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A Magnetoencephalography Study of Pediatric Interictal Neuromagnetic Activity Changes and Brain Network Alterations Caused by Epilepsy in the High Frequency(80-1000Hz)

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Abstract

More and more studies propose that high frequency brain signals are promising biomarkers of epileptogenic zone. In this study, our aim is to investigate the neuromagnetic changes and brain network topological alterations during an interictal period at high frequency ranges (80–1000Hz) between healthy controls and epileptic patients with Magnetoencephalography (MEG). We analyzed neuromagnetic activities with accumulated source imaging, and constructed brain network based on graph theory. Neuromagnetic activity changes and brain network alterations between two groups were analyzed in three frequency bands: ripple (80–250Hz), fast ripples (FRs, 250–500Hz), and very high frequency oscillations (VHFO, 500–1000Hz). We found that epileptic patients showed significantly altered patterns of neuromagnetic source localization and altered brain network patterns. And we also found that mean functional connectivity and number of modules from epileptic patients significantly increased in the ripple and FRs bands, and mean clustering coefficient from epileptic patients significantly decreased in the ripple and FRs bands. We also found mean functional connectivity was positively correlated with duration of epilepsy in the ripple and VHFO bands, and number of modules was positively correlated with duration of epilepsy in the ripple, FRs and VHFO bands. Our results indicate that epilepsy can alter patients' neuromagnetic activities and brain network in the high frequency ranges, and these alterations become more pathological as the duration of epilepsy grows longer.

Index Terms

MEG; high frequency brain signals; epilepsy; brain network; neuromagnetic activities

I. Introduction

HIGH frequency brain signals (HFBS) are defined as neural signals with a frequency greater than 80Hz. HFBS can be categorized into two types: physiological HFBS generated by healthy brain tissue (e.g. networks of pyramidal cells), and pathological HFBS provoked by abnormal brain regions (e.g. epilepsy). Low frequency brain signals can be categorized into five types: delta waves (0.1–3Hz), theta waves(3–8Hz), alpha waves(8–12Hz), beta waves(12–40Hz), and gamma waves(40–80Hz), moreover, each type represents different meaning in the neural system, for example, delta waves occur during deep and dreamless sleep, alpha waves coincide with quietly flowing thoughts, and gamma waves are generated

while human is in the working state. Compared with low-rate oscillations, HFBS have different waveforms (shown in Fig.1), have much lower power, represent new neural mechanisms (e.g. gap-gap conjunction, not synapse), can significantly improve clinical outcomes (e.g. epilepsy surgery)[1–3], and HFBS can be seen as a new biomarker. Especially, high frequency oscillations (HFOs), defined as a spontaneous sinusoid-like field EEG/MEG potentials in the 80–1000Hz frequency range, is one of the most typical biomarker for epilepsy[4]. Similar to the classification of low-rate oscillation, HFBS can also be divided into three categories based on the band values. According to previous studies[3–12], we split the high frequency brain signals into three parts, the ripple band (80–250 Hz), the fast ripple (FRs) band (250–500 Hz), and the very high frequency oscillations (VHFO) band (500–1000Hz). Although we can obtain both low and high frequency brain signals, in this paper, we focused on the HFBS, which can be categorized into three groups.

HFBS has many pathological and physiological manifestations that correspond to multiple kinds of neuron generators[8]. However, until now, there are no consensus on what criteria can be used to distinguish normal physiological HFBS from pathological HFBS, and the mechanism of HFBS remains unknown. And some previous reports have pointed that fast ripples seem to be a more specific biomarker for epileptogenic zones than epileptic spikes[13–15]. It has been found that the generation of fast ripples may be due to the synchronous burst from a large amount of neighboring cells[16].

Recently, more and more studies tried to find the relationship between HFBS and epilepsy. Kerber found that the patients who had the resection surgery of the areas generating FRs may have a seizure-free postsurgical outcome[17]. Fujiwara and colleagues analyzed the postsurgical outcome from 22 children with seizures, and 82% children had seizure-free postsurgical outcome, whose brain regions identified by HFOs were completely removed, and only 21% children had seizure-free outcome, whose brain regions identified by HFOs were incompletely removed[18]. Haegelen also got the similar conclusion that removal of areas that generate HFO may improve surgical outcome[11]. All these reports have shown that complete removal of tissue generating HFBS, especially FRs, correlates better with post-operative seizure freedom than removal of only tissue generating interictal spikes[5, 6, 19]. Increasing evidences indicate that HFBS can be seen as a promisingly new biomarker for the localization of seizure onset zone (SOZ), because HFBS is more sensitive to SOZ than spikes. This characterization may help neurosurgeons to solve the question that whether the resection of epileptogenic zone will make bigger harm than the epilepsy itself[10].

