Title: Developmental Changes of Brain Oscillatory Pattern in Children with and without Epilepsy

Authors: Abdollah Mohammadian[1], Reza Khosrowabadi[2,*], Bahram Yarali[3,*], Alireza Moradi[1]

1. *Institute for Cognitive Science Studies, Tehran, Iran.*
2. *Institute for Cognitive and Brain Sciences, Shahid Beheshti University, Tehran, Iran.*
3. *Subspecialist in Children and Adolescents Neurology, Epilepsy Fellowship, Tehran, Iran.*

***Corresponding Author**: Reza Khosrowabadi, Institute for Cognitive and Brain Sciences, Shahid Beheshti University, Tehran, Iran. Email: r_khosroabadi@sbu.ac.ir. Bahram Yarali, Subspecialist in Children and Adolescents Neurology, Epilepsy Fellowship, Tehran, Iran. E-mail: bahramyarali@gmail.com

To appear in: **Basic and Clinical Neuroscience**

Received date: 2022/10/15

Revised date: 2022/11/06

Accepted date: 2022/11/21

Please cite this article as:

Mohammadian, A., Khosrowabadi, R., Yarali, B., Moradi, A. (In Press). Developmental Changes of Brain Oscillatory Pattern in Children with and without Epilepsy. Basic and Clinical Neuroscience. Just Accepted publication Jul. 10, 2022. Doi: http://dx.doi.org/10.32598/bcn.2022.4230.1

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Abstract

The neural oscillations or brain waves refer to repetitive neural activities in the central nerves system. It is believed that brain processes the information though converging and diverging of these neural oscillations. The neural oscillatory pattern changes during the development and it has been reported that follows a specific trend during a typical development. Nevertheless, it is largely unknown whether this pattern would be differentiable in neurodevelopmental disorders. In this study, we aimed to explore developmental pattern of changes in the typically developed children with the age matched epileptic children. Therefore, eyes-open resting state EEG of epileptic and healthy children were acquired. Subsequently, changes in power spectrum of clean segments of EEG activities (with no seizure and removed from artifacts) in two groups were statistically compared in the age children within the ranges of 6-9 and 9-12 years-old. The results only showed significantly lower activities at the superior frontal and central regions in the frequency range of 1-4 Hz in epileptic children. We hope this finding could help to pave the way for better understanding of epilepsy effect on the brain development.

Keywords: Electroencephalography, Neurodevelopment, Power spectrum, Children

Introduction

Studying developmental pattern of changes in brain structure and functions has been area of research interest for many years (Sporns, O., 2014). Researchers are increasingly interested in understanding the procedures and factors that shape and happen in a healthy brain and its typical changes during a normal development. They believe such a pattern will help to recognize and prognose the abnormal brain developments such as neurodevelopmental disorders, and may help to find a clues on how the brain could be treated. Undoubtedly, most of changes occur during the infancy period and is followed by significant changes in the childhood and these changes are gradually decreased by growing up (Donald F. Huelke., ۱۹۹۸). Therefore, it seems necessary to investigate the normal growth pattern and its changes in neurodevelopmental disorders. However, as far as we know, there is limited information about the typical developmental pattern in children with epilepsy.

In this regard, advanced neuroimaging technologies can help us measure and track topographical changes in brain networks. Various types of neuroimaging technics could be implied that among them electroencephalography (EEG) because of its low running cost, and good temporal resolution could be a practical choice. In addition, it is believed that information processing in the brain is a product of convergence and divergence of the neural oscillations (Hermann BP., 2002). As a result, knowing the pattern of changes in brain waves during development helps to understand diseases. On the other hand, it is not well recognized whether pattern of developmental changes in epileptic children is similar to the typically developed children or not (Stam, C.J., Nolte., 2007). Given that epilepsy is one of the most common and important neurodevelopmental problems. (Lebel, C., 2008). Since in epilepsy, changes in the electrical activity of the brain cause sudden changes in behavior, we hypothesized that seizures occur only at a moment in time and have no long-term effects. Our aim is to show that epilepsy disorder may have an effect on the pattern of neurodevelopmental changes. For this purpose, using a cross sectional study we compared changes of the brain waves in various regions of the brain in a group of epileptic children with an age and gender matched typical developed children as is explained in the following section.

Methodology

The implementation of the study includes three basic parts including signal recording, required preprocessing and feature extraction, and modeling; each of which is fully described below. Figure 1 shows a diagram of the steps of the proposed method.

