feature is easily seen in the graphical presentation showing only edges with differences showing statistical significance (Figure 3).

Table 1. Demographics, onset age, age at EEG, and number of epochs of 30 patients and their age and gender matched disease-free controls.

Case Number	Gender	Patient				Control	
		Onset Age	Age at EEG	Follow-up duration	Epoch #	Age at EEG	Epoch #
1	F	6.6	6.6	7.3	24	6.7	46
2	M	10.2	10.2	5.8	20	10.2	78
3	M	5.6	5.9	4.1	30	6.9	42
4	M	8.5	8.7	3.9	21	8.3	44
5	M	5.8	5.8	4.8	25	6.4	43
6	F	11.4	12.0	4.6	53	12.4	25
7	M	10.5	10.7	3.7	38	11.1	73
8	F	8.5	8.5	6.0	22	7.8	67
9	M	8.8	9.0	4.9	22	8.7	46
10	F	6.8	6.9	3.3	33	7.2	19
11	F	7.1	7.6	3.9	26	7.6	19
12	F	7.7	7.9	5.4	46	7.9	25
13	F	10.6	12.1	3.9	28	12.1	45
14	M	6.3	6.8	9.5	18	6.2	31
15	F	6.2	6.6	4.0	21	6.3	20
16	M	8.6	9.3	6.0	24	9.7	47
17	F	9.4	9.4	3.5	27	9.0	47
18	F	9.6	9.6	4.8	41	9.5	19
19	M	10.7	10.9	5.5	25	11.2	52
20	M	10.9	10.9	4.9	32	10.6	43
21	M	7.6	7.7	4.8	29	7.9	35
22	M	11.0	11.7	5.2	12	11.6	154
23	M	7.5	8.1	3.7	17	8.2	40
24	M	9.0	9.0	5.6	35	8.8	64
25	F	5.5	5.5	5.1	32	5.8	21
26	M	6.2	6.3	7.0	17	7.2	12
27	M	10.5	10.6	6.3	67	11.3	51
28	F	10.2	10.2	5.0	19	10.3	37
29	M	8.9	9.3	4.3	20	9.1	44
30	F	7.7	7.9	3.5	26	7.8	16

Figure 1. Power spectral density graphs of overall EEG activity.