Brain can be viewed as a complex and large network or graph[20], in which there are a huge amount of functional connections between local and remote brain areas, these connections are formed by physical existence (such as fiber pathways, synapses pathways) or invisibly statistical relationships (such as cross-correlations, information flow, coherence). By using this framework of brain network, some recent studies[21–23] have proposed that the initialization and spreading of epilepsy can be explained as a disorder of network. And the graph theory is one of the best mathematical tool to analyze and characterize the brain network, which is built using scalp EEG[24], ECoG[25], MEG[26, 27], MRI[28], and functional MRI[29, 30]. However, only a few studies have investigated the epileptic brain network in the high frequency bands. Fuertinger et al[7] recorded 24 interictal and 24

seizure periods from patients with intractable epilepsy by electroencephalographic, analyzed the brain network by graph theory in the high frequency bands, and found that epilepsy may break the community structure of brain network in the high frequency bands. van Diessen et al[31] recorded twelve patients with temporal lobe epilepsy by depth electrode, and found that the number of the detected HFOs in the fast ripples frequency band was negatively correlated with the hub-value. Nissen and colleagues[32] recorded twelve patients with refractory epilepsy by resting-state MEG, and found significantly increase in node centrality in the high frequency bands. Zweiphenning and colleagues[5] built the high frequency brain network, analyzed the functional connectivity, and functional integration was detected in the FR-band network covering the putative epileptogenic tissue channels.

Most of the current studies analyzed the high frequency brain signals at the sensor level. However, the background noise may be included in the HFBS at the sensor level. Therefore, we used accumulated source imaging (ASI) method[33, 34] to analyzed the interictal high frequency neuromagnetic activities and brain network in the source level. ASI method can summarize the values of source activity during a period based on a wavelet transformation.

The objective of this study was to investigate both the neuromagnetic activities changes and the brain network topological difference at high frequency ranges (80–1000Hz) using MEG at the source level during an interictal period. We hypothesized that the neuromagnetic activities and measures of brain network at high frequency ranges were influenced by epilepsy, and the duration of epilepsy also caused a measurable alteration in the brain network topology.

II. Materials and methods

A. Subjects

In this study, twenty epileptic patients (details of the patients can be obtained from Table 1) and twenty age- and gender-matched healthy controls (10 males and 10 females, age mean 9.00 ± 5.63) were recruited from Cincinnati Children's Hospital Medical Center and Nanjing Brain Hospital. The research protocol received approval by the medical ethics committees of Cincinnati Children's Hospital and Nanjing Brain Hospital prior to study recruitment. Written informed consent was obtained from the guardians of each child, and informed assent was obtained from each child. This study was approved by the Institutional Review Board (IRB) at CCHMC.

B. MEG recordings

In this study, MEG data were recorded with a whole-head CTF 275 channel MEG system (VSM Medical Technology Company, Canada). Prior to MEG data acquisition, three small coils were attached to the nasion, and the left and right pre-auricular points of each subject, all these coils were used as landmarks to co-register with magnetic resonance imaging (MRI) scans. Subjects were asked to lie in a supine position, keep their eyes closed and stay still (avoid swallowing or teeth clenching). The large head movement during MEG recordings might affect the accuracy of source localization, therefore, the head movement during each recording was limited to 5mm. MEG signal was acquired at a sampling rate of

6000 Hz with a noise cancelation of third order gradients. Besides, before the experiments, empty-room MEG was recorded to identify the environmental noise.