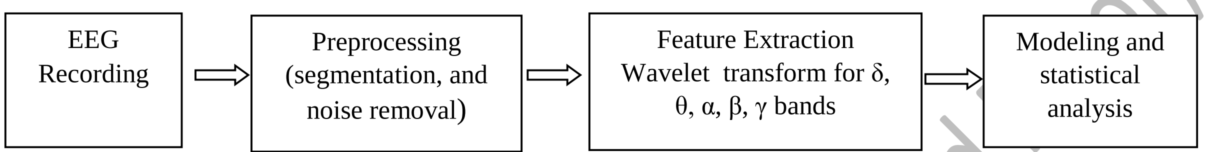


Figure 1. Experimental paradigm

Participants

In this study, electroencephalographic signals were recorded from 57 children with epilepsy and 57 age and gender matched typically developed children. Typically developed children did not have any neurological disorders or other illnesses and did not take any medication. These children aged from 6 to 12 and participated in the study by their parents' or care givers' consent. Children with epilepsy were diagnosed with epilepsy by a pediatric neurologist based on clinical interview and examination using EEG. All participants were resting in a quiet environment while recording of the signal was performed. The experiment was conducted in accordance with ethical principles for medical research as stated in the Helsinki declarations and it was approved by the ethical committee of the Institute for cognitive science studies with the IRB code of IR.IUMS.REC.1401.495.

Table1. Demographics of the participants

Number	Groups of patients with epilepsy		Groups of Normal	
	Sex	Hand	Sex	Hand
57	Boy/ Girl	R/L	Boy/ Girl	R/L

EEG Data Recording

Prior to the data recording, participants were informed of the procedure and an agreement was taken upon by their parents. A Nihon Kohden amplifier with a 28-electrode cap was used to record the EEG signal. Signal acquisition was done for 57 healthy children while their eyes were open during 60 minutes of Long-Term Monitoring at the Department of Neurology, Children's Medical Center. The use of PEMU (Pediatric EEG Monitoring Usage) is to determine the nature of seizures in children as well as to determine its focus to take preoperative measures for epilepsy surgery (Figure 2). This ward includes a double room for patients and technicians and a room for Pediatric neurologist. The patient's room is equipped with two cameras for live imaging of the patients and an EEG device recording with 28 channels. In this room, the nurse and the patient's companion have the opportunity to report suspicious activity of the patient live. In this room, the nurses can watch a live ECG as well as a video of the patient. The doctor's room includes a server computer with the ability to store data for a long time and a computer equipped with one of the most advanced systems available. Using this software, the doctor is able to review the images and data of the electroencephalogram online and offline and prepare the final report (Figure 3).

Figure 2. Long-Term Monitoring Room

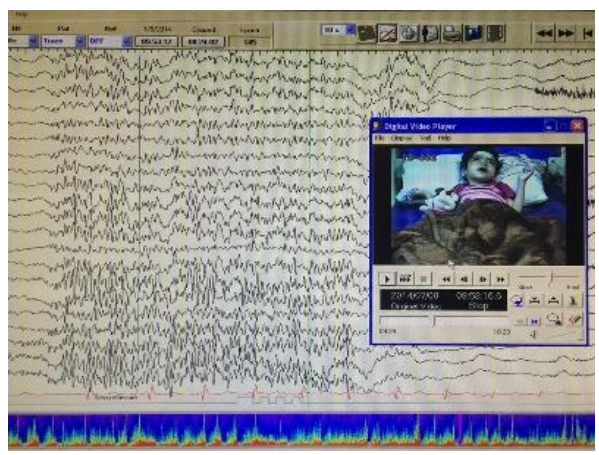


Figure 3. A view of the EEG recorded

Signal Analysis and Preprocessing

Signals related to each person have been recorded for an hour in the mentioned state and then, the parts which had the least amount of noise were selected from the artifact free signals. Specially, ocular and motion artifacts and electromyograms were removed by a skilled operator supervised by neurologist. For initial signal preparation, the artifact effect and the city electrical interference were removed through the software. The information of 28 EEG electrodes that were available in an array form was converted to be readable in MATLAB. The EEG signals were then filtered in the range of 0.1 to 70 Hz using a FIR filter.

Feature Extraction

Extracting appropriate features from electroencephalographic signals is of special importance. By choosing these features correctly and paying attention to the presented model, we can show better function of the brain. In this study, energy of EEG signal was calculated by wavelet transform, at the conventional frequency bans including δ, θ, α, β, γ bands, and finally the obtained values were given to the proposed model as input.

Wavelet is a set of mathematical functions used to decompose a continuous signal into its frequency components, and the resolution of each component equals its scale. Considering the better performance and discrimination of wavelet transform in epilepsy activity than short time Fourier transform, We use discrete wavelet transform to extract the features of the signals (Liu, Y., 2012). EEG signal is divided to sub frequency bands as is shown in Table 2.