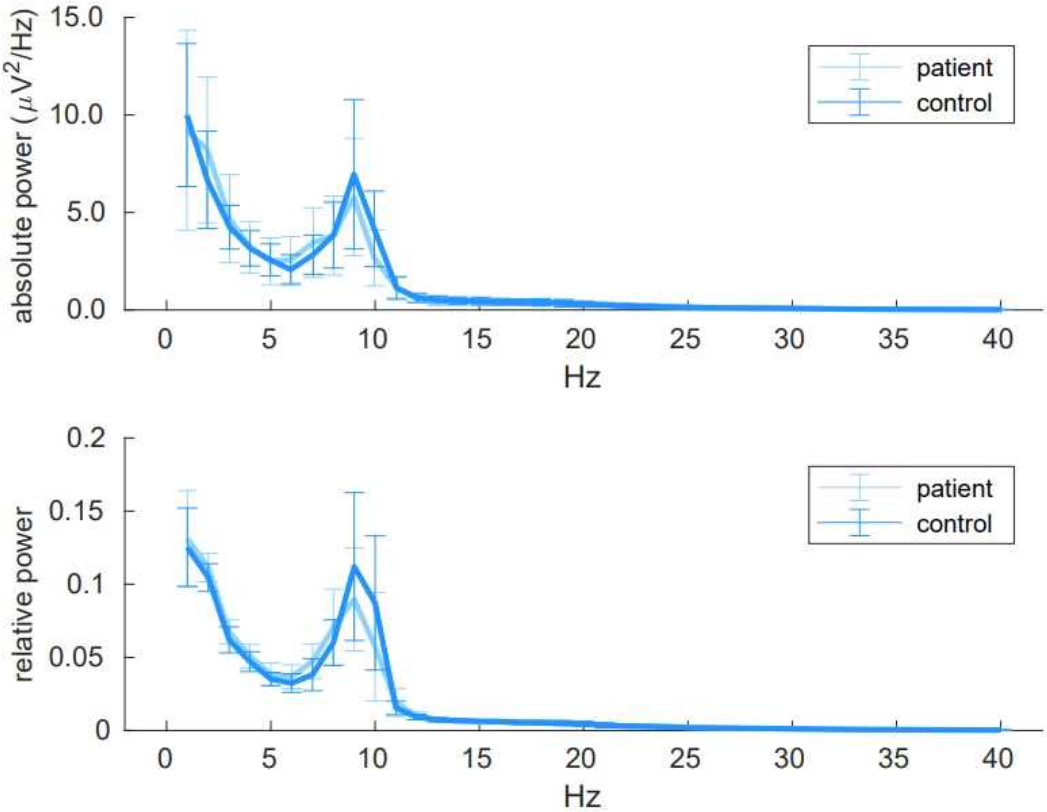

Figure 2. Heatmap of adjacency matrix plot of band specific resting state functional connectivity (A) and difference of edges (B).