In comparison to the acquisition of resting state data from adults, one challenge of the acquisition of resting state data from children is to keep still. According to our experience, the techniques to keep children still are: (1) pamphlet: to prepare the children for what would happen during the procedure, a story pamphlet entitled “A Visit to the MEG” was written. The pamphlet explained the task and giving instructions to avoid movements, eye-blinks and eye movements during the data recording. We sent the pamphlet to children and their parents/guardians so that they would be familiar the study before coming to hospital for the study. (2) Familiar/comfortable: before data acquisition commenced, children would have time to get familiar with the MEG system and the environment. For some small children, who had difficult to keep still (typically in the age range of 6–9 years), one parent/guardian was allowed to stay in the magnetically shielded room to keep children still. (3) Minimizing head movement: we used soft towel to fill the gap between child’s head and the MEG dewar so as to minimize possible head movement. (4) Encouragement: A built-in audio-video monitor system in the MEG suite allowed investigators to encourage children to keep still.

The best way to avoid the artifact originated by eye ball movement is to explain the task and give instructions to avoid eye movements. since some participants may not be able to avoid eye ball movement, we simultaneously recorded electro-oculogram (EOG) with MEG data acquisition. We recorded both EOG for both horizontal and vertical eye movement. We identified EoG artifact during data acquisition and during data analyses. If there were visually identifiable EOG artifacts, the entire dataset was excluded from data analyses.

C. MRI scans

MRI scans were recorded for all participants with a 1.5T MRI scanner (Sigma, GE, USA), and the acquisition parameters are as following: TR=8.5ms, TE=3.4ms, FOV=25cm×25cm, matrix=256×256, voxel size=1×1×1mm, number of slices=128. Three fiduciary coins were also placed in the same positions as the ones used during the MEG recording, so that the co-registration between MEG data and MRI scans can be accurately performed.

D. Neuromagnetic activities analysis

Firstly, we need to minimize the negative influence of noise and artifacts in the MEG recordings, which stem from eye blinks, eye movements, head movements, swallowing, and neck contraction. Then, MEG data was filtered into three frequency bands, ripple band (80–250Hz), FRs band (250–500Hz), and VHFO (500–1000Hz). Next, the neuromagnetic activities were analyzed by accumulated source imaging, which was previously proposed by our group[33]. In the view of signal processing, accumulate source imaging can be defined as a volumetric summation of source activity of MEG signals in frequency domain over a period of time. The steps of ASI are:

(1) We divide the original MEG data into many small segments, whose time-windows are five seconds. And some extra empty data points are added in the last segment, if the time-window of the last segment is less than five seconds. Then, we transform the MEG signals of

each segment from time-domain to frequency-domain using Morlet continuous wavelet transformation,

$$G(t, f) = \frac{1}{\sqrt{2\pi}f} e^{\left(\frac{-t^2}{2\sigma^2}\right)} e^{i2\pi ft} \quad (1)$$

σ indicates the standard deviation, f represents frequency of MEG signals, and t represents the time domain.

(2) Given the low signal-noise-ratio (SNR) and a small percentage of HFBS in the MEG recordings, we sum up the spectrums from all segments. Because all the segments have the same time-window, they can be accumulated together as one new spectrum, which could minimize the noise from a single MEG channel or random frequency bands, in order to increase SNR.

$$A(T, F) = \sum_{t=1}^T \sum_{f=1}^F G(t, f) \quad (2)$$

A represents the accumulated spectrum, T indicates total time points of MEG data and F indicates the total frequency bands. And the intensity of brain neuromagnetic activities can be accurately described by the strength of ASI. The bigger the strength is, means the greater activity.

After calculating ASI, we need to localize it in the brain. We localize the ASI based on the two-steps beamforming, which was also previously proposed by our group[33, 34]. The steps of the localization are: (1) compute lead fields for each source; (2) generate covariance matrices with MEG data; (3) select sensors for partial sensor coverage (pSc) for each voxel; (4) compute covariance for all sensors and location-beam (LB) sensors; (5) compute two sets magnetic source images using a 3D vector beamformer grid; (6) estimate coherent source and source orientation; (7) build a grid frequency kernel (GFK); (8) prepare the data for scalar spatial filter; (9) perform scalar beamforming to localize the source.

We analyzed the neuromagnetic activities at the source level. We scanned the whole brain at 6-mm resolution, and used a 3D grid to divide the entire brain into 13728 sub-regions (the grid's size is 26×16×33). We used this resolution because the distance between two nodes must be > 6-mm to exclude the highly correlated local connections. All the above-mentioned algorithms were performed by using MEG Processor Software[33–37] (develop by Jing Xiang, Cincinnati Children's Hospital Medical, USA).