Table 2. Different Sub frequency bands for decomposition of EEG signals

Frequency Range (Hz)	Frequency Bands	Frequency Bandwidth (Hz)
1-4	Δ	1
4-8	θ	4
8-10	$\alpha 1$	8
10-12	$\alpha 2$	10
12-15	β1	12
15-18	β2	15
18-25	β3	18
25-30	β4	25
30-40	ϒ	30

A discrete wavelet transform is used to analyze the signal at different frequency bands with different resolutions, by decomposing the signal into cumulative estimation ($C_{j,k}$) and detailed estimation ($d_{j,k}$). These coefficients are calculated by equation 1 and 2.

$$C_{j,k} = \int f(t)\, 2^{-j/2} \overline{\emptyset(2^{-j}t - k)dt} \qquad 1$$

$$d_{j,k} = \int f(t)\, 2^{-j/2} \overline{\psi(2^{-j}t - k)}dt \qquad 2$$

$\emptyset(t)$ indicates the basic scaling, ψ(t) indicates mother wavelet, k indicates translation parameter and j indicates scale index. Inverse discrete wavelet transform is calculated by equation 3.

$$f(t) = \sum_K C_{j,k}\, 2^{-j/2} \emptyset\left(2^{-j}t - k\right) + \sum_K d_{j,k}\, 2^{-j/2} \psi\left(2^{-j}t - k\right) \qquad 3$$

In signal processing, the total energy of the discrete time signal x [n] at distance n1≤n≤ n2 is defined as:

$$E(l) = \sum_{i=1}^{N} d_i^2 \times T/N \qquad 4$$

So that N is the number of $\boldsymbol{d_i}$ coefficients on the scale **l** and **T** is the sampling interval. In this study, to calculate the energy, the related energy of each subband is used. The associated energy calculates the signal strength at each time interval. The associated signal energy $E_r(l)$ is calculated by equation 5.

$$E_r(l) = E(l) \Big/ \sum_{i=1}^{S} E(i) \qquad 5$$

S is the number of wavelet scales.

Examining frequency bands separately plays an important role in obtaining high quality results. The choose of frequency bands has been done based on the results of Power spectrum analysis. Using fast Fourier transform (FFT), the power of the EEG signal spectrum is converted to frequency from time frame. By calculating the ratio of the power spectrum of each frequency band to the total power of 1 to 40 Hz and the frequency separation of 0.001 Hz, the relative spectrum power of all 28 channels is obtained. The paradigm of power spectral analysis based on frequency changes in frequency bands described at the Table2 were selected for the further analysis (P. Samimi sabet., 2019).

Statistical analysis

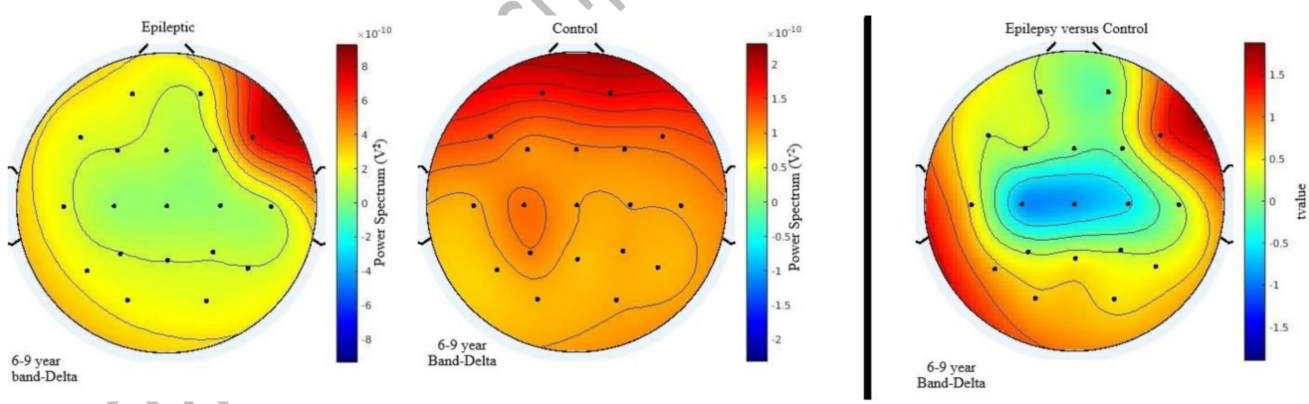
After performing a normalization test of Kolmogorov Simronov, analysis of variance with a post hoc of t were implied on the power spectrum features. The power spectrum was calculated with a frequency resolution of 1 Hz, and for each frequency the band comparisons have been made separately.