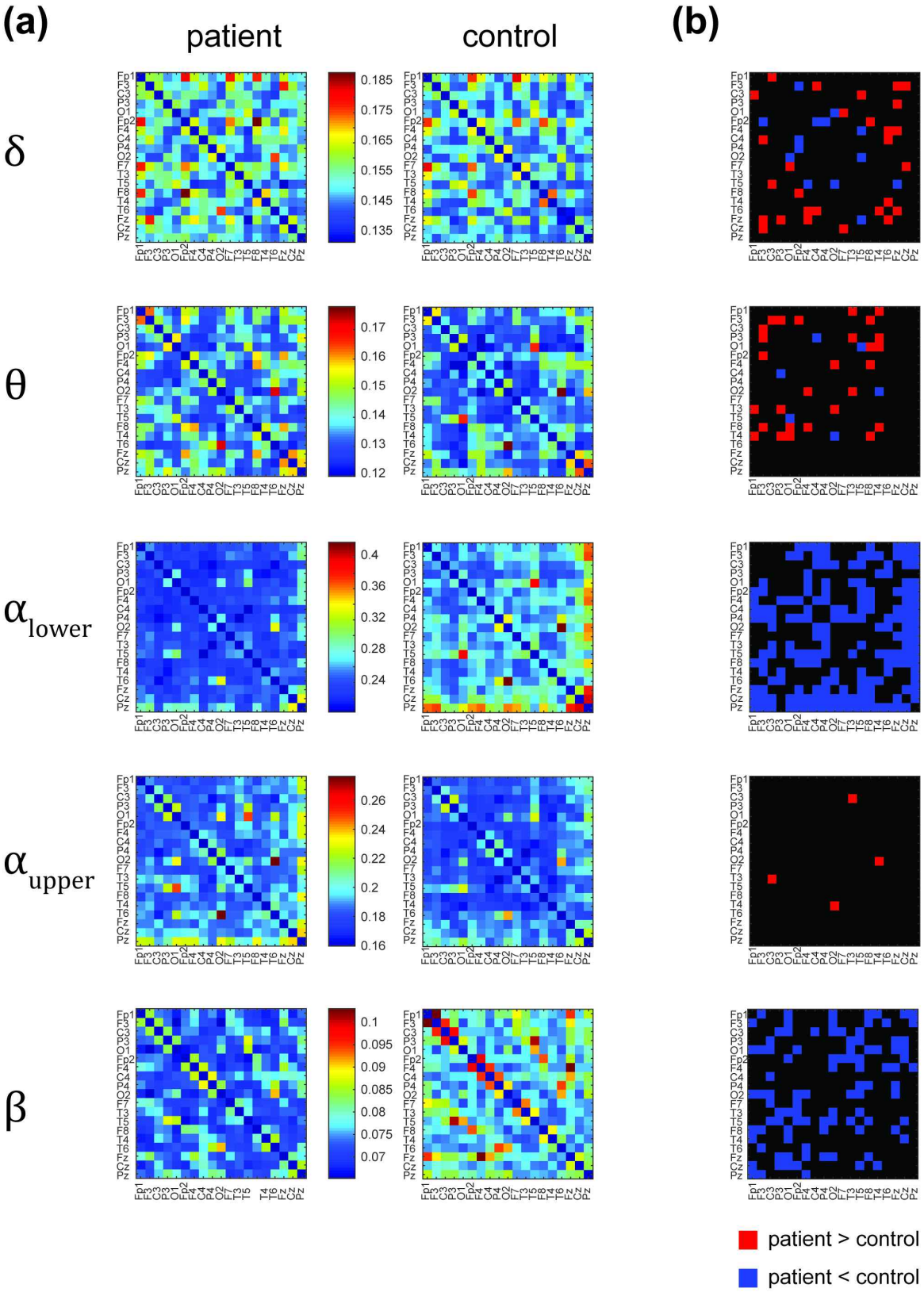

Figure 6. Global network topology measures of band specific resting state functional connectivity.