E. Brain network construction and analysis

Schematic of brain network analysis was shown in Fig.2. The 13728 sub-regions were defined as the nodes of brain network, and we calculated phase lag index (PLI)[38] between two nodes, which were used as edges of brain network.

$$PLI = | \langle \text{sign}[\Delta\varphi(t_k)] \rangle | \quad (3)$$

$\varphi(t_k)$ represents a time series of phase difference at time k , sign denotes signum function, $\langle \rangle$ denotes mean value, $||$ indicates absolute value. We used PLI as the measure of functional connectivity between nodes of brain network, because PLI can measure the phase difference of MEG signals, and PLI is less influenced by the common sources and amplitude effects. To remove the weak functional connectivity, we used a threshold, and the edges were available if the value of PLI was above the threshold. However, setting an appropriate threshold for the edges of brain network still remains unsolved[27], we used fixed density approach proposed by Kim[39] to calculate the threshold, whereby the weights were rank sorted and a fixed proportion of the highest links ($0 < k < 1$) was used.

The mean functional connectivity, the mean clustering coefficient, the average shortest path length, and the number of modules were used as graph theoretical measures to analyze the brain network topology.

Clustering coefficient, shown in equation (4) and (5), quantifies the degree to which the nodes tend to cluster together.

$$C_i = \frac{1}{k_i(k_i - 1)} \sum_{\substack{j, k \in G \\ j, k \neq i}} (w_{ij} \cdot w_{jk} \cdot w_{ki})^{1/3} \quad (4)$$

G represents a graph with N nodes and K edges, C_i represents the clustering coefficient of node i , k_i is defined as the number of edges directly connecting to node i , w is defined as the weight between two nodes. Then mean clustering coefficient is defined as:

$$C_M = \frac{1}{N} \sum_{i=1}^N C_i \quad (5)$$

According to the graph theory, path length, indicates the distance from one node to another one, and the distance refers to not only a mathematical value in space but also a measure of functional connectivity in the brain network. Therefore, the shortest path length can delineate how efficiently one node is connected to all the other nodes in the network[40]. Epileptic network always has random brain network structure, which may cause the mean path length shorter.

$$L_A = \frac{1}{N(N-1) \sum_{i=1}^N \sum_{j \neq i}^N \left(\frac{1}{L_{ij}} \right)} \quad (6)$$

L_{ij} represents the shortest path length between node i and j , L_A represents the average shortest path length in the graph G with N nodes and K edges.

Brain network is consist of nodes and edges, and it's been found that some nodes are grouped together by densely connected edges, which can be named as network module or network community. There are minimal connections between network modules and maximal connections within the network modules, shown as Fig.3.

We decomposed the brain network into modules based on the previous work from[7]: (1) we assigned a specific module number to each node, which indicated that each module was initially only comprised of one node; (2) used a community detection strategy to update the community structure based on the Kernighan-Lin algorithm[41]; (3) repeated community detection 100 times; (4) calculated the average network partition to obtain the final community structure.

F. Statistical analysis

There are two main steps in the statistical analysis. First, we need to figure out if there are significantly differences of neuromagnetic source location and brain network topography between epileptic patients and healthy controls, and we used Brain Explorer 2 (<http://mouse.brain-map.org/static/brainexplorer>) as atlas. Therefore, two-tailed unpaired t-test were performed to assess the differences of neuromagnetic source location and brain network topography (mean functional connectivity, average shortest path length, mean clustering coefficient, and the number of modules) between two groups in three frequency bands (ripple, FRs and VHFO). Generally, statistical significance of differences can be determined, if the p value is less than 0.05. However, due to multiple frequency bands and brain network measures, we used Bonferroni correction approach to correct the influence of multiple comparisons,

$$P_{corrected} = p/N \quad (7)$$

where $p = 0.05$, N indicates the number of comparisons, there are three frequency bands and four measures in each band, so $N = 12$, so the threshold of statistical significance in each test should be set at $p < 0.0042$.

In the second step, we performed Pearson correlation analysis on duration of epilepsy and several measures, including mean clustering coefficient, shortest path length and the number of modules. If the p value is less than 0.05, we can conclude that there are significantly linear correlations between duration of epilepsy and the corresponding measure. We used IBM SPSS Statistics software package (version 19.0) to perform all these statistical analyses.