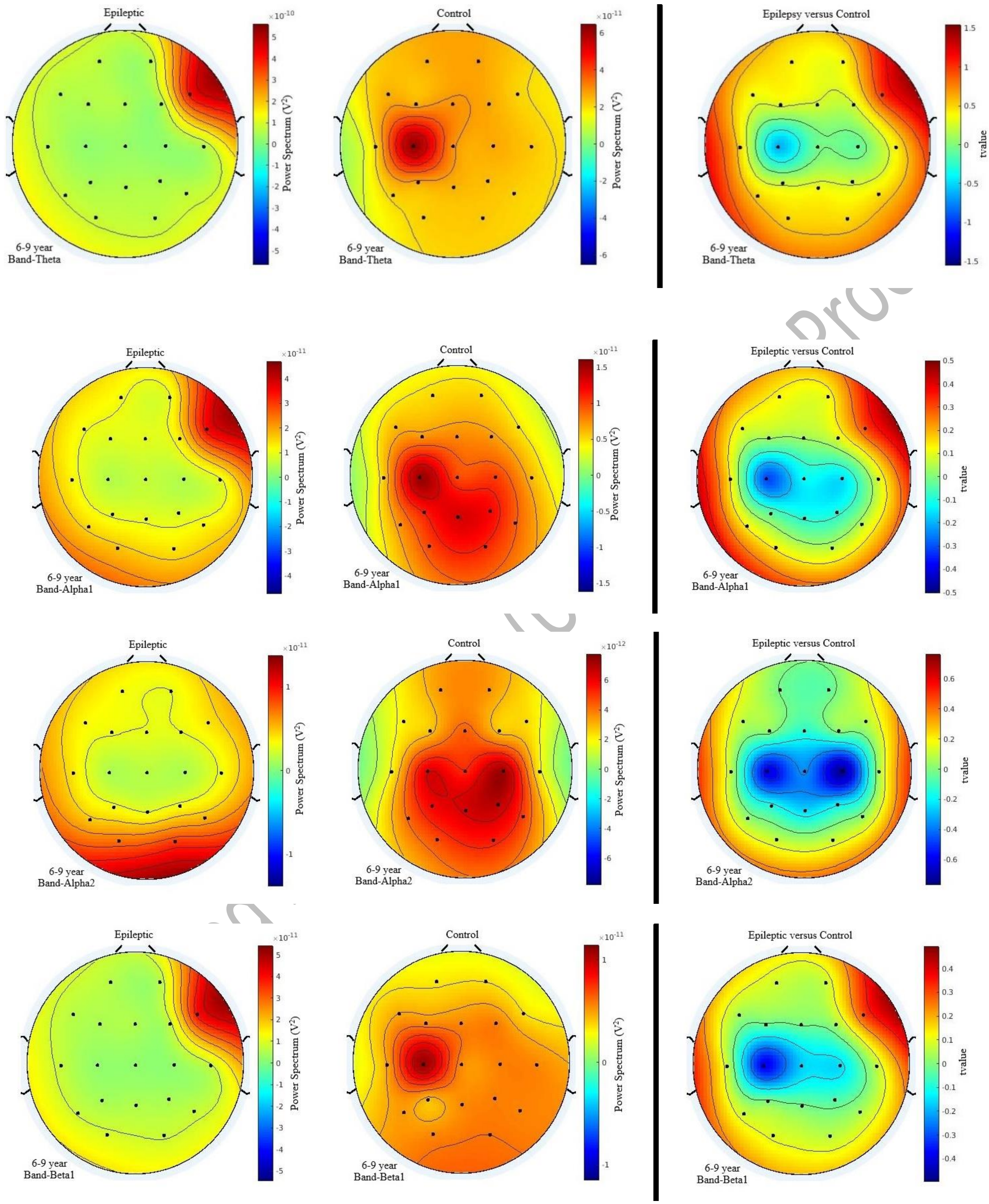
Results

Power spectrum of resting state EEG data of epileptic and typically developed children were statistically compared at the age range of 6-9, and 9-12 separately. Average of EEG power spectral in each group and the t value of their comparisons are presented in Figure3. Results of each frequency band is presented separately in the figure.

Comparison between epileptic and normal children at the age of 6-9

As presented if Figure3, smaller lower frequency activities were observed in epileptic children at the C3, C4 and Cz in the frequency range of 1-4 Hz. For the Theta, lower alpha, β1, and β2 frequency bands, lower activities were also observed at the C3 in epileptic children. While this effect was bilateral at C3 and C4, for upper alpha band and β3, β3, and lower Gamma frequencies.




Epileptic
×10-10
Power Spectrum (V2)
6-9 year
Band-Theta
Control
×10-11
Power Spectrum (V2)
6-9 year
Band-Theta
Epilepsy versus Control
tvalue
6-9 year
Band-Theta
Epileptic
×10-11
Power Spectrum (V2)
6-9 year
Band-Alpha1
Control
×10-11
Power Spectrum (V2)
6-9 year
Band-Alpha1
Epileptic versus Control
tvalue
6-9 year
Band-Alpha1
Epileptic
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Band-Alpha2
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Band-Beta1