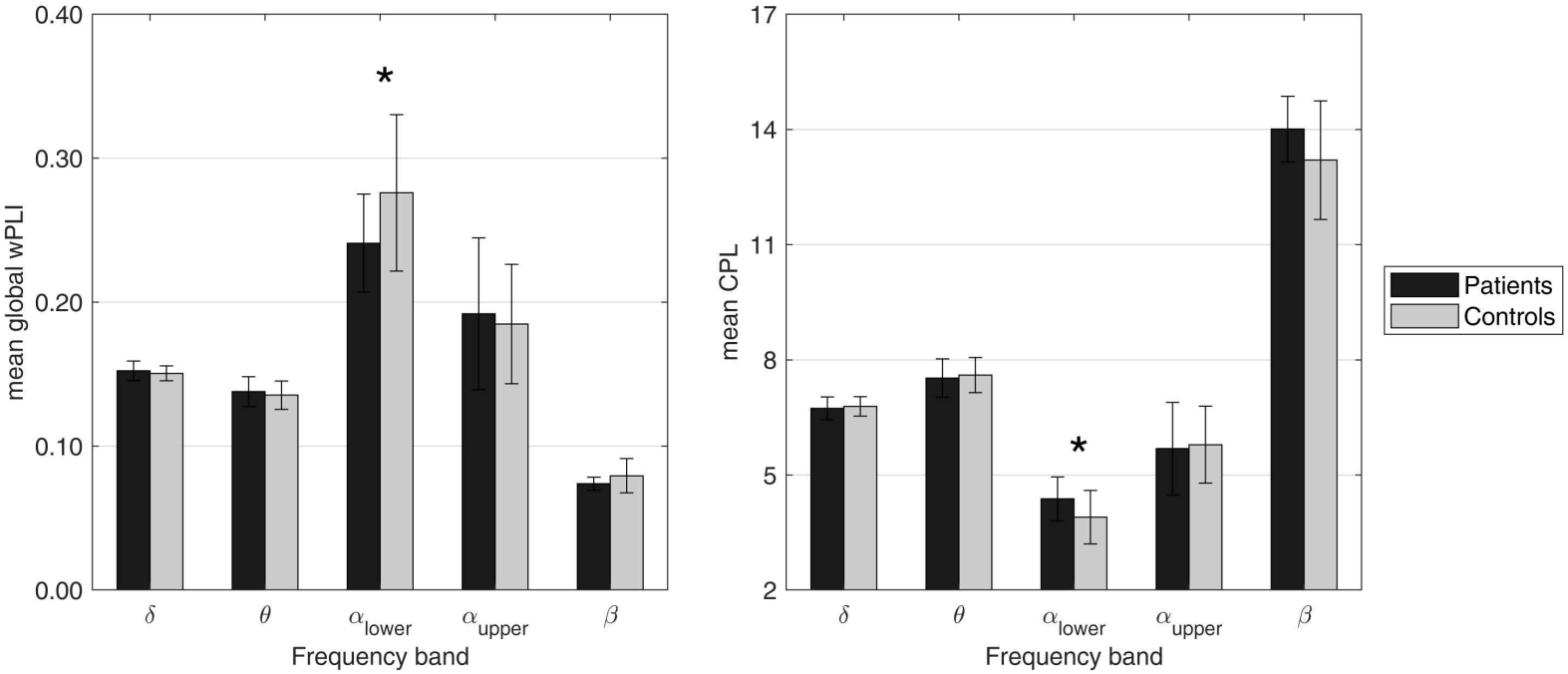

Table 2. Global network topology measures of band specific connectivity.

	mean global wPLI		mean CPL		mean CC	
	Patients	Controls	Patients	Controls	Patients	Controls
δ	0.152 ± 0.007	0.151 ± 0.005	6.738 ± 0.297	6.785 ± 0.254	0.153 ± 0.007	0.151 ± 0.005
θ	0.138 ± 0.010	0.136 ± 0.010	7.527 ± 0.502	7.601 ± 0.457	0.139 ± 0.011	0.136 ± 0.011
α_{Lower}	**0.241 ± 0.034**	**0.276 ± 0.054**	**4.379 ± 0.574**	**3.904 ± 0.695**	0.247 ± 0.040	0.282 ± 0.059
α_{Upper}	0.192 ± 0.053	0.185 ± 0.041	5.687 ± 1.208	5.791 ± 1.003	0.195 ± 0.056	0.188 ± 0.046
β	0.074 ± 0.005	0.080 ± 0.012	14.011 ± 0.853	13.203 ± 1.545	0.074 ± 0.005	0.080 ± 0.013

Values represent means with ± standard deviations. wPLI = weighted phase lag index, CPL = characteristic path length, CC: clustering coefficient, BECTS = benign epilepsy with centrotemporal spikes. Significant differences between patients and controls are shown in bold (paired t-test, p 0.05, Bonferroni corrected).

Discussion

1. Difference of Resting-state Functional Connectivity Identified from Normal Waking EEG

The purpose of this study was to reveal the difference between visually interpreted normal waking EEG of BECTS patients and disease-free healthy controls. By performing connectivity analysis using resting stage waking EEG, several differences were observed. Most of the findings were observed in the lower alpha band connectivity. Connectivity itself, represented as a matrix of wPLI values between the nodes was decreased compared to the controls in certain edges. Node strength was also decreased in patient groups. Regarding the global network topology, resting stage connectivity of the BECTS patients showed less efficient connectivity compared to the controls. There were recognizable differences in the connectivity in waking EEG of BECTS patients even though they are considered normal in the routine visual analysis. There are reports of functional and structural brain network aberration in both interictal and ictal EEGs.[28] Several studies reported a difference in otherwise normal waking EEGs from focal epilepsy onset,[29] patients and family members of idiopathic generalized epilepsies (IGE),[30] and from normal brain maturation in children.[31] In a study that enrolled adults with mesial temporal lobe epilepsy (mTLE) and frontal nocturnal epilepsy (FNE), they found global as well as regional difference in functional connectivity.[32] Several studies that enrolled BECTS showed similar results of alterations of connectivity that is not identified

by routine visual inspection.[33-35] The findings of previous studies as well as the result of this study suggest that resting state EEG connectivity analysis provide novel information otherwise not recognized in previous analysis and this additional information can be helpful in understanding the pathophysiology of epilepsy and can be useful as a possible electrophysiological marker for decision making in BECTS treatment.