III. Experimental Results

A. Neuromagnetic activity location

The localizations of neuromagnetic activities in the accumulated source imaging were determined by the two-steps beamforming method in the ripple band, FRs band and VHFO band. Comparisons of representative source images from an epileptic patient and a healthy control are shown in Fig.4, the alterations are not consistent for all epileptic patients, due to

the limit of pages, we can't show all the twenty patients' image in the paper, and we list all the neuromagnetic source localizations in Table 2.

Ripple band (80–250Hz)—MEG neuromagnetic activities from healthy controls were localized to inferior frontal gyrus (Fig.4). However, epileptic patients (18/20) showed significantly altered patterns of neuromagnetic source localization (Table 2), and these alterations were not consistent for all epileptic patients.

FRs band (250–500Hz)—MEG neuromagnetic activities from healthy controls were localized to inferior frontal gyrus (Fig.4). However, epileptic patients (17/20) showed significantly altered patterns of neuromagnetic source localization (Table 2), and these alterations were not consistent for all epileptic patients.

VHFO band (500–1000Hz)—MEG neuromagnetic activities from healthy controls were localized to supramarginal gyrus and angular gyrus (Fig.4). However, epileptic patients (20/20) showed significantly altered patterns of neuromagnetic source localization (Table 2), and these alterations were not consistent for all epileptic patients.

B. Brain network patterns and measures

The brain networks from healthy controls and epileptic patients were co-registered to MRI data based on the fiducial points. And we used four measures (the mean functional connectivity, the average shortest path length, the mean clustering coefficient, and the number of modules) to analyze the alterations of brain network between two groups in the ripple, FRs and VHFO frequency bands.

We used PLI as the measure of functional connectivity between nodes of brain network to delineate the connection strength, therefore, the value of functional connectivity represents the degree of similarity of activations between different brain regions. The functional connectivity values can be influenced by epilepsy, and an alteration in functional connectivity means the brain physical or functional structures may be changed by epilepsy. If we use the healthy controls as baseline, and compare epileptic patients with the healthy controls, we may conclude significantly changed functional connectivity values.

Ripple band (80–250Hz)—All the twenty epileptic patients showed significantly altered brain network patterns in the ripple frequency band, and the alterations were mainly reflected by more connections in the frontal gyrus (Fig.5). We found that mean functional connectivity of patients with epilepsy was significantly higher than healthy controls in the ripple frequency band (Fig.6A, $p=0.004$). Moreover, we found significant differences of brain network measures between two groups in the ripple frequency band, and the alterations of epileptic brain network were lower mean clustering coefficient (Fig.6C, $p=0.0025$) and higher number of modules (Fig.6D, $p=0.001$). However, we found no significant differences in the average shortest path length between two groups.

FRs band (250–500Hz)—All the twenty epileptic patients showed significantly altered brain network patterns in the ripple frequency band, and the alterations were mainly reflected by more connections in the left frontal-temporal junction (Fig.5). We found that

mean functional connectivity of patients with epilepsy was significantly higher than healthy controls in the FRs frequency band (Fig.6A, $p=0.003$). Moreover, we found significant differences of brain network measures between two groups in the FRs frequency band, and the alterations of epileptic brain network were lower mean clustering coefficient (Fig.6C, $p<0.003$) and higher number of modules (Fig.6D, $p=0.001$). However, we found no significant differences in the average shortest path length between two groups.

VHFO band (500–1000Hz)—No significantly altered brain network patterns were found in the VHFO frequency band. We found that mean functional connectivity of patients with epilepsy was significantly higher than healthy controls in the VHFO frequency band (Fig. 6A, $p=0.004$). Moreover, we found significant differences of brain network measures between two groups in the VHFO frequency band, and the alterations of epileptic brain network were higher number of modules (Fig.6D, $p=0.001$). However, we found no significant differences in the mean clustering coefficient or average shortest path length between two groups.

C. Correlations between measures and duration of epilepsy

We try to find correlations between brain network measures and the duration of epilepsy in ripple, FRs, and VHFO frequency bands (sample size is 20). The brain network measures include the mean functional connectivity, the average shortest path length, the mean clustering coefficient, and the number of modules. Duration of epilepsy represents how many years the patient's epilepsy has lasted.