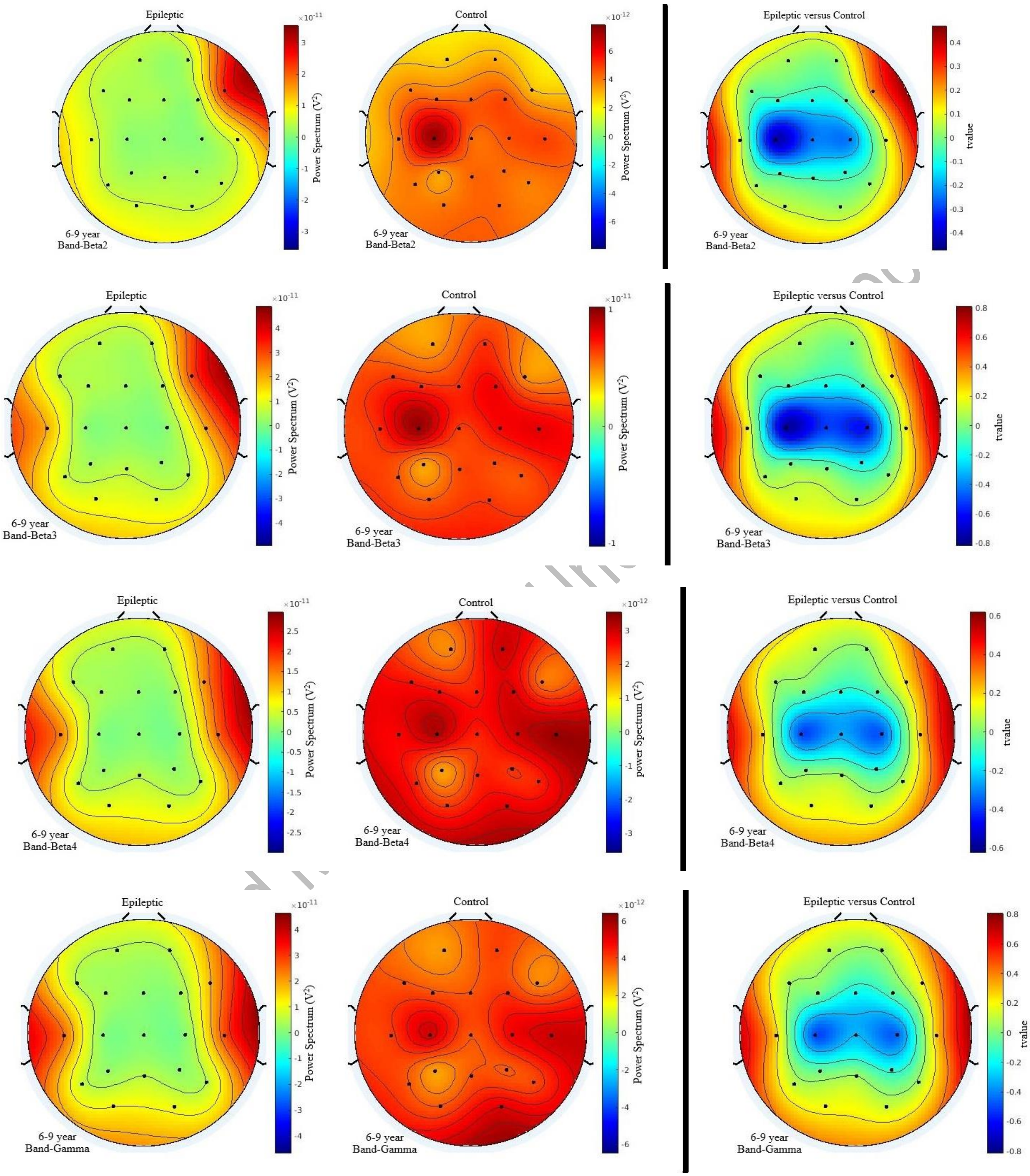
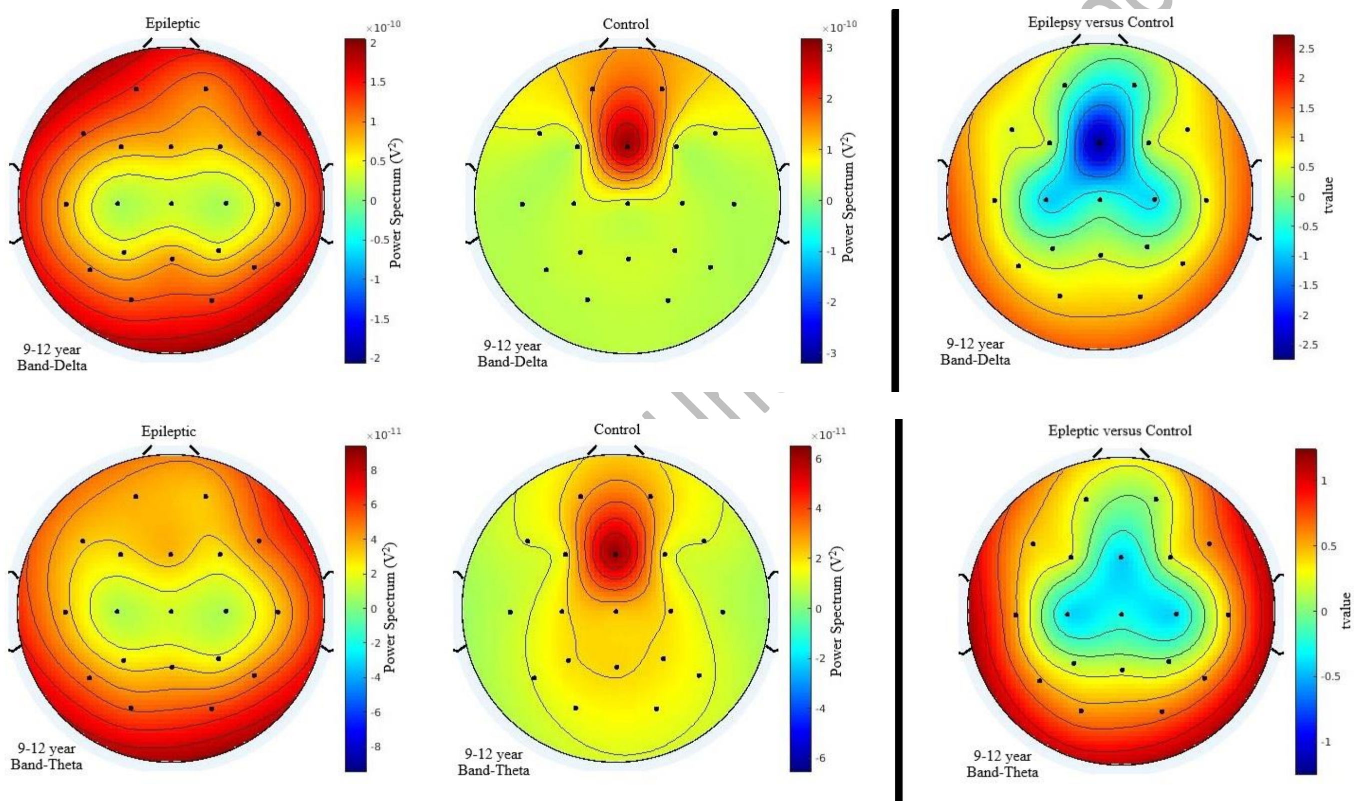