2. Decreased functional connectivity in BECTS

The association measure in this study was wPLI, and it is one of the measures of phase synchronization. When connectivity itself was compared, significant differences were the decreased connectivity in specific edges as well as the decrease in node strength in BECTS patients. This finding implies that synchronization of brain electrical activity between combinations of each electrode in BECTS is reduced compared to controls. In a similar study that compared 11 patients to controls using lagged phase synchronization (LPS) as an association measure, beta band LPS values were lower, but alpha band values were higher.[34] A similar study using LORETA (Low-Resolution Electromagnetic tomography) EEG functional connectivity in BECTS, showed increased alpha band functional connectivity in 17 BECTS patients compared to 19 healthy controls.[35] Contrast to EEG studies, fMRI studies of BECTS showed consistent findings of decreased connectivity between eloquent cortices.[36,37] Moreover, interhemispheric hyposynchrony was observed in a recent fMRI study.[38] If focal epilepsy is considered, decreased EEG correlation was seen in

patients.[39] When multiple features were simultaneously applied, decreased functional connectivity was revealed in pediatric focal epilepsy.[40] However, theta band global synchronization likelihood (SL) was higher compared to non-epilepsy controls focal epilepsy at disease onset.[29] When phase locking factor (PLI) was applied to EEGs of patients with IGE, node degree was significantly higher in patients. However, a recent study revealed no difference in global PLI values between patients and controls.[41] This difference may arise from the different association measures used for different studies. Each measure can only represent specific part of information of very complex time series data. Using multiple association measures to include as much information from the EEG signal is a critical next step in EEG connectivity analysis. The clinical implication of this decreased connectivity could be either compensatory measure for abnormal hyperexcitability and hypersynchrony or the effect of epilepsy on higher cognitive function. It was not the aim of this study to confirm these implications. By revealing whether this decreased connectivity normalizes as the BECTS remits or decreased connectivity is related to cognitive dysfunction can prove the clinical significance of this finding.

3. Resting state functional connectivity of BECTS showed low global efficiency.

Characteristic path length (CPL) which is a global network topology measure of integration was longer in alpha and beta band connectivity in BECTS. Since the global efficiency is the inverse value of CPL, we can infer that alpha and beta

band resting state functional connectivity of BECTS is less integrated and less efficient compared to normal controls. Interestingly, it is a consistent finding of focal epilepsy connectivity. A recent systematic review that addressed connectivity analysis in focal epilepsy concluded the increase of CPL as a typical feature in global topology in EEG studies.[42] Increased CPL was revealed from studies in patients with focal epilepsy due to tumors,[43-45] and temporal lobe epilepsy (TLE).[46] There was also a study of focal epilepsy using fMRI that revealed increased CPL.[47] The mean CPL of lower alpha band connectivity of BECTS patients was significantly longer, and this is a consistent finding of previous studies in focal epilepsy. This finding adds BECTS as another evidence of increased CPL in focal epilepsy connectivity. Since CPL is a measure of integration, increased CPL means it requires more steps for parallel information transfer, low efficiency, and less integration. Clinical significance or consequence of decreased efficiency is still unknown. It could be related to global dysfunction due to epilepsy or a countermeasure against focal hyperexcitation and hypersynchrony. Further research regarding the functional efficiency and the function of the brain should be performed to correctly and precisely understand the significance of network topology.

4. Weighted phase lag index and the results from other studies

This is the first study that applied wPLI as an association measure for connectivity analysis. It is a phase based measure with the advantage of reduced sensitivity to volume conduction and improved detection of phase

synchronization changes.[24] It showed good agreement with MEG connectivity findings with adults in alpha bands and was suggested as a useful measure for connectivity analysis.[48] Its reproducibility and reliability were reported using high-resolution EEG studies.[49] Due to the scarcity of application of wPLI in epilepsy, it is difficult to generate the clinical significance of the findings in this study beyond the general network topology. Connectivity studies using wPLI is more popular in the field of psychiatry and anesthesiology than in epilepsy. In a study of mild cognitive impairment with type 2 diabetes, decreased PLI values, lower CC, and increased CPL was related to cognitive impairment.[50] Theta band connectivity measures were related to dyslexia in children.[51] Increased beta band wPLI connectivity was observed in patients with generalized social anxiety disorder.[52] The strength of wPLI in connectivity analysis and the findings of preexisting studies suggest the usefulness of wPLI. The previous findings are not directly related to the findings of this study and the field of epilepsy. It is helpful to utilize known findings to plan further research to related connectivity analysis findings to epilepsy pathophysiology.