Ripple band (80–250Hz)—We found a significant positive correlation between duration of epilepsy and mean functional connectivity ($R^2=0.21$, $p=0.042$, $y=0.024x+0.474$, Fig.7), and we also found a significant positive correlation between duration of epilepsy and number of modules ($R^2=0.216$, $p=0.039$, $y=16.58x+683$, Fig.7). And we found no correlation between duration of epilepsy and mean clustering coefficient, shortest path length.

FRs band (250–500Hz)—We found a significant positive correlation between duration of epilepsy and number of modules ($R^2=0.253$, $p=0.024$, $y=18.41x+680$, Fig.7). And we found no correlation between duration of epilepsy and mean clustering coefficient, shortest path length.

VHFO band (500–1000Hz)—We found a significant positive correlation between duration of epilepsy and mean functional connectivity ($R^2=0.37$, $p=0.004$, $y=0.034x+0.1$, Fig.7), and we also found a significant positive correlation between duration of epilepsy and number of modules ($R^2=0.22$, $p=0.037$, $y=15.91x+707.4$, Fig.7). And we found no correlation between duration of epilepsy and mean clustering coefficient, shortest path length.

IV. Discussion

In this study, we found that the epileptic patients demonstrated alterations on interictal neuromagnetic activities location and brain network topography in the high frequency bands.

In epileptic patients, several brain network measures showed significantly different patterns compared with healthy controls, including functional connectivity, mean clustering coefficient, shortest path length, and the number of modules. We also found that functional connectivity and the number of modules were positively correlated with the duration of epilepsy. As far as we know, this study is the first one focusing on the high frequency (80–1000Hz) interictal neuromagnetic activities and brain network analysis for the pediatric epileptic patients.

Visual identification of epileptic spikes (14–70 Hz) in intracranial EEG is the widely used, which is an invasive method for estimating epileptogenic zones. Our method uses MEG to quantitatively examine the relationship between HFBS (80–1000Hz) and epileptogenic zones non-invasively. Compared with MEG, intracranial EEG has several disadvantages, which is very invasive, risky and costly. Previous MEG investigations of epilepsy have typically focused on measuring the amplitudes of MEG waveforms at the sensor level. Our newly developed methods can quantify cortical excitability with spectral and frequency signatures at source levels. Our wavelet-based beamformer is a new MEG method: the unique innovation of our method is its ability to measure the cortical excitability of the entire brain at a high spatial resolution.

We used accumulated source imaging to localize the neuromagnetic activities. In the clinical practice, it is a subjective decision to detect noise and artifacts by visual detection and manually remove them. There are still some protocols that we can depend on, for example, (1) the amplitude of normal MEG signals should be less than 6pT, (2) the line noise should be at 50Hz or 60Hz, (3) slow drift of MEG signals is mostly due to a head movement, and so on. We found that high frequency neuromagnetic activities of epileptic patients were significantly localized to different brain regions, compared with healthy controls. Moreover, we found that the altered high frequency neuromagnetic activities were mainly localized to the temporal-frontal junction, frontal gyrus, angular gyrus and supramarginal gyrus. Potential explanations for the aberrant neuromagnetic activities could be the disconnection between gray and white matter[42] or thalamic dysfunction[43]. These alterations coincide with previous studies[44–47], which found temporal-frontal junction and frontal gyrus play an important role in epileptic pathophysiology and cause morphologic alterations and aberrant neuromagnetic activities. These altered and increased neuromagnetic activities may lead to more frequent discharges, and even seizures. The altered patterns of neuromagnetic activities localization were not consistent for all the epileptic patients, we guessed the main reasons were different types of epilepsy, different epileptogenic zone, and different duration of epilepsy between all these epileptic patients. Previous studies have revealed that HFOs was a promising biomarker of epileptogenic zone and especially high frequency neuromagnetic activities between 200Hz and 700Hz were epileptogenic[12, 48], and further evidences indicated that the post-surgical outcome was better when the brain regions generating HFOs were removed[11]. Therefore, neuromagnetic activities from the temporal-frontal junctions, frontal gyrus, angular gyrus and supramarginal gyrus in the high frequency bands can be very strong, and may cloud the normal brain signals in these regions. Besides altered patterns of neuromagnetic activities localization, we also found altered patterns of brain network in the ripple and FRs frequency bands, especially more connections in the frontal gyrus and left frontal-temporal junction. Put these abnormal patterns together, we

may conclude that the aberrant neuromagnetic activities localizations in the high frequency do not represent the abnormal brain regions, but represent the brain tissues which are involved in the epileptogenic network initiating and propagating the seizure.