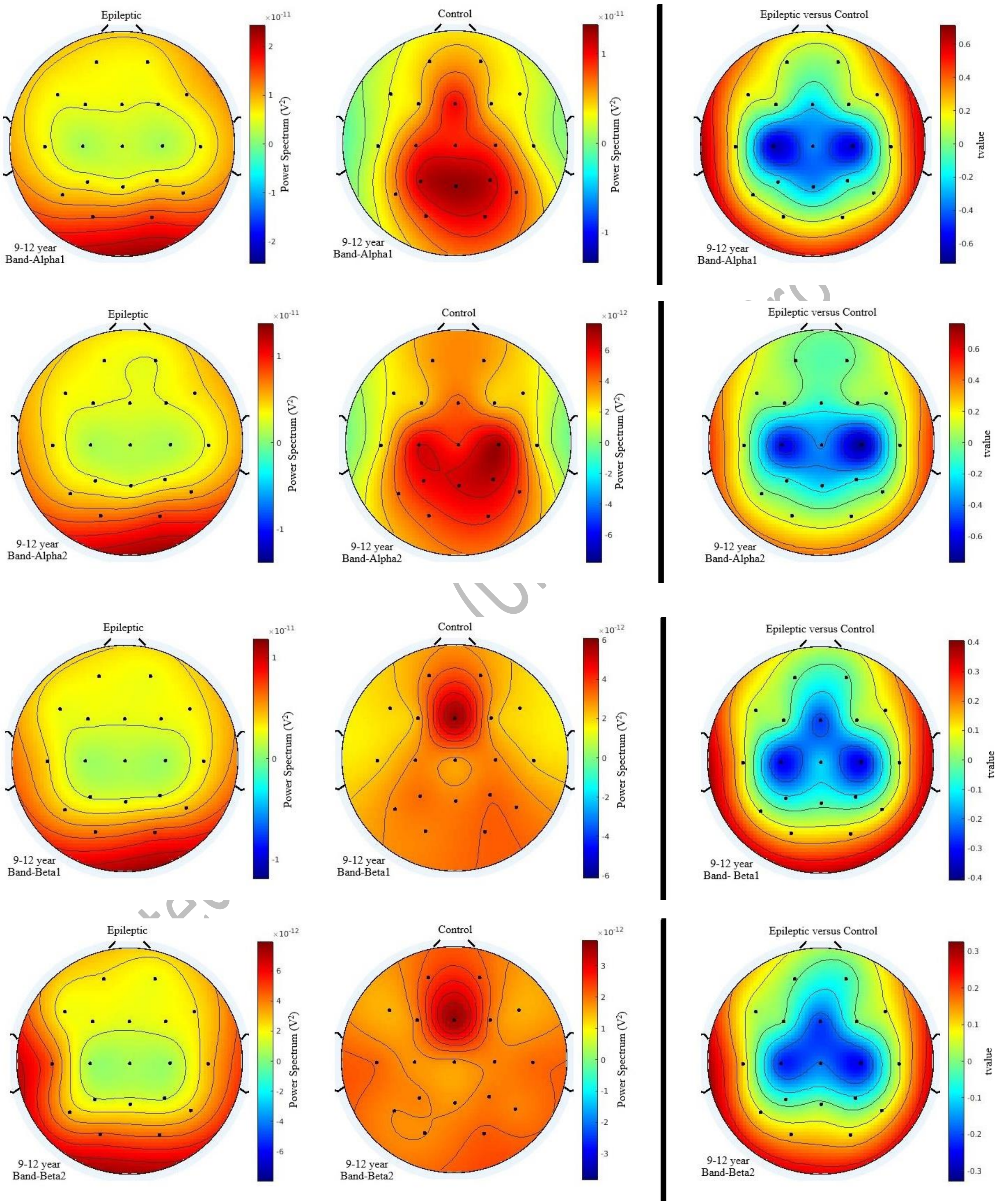