5. Lower alpha band frequency for analysis

There was band specificity in the connectivity results. When connectivity itself was compared, different edges showed varying degrees of increase or decrease of wPLI values in the delta and theta band. However, in the lower alpha and beta band, the difference was consistently lower wPLI in BECTS. Likewise, the difference in network topology measures, such as mean CPL differed only in the

lower alpha band. Since we can measure up to 200 Hz activity with sampling rate 400 Hz EEG machine, a wide range of EEG activities are recorded. It is a crucial issue to select appropriate frequency bands for analysis.[24] Besides the rare condition where broad-band analysis is helpful, band specific analysis results in different findings according to the specific bands.[53-55] Most studies report connectivity changes in theta, alpha, beta bands and rarely in delta bands. The recommendation for specific band selection is using a power spectral density graph.[24] It is reasonable to select the most prominent band of activity from the EEG epochs. Power spectral density graph of patients and controls showed most prominent activity at the alpha band and the significant differences were identified from the lower alpha band connectivity. This study adds evidence in selecting the alpha and beta bands for analysis of pediatric epilepsy or pediatric EEG for connectivity analysis. It is also advisable to utilize lower alpha band wPLI for further analysis of serial EEG connectivity analysis to reveal changes following the disease course and adding this marker for clinical decision making. However, a small number of patients with a wide age range (5.5 - 11.0 years) should be further analyzed by dividing the age groups.

6. Using routine EEG as substrate for analysis

Unlike other studies that perform EEG separately for a research setting, EEGs performed at the hospital at the EEG lab were used. A big hurdle for EEG analysis is minimizing artifact and ensuring the resting state.[24,56] Performing EEG separately in a research setting may not be so difficult for adults.

However, performing research in children is even harder and recruiting healthy controls is a significant obstacle for research success. An artifact can be removed using various methods, but there is always a concern of original signal distortion by artifact removal.[57] By carefully selecting epochs with good resting state and avoiding artifact as much as possible, it was available to perform resting stage EEG connectivity analysis with routine clinical EEGs. The smaller number of epochs for analysis may be a limitation of this protocol, but increasing the number of the patients as well as control groups can overcome this limitation.

7. Limitations

As with all the other association measures of EEG, wPLI only represents and provide a limited amount of information EEG signal contains. Each measure has its limitation and strength, so it is necessary to combine different measures to contain as much information as possible and construct connectivity and perform network topology analysis. Electroencephalograms from patients whose diagnosis is other than brain disease and free of the neurological condition cannot guarantee a normal EEG. Recruiting normal controls separately and performing specific tests to recruit healthy controls can solve this problem. It was unavailable to divide the age group according to maturation for precise analysis due to small sample size. Inability to link the findings in this study to the pathophysiology of BECTS or clinical significance findings is a limitation that should be resolved by further research such as serial EEG connectivity analysis,

combining the laterality of spikes, and neuropsychological testing to check cognitive functioning.

Conclusion

Resting state EEG connectivity constructed using wPLI in BECTS patients was different from those of the controls. Certain connections in lower alpha and beta band connectivity were significantly lower, and certain node strengths were significantly lower. Global network topology showed less integrated and less efficient connectivity compared to the controls. Even though the waking EEG without spikes is thought to be normal and same as the healthy controls, they were different regarding connectivity. This difference in resting state connectivity can be a candidate for electrophysiological biomarker along with centrotemporal spikes.