We found that, compared with healthy controls, mean functional connectivity of epileptic brain network increased in the ripple, FRs, and VHFO frequency bands, and many previous reports found similar results both in the low frequency and high frequency bands. Bela Clemens et al[49] recorded 17 epileptic children and 19 healthy controls using 21-channel EEG, and concluded that in the beta frequency band, functional connectivity was significantly higher in the epileptic group as compared to the controls. Hsiao FJ and et al[50] analyzed the MEG data from patients with temporal lobe epilepsy using minimum norm estimate (MNE), and found that the functional connectivity of default mode network was increased at the delta and theta frequency bands. Haneef et al[51] recorded functional MRI from 43 subjects (16 healthy controls and 27 epileptic patients), and they found that hippocampal connectivity of limbic network increased in the patients with epilepsy. Nissen et al[32] recorded resting state MEG data from 12 epileptic patients, and analyzed the functional connectivity in the high frequency bands, they found that in the center of irritative zone, functional connectivity of epileptic patients was significantly higher than healthy controls. These previous reports used different data source (MEG, EEG and fMRI) and analyzed the data in different frequency bands (delta, theta, alpha, beta, gamma, ripple and fast ripples), but they found similar results. Therefore, we may conclude that epileptic activity could alter the brain network and significantly increase the functional connectivity both in low and high frequency bands. Inspired by Kitchigina and colleagues' study[52], we proposed that the functional connectivity imbalance may be caused by two main reasons, (1) septohippocampal system is disturbed by epilepsy, (2) hippocampal GABAergic cells are damaged by epilepsy. And the findings of the present study suggest this may be worth studying in the future for other types of epilepsy as well.

We found that the mean clustering coefficient of epileptic patients was significantly lower than healthy controls in the ripple frequency band and FRs frequency band. Similarly, Haneef et al[53] recorded 48 subjects (24 epileptic patients and 24 healthy controls), they analyzed the reported abnormal regions based on graph theory, and concluded that clustering coefficient were decreased in TLE, compared to control subjects. Fuertringer et al[7] recorded high resolution intracranial electroencephalographic from 48 epileptic patients, and analyzed the spatiotemporal evolution of community structure based on graph theory. And they found a significant decrease clustering coefficient in the high frequency band, which represented a functional pathology of the brain network that underlies epileptogenesis. Englot et al[54] recorded MEG data from 92 subjects (31 healthy controls and 61 epileptic patients), and found that functional connectivity of epileptic patients was significantly lower in the brain network of orbitofrontal, perisylvian, and posterior temporo-parietal cortices. Decreased clustering coefficient indicates that the inter-connectivity of neighboring nodes becomes weaker in the high frequency brain network. However, clustering coefficient of epileptic patients has also been reported to be increased in some studies[27, 55, 56]. This variance can be explained by several factors, including diagnostic/evaluation criteria, different analysis methods, differences of subjects' age, pathology, medications, and so on[57].

Shortest path length and mean clustering coefficient can be combined together to delineate the topology of brain network, which are categorized into three groups: ordered topology, random topology, and small-world topology[58]. Ordered topology network has high shortest path length and high clustering coefficient. Random topology network has low shortest path length and low clustering coefficient. And small-world topology network has low shortest path length and high clustering coefficient, and healthy brain networks always have the small-world topology[59, 60]. We found significantly decreased clustering coefficient and no change of shortest path length in the high frequency bands. This result indicated that the brain network topology of epileptic patients became more random, and less small-world in the high frequency band. This alteration of brain network may influence the optimization of local and global functional connectivity, and increase the vulnerability for seizures. Similarly, Bartolomei et al[61] also found less small-world topology in the interictal epilepto-genic networks.