Figure3. Statistical differences between EEG power spectrum of epileptic and typically developed children at the age of 6-9

Comparison between epileptic and normal children at the age of 9-12

As presented if Figure4, smaller lower frequency activities were observed in epileptic children at the middle frontal region (Fz) in the frequency range of 1-4 Hz, β4, and lower gamma band activities. For the Theta, β1, β2, β3 frequency bands, lower activities were also observed at the Fz, C3 and C4 in epileptic children. While this effect was bilateral at C3 and C4, for the alpha band frequencies.




Epileptic
Control
Epileptic versus Control
9-12 year
Band-Alpha1
Band-Alpha2
Band-Beta1
Band- Beta1
Band-Beta2
Power Spectrum (V²)
tvalue
×10⁻¹¹
×10⁻¹²

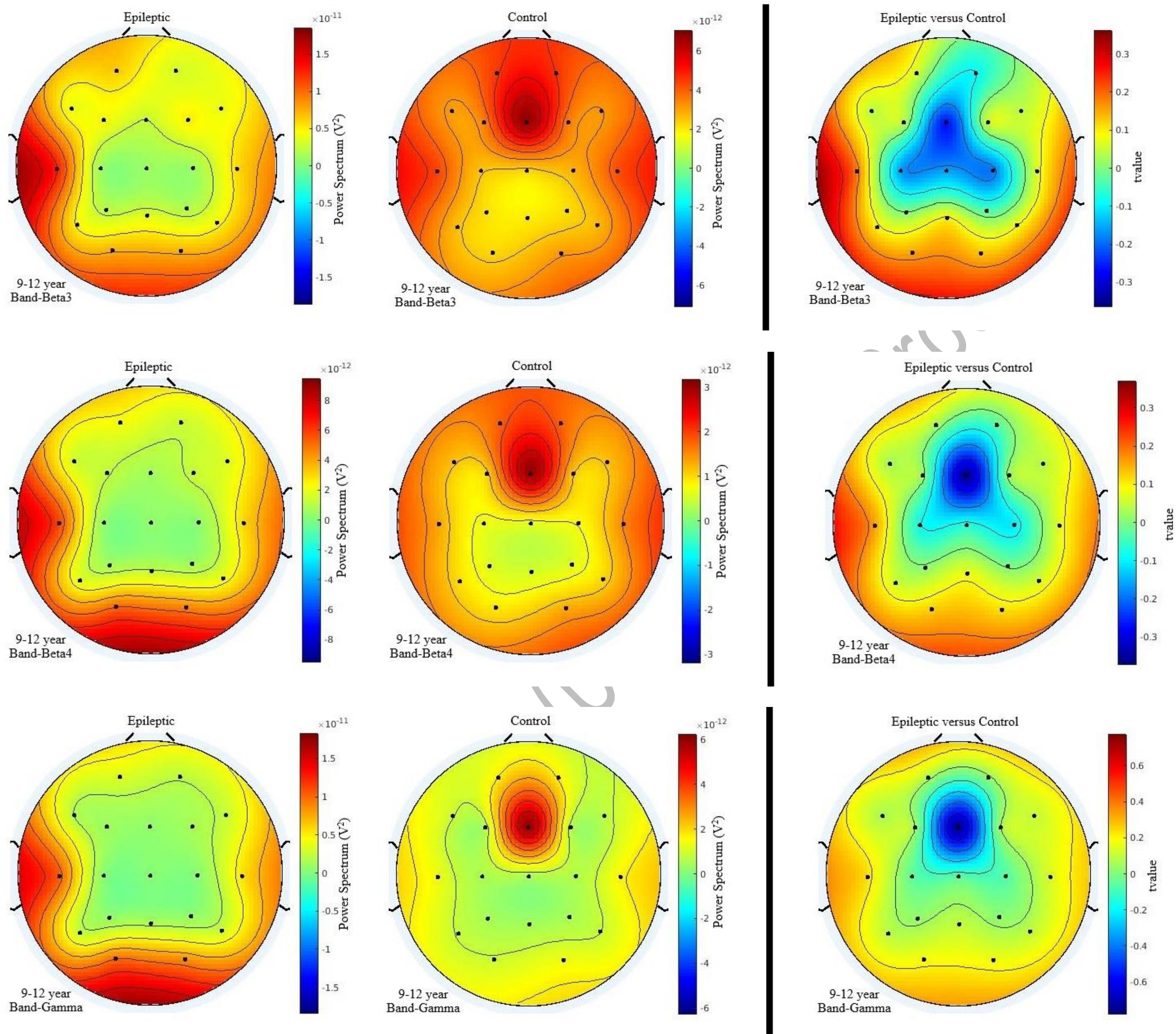


Figure4. Statistical differences between EEG power spectrum of epileptic and typically developed children at the age of 9-12