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국문 요약

중심 측두부 극파를 보이는 소아기 양성 뇌전증 환자의 각성기 뇌파는 중심 측두부 극파가 각성기에 출현하는 소견을 제외하면 배경파의 이상 소견이 없어 정상 각성기 뇌파와 차이가 없다. 본 연구는 목적은 정상 배경파를 보이는 환자의 각성기 뇌파 연결성 분석을 통해 질환이 없는 대조군의 정상 뇌파에 대조되는 안정시 연결성의 차이를 밝히기 위해 시행하였다. 충분한 기간 동안의 추적 관찰 자료가 있고 연속적인 뇌파를 확인하여 전형적인 뇌파 및 발작의 양호한 경과를 확인한 전형적인 중심 측두부 극파를 보이는 양성 뇌전증이라고 확진할 수 있는 30명의 환자와 나이와 성별을 짝짓기한 질병이 없는 대조군을 선정하였다. 각성시 충분히 안정 상태가 파악할 수 있으며 잡파가 없어 연결성 분석이 용이한 부분의 뇌파를 8초 선택하여 분석하였다. 뇌파를 델타, 세타, 높은 알파, 낮은 알파, 베타 주파수 대역으로 분리하여 각각의 대역 특이 연결성을 구축하였다. 연결성 분석을 위한 뇌파의 관련성 지표로 가중 위상 지연 지표를 사용하였다. 19개의 뇌파 전극을 통신망의 교점으로 정하고 각각의 교점 간의 연결성을 구하여 19 x 19 행렬의 각성기 뇌파를 통해 구축된 연결성 지도를 작성하였다. 환자와 대조군의 연결성 자체를 각 연결에서의 가중 위상 지연 지표 값을 비교하여 분석하였다. 네트워크의 성질을 반영하는 지표로 각각의 교점의 강도 (node strength), 평균 경로 길이 (characteristic path length), 평균 클러스터 계수 (mean clustering coefficient)를 계산하여 비교하였다. 연결성 자체를 분석하였을 때, 델타와 세타 주파수 대역의 연결성에서는 일부 연결에서의 연결이 증가하거나 소수 연결에서는 감소하는 혼재된 양상이 관찰되었다. 낮은 알파와 베타 주파수 대역에서는 두 군 간의 유의한 차이가 있는 연결이 환자군에서 연결이 모두 떨어져있는 차이를 발견하였다. 동일한 주파수 대역에서 일부 교점의 차수가 환자의 경우에 유의하게 떨어져 있는 점이 발견되었다. 연결성의 특징을 분

석했을 때, 낮은 알파 주파수 대역의 네트워크에서 환자군의 경우 평균 경로 길이가 길게 나타났고 전체 평균 가중 위상 지연 지표도 낮게 나타났다. 이는 환자의 경우 휴지기 기능적 연결성의 통합되어 있는 정도가 낮음을 나타내는데 이는 전반적인 효율성이 떨어지는 것을 의미한다. 본 연구를 통해 극파를 제외하고는 정상 배경파를 보여 정상 뇌파와 차이가 없다고 알려진 중심 측두부 극파를 보이는 소아기 양성 뇌전증 환자의 각성기 뇌파가 일반 시각적인 판독에서는 정상과 차이가 없더라도 연결성 분석을 할 경우 차이가 있음이 밝혀졌다. 또한 그 차이는 안정기 연결성 측면에서 볼 때 환자의 경우 전반적인 효율이 떨어지고 전반적인 연결 강도가 낮은 것으로 밝혀졌다. 본 연구를 통해 볼 때, 연결성 분석을 통해 밝혀낸 이상 소견은 향후 다른 연구에서 추가로 이용될 수 있고, 환자의 진료에 발작파 이외의 추가 정보를 제공하는 전기 생리학적 지표로도 이용될 수 있음을 시사한다.

주요어: 연결성 분석, 네트워크, 뇌전증, 중심 측두부 극파를 보이는 양성 뇌전증, 안정기, 뇌파

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