Discussion

Studies of functional brain connectivity in humans have shown that most studies point in the direction of a small-world pattern for functional connectivity, although scale-free networks have also been described (Eguiluz et al., 2005); The architecture of functional brain networks may reflect genetic factors and is related to cognitive performance; Different types of brain disease can sometimes giving rise to more random networks which may be associated with cognitive problems as well as a lower threshold for seizures (pathological hypersynchronization). (Stam CJ, 2007). According to the previous studies conducted in the modern theory of networks on large-scale networks such as the brain, the following reasons can be put forward for the use of brain network modeling: (1) The new theory of powerful realistic models of complex networks It gives us access to the brain. (b) a large number of efforts to study the topological and dynamical properties of these networks are still growing. (iii) This theory allows us to better understand the correlations between network structure and the processes taking place in these networks, especially synchronization processes. (iv) By relating structure to function, network changes can be investigated. (v) and these investigations provide scenarios of how complex networks might develop, and how they might respond to different types of diseases.

Other studies have shown that the small-world topology of functional brain networks is highly consistent across techniques, conditions, and frequency bands, and the architecture of functional brain networks may reflect genetic factors and be related to cognitive function. Different types of brain diseases can disrupt the optimal pattern of the small world, sometimes causing more random networks that may be associated with cognitive problems as well as a lower threshold for seizures (pathological hypersynchrony). It has been shown in studies that various types of brain disease such as Alzheimer's disease, schizophrenia, brain tumours and epilepsy may be associated with deviations of the functional network topology from the optimal small-world pattern (Cornelis J Stam., 200۷). Developmental studies conducted on the activity patterns, and organization of brain have indicated specific association between the brain structural and functional organization and abnormalities observed in the neurodevelopmental diseases. Considering the fact that developmental process leads to a significant change in network topology, it provides a possibility to investigate optimal changes in typically developed children and compare it with other network topologies such as neurodevelopmental disorders. If we consider the brain signals as the language of the brain, through which the brain gives us reliable information about some of its activities and interactions, some information and features can be extracted by accurately recording electroencephalography signals and processing them accurately.

The brain shows significant growth over the time on a macroscopic and microscopic scale. At the cellular level, the brain begins to grow an abundance of synaptic connections, which almost half of them are lost by the age around 6. This pruning process could potentially influence the brain oscillatory pattern and deviation of it may cause drastically changes in behavior and cognitive functions. The question raised in this study was whether this process differs in typically developed and epileptic children. Therefore, in a cross-sectional study, brain oscillatory pattern of the two groups were statistically compared.

In fact, epilepsy is known as a brain network disease that is manifested by sudden and temporary electrical discharge of a group of interconnected neurons. Our goal was to understand whether this effect is also temporal or it may influence the typical developmental process as well. Our results only showed significant difference is observed in power of brain oscillation at the frequency band of delta at the middle frontal region (at the age of 9-12). Based on these results, we think this effect is more probable to be temporal and my not influence the brain oscillatory pattern drastically. So, it seems that backbone of the brain functional network is untouched. However, more investigation using more sophisticated algorithm such as investigation of brain functional network such as graph theory is proposed, but meanwhile we believe the effect observed in the local addresses are somehow easier to be treated.

Although we had a similar number of boy and girl in this study but investigation of gender effect with a bigger population is proposed for the future works. Moreover, structure and hemodynamic also play a major role and should be taking into the account. Therefore, a longitudinal study and adding the f/MRI data could potentially improve the insight into the findings.

Conclusion

It is believed that behavior and cognitive functions are based on divergence and convergence of oscillatory activities in the brain. Since this oscillatory pattern follows a typical trend during the development, it is interesting to know whether this pattern is influence by the abnormal development. In this regard, in a cross-sectional study, two groups of normal and epileptic children at the age 0f 6-9 and 9-12 were compared. The results did not show significant changes in the power brain waves and effect of epilepsy seems to be temporal with no lasting effect. The results are interesting, but more investigation at the network level using functional connectivity approaches is required. Regional and global parameters of the brain functional connectome may provide a better insight. Nevertheless, based on the current results, it seems that backbone of the brain functional network is untouched in epileptic children and disease only target local addresses.

If it is correct, it will be very influential in planning the treatment process and brings a hope of implying brain stimulation techniques to compensate the negative effects.

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