Complex networks can be viewed as network communities, which is composed of many modules. The modules are defined a group nodes that are densely interconnected, but there are few connections between every two modules[59]. We partitioned brain network into several non-overlapping modules, and the organization of all these modules can be defined as “community structure” [62], and we used the number of modules to delineate the evolution of high frequency brain network of epileptic patients. The present study found that in the ripple, FRs and VHFO frequency bands, the number of modules was significantly increased in the patients of epilepsy, and the number of modules was also positively correlated with the duration of epilepsy. Similarly, Fuertinger et al[7] recorded intracranial electroencephalographic from 24 epileptic patients, and analyzed the community structure of epileptic patients using the number of modules in the ripple band and FRs band. They found that the number of modules remained stable (ranging from 3.3–7.2) while the subjects were in the resting-state, however, during the preictal period, increased average number of modules (ranging from 22.7 to 29.4) was observed at the ripple band and FRs band. These results indicated that epileptogenesis could cause the breakdown of community structure in the high frequency brain network. Combined with our results, the ‘breakdown’ may damage the brain network, cause permanent functional connectivity abnormalities to the brain network, and these abnormalities may become worse as the duration of epilepsy gets longer.

Significant positive correlation was found between mean functional connectivity, the number of modules and duration of epilepsy. Our results indicated that longer the duration was, more or worse damage could happen on the brain network. Given that there are more connections in the frontal gyrus and left frontal-temporal junction for the epileptic patients as discussed above, and frontal lobe is associated with cognitive function. More damage on the brain network may mainly occur on the frontal gyrus and lead to a worse performance on cognition, and these influences could lead to lower academic achievement for children in the school. This finding could shed a light on the relationship between brain network, epilepsy and cognitive function.

Above all, epileptic patients have alterations on interictal neuromagnetic activities, locations, and brain network in three high frequency bands. From our experimental results, shortest path length seems to be a brain network measure with less effect, because it has no

significant alterations in all three frequency bands. Comparatively, number of modules has significant alterations in all three frequency bands, and can be regarded as a sensitive brain network measure to evaluate the progress of epilepsy duration. There are also some interesting findings from the comparisons between ripple frequency band and FRs frequency band, such as, epileptic patients show significantly altered pattern of brain networks in the both ripple and FRs frequency bands, but the alterations go into the opposite directions, in the ripple frequency band, functional connectivities of epileptic patients become less than healthy controls, and in the FRs frequency band, functional connectivities of epileptic patient become more than healthy controls (shown as Fig.5). Except that, alterations of interictal neuromagnetic activities, locations, and brain network from ripple and FRs frequency bands remain in line with each other

V. Conclusion

In this study, our results indicate that the characteristics and topology of high frequency brain network are influenced by epileptic activity, and these alterations become more pathological as the duration of epilepsy grows longer. All these findings suggest that HFBS seems to be a promising biomarker of epileptogenesis. It is reasonable to anticipate that HFBS may improve the diagnosis and treatment of epilepsy in the forthcoming decades. Next, we will focus on collecting and analyzing the patients' clinical data whose brain area generating HFBS are removed.

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Fig. 1.

Example of MEG waveform from one MEG channel "MLC11", the waveforms are categorized into six types: 0.1–3Hz, 3–8Hz, 8–12Hz, 12–40Hz, 40–80Hz, and 80–1000Hz. Different frequency bands can provide different information to physiologist and clinician.

Fig. 2.

Schematic of brain network analysis. First, MEG raw data are recorded. Second, artifact and noise are identified with visual inspection. Then, beamformer analysis is used to project MEG sensor level signals to brain anatomical region at source level according to individual MRI. Then, correlation matrix of the brain functional connectivity is computed, and the brain network is built. Then, the brain network is analyzed based on the mean clustering coefficient, the average path length and the number of modules. Finally, differences of brain network measures between epileptic group and healthy subjects group are analyzed, and the correlations between network measures and the duration of epilepsy are analyzed.

Fig. 3.

Schematic of brain network modules structure, (a) nodes and edges in a brain network, (b) based on the connections between nodes, the brain network can be decomposed into four modules, there are maximal number of functional connectivities within each module, and minimal number of functional connectivities between two modules. Four brain network modules are identified by four colors.

Fig. 4.

Neuromagnetic activities of accumulated source images in 80–1000Hz from an epileptic patient and a healthy control, the alterations are not consistent for all epileptic patients, due to the limit of pages, we can't show all the twenty patients' image in the paper, and we list all the neuromagnetic source localizations in Table 2. Compared with the healthy control, the epileptic patients (20/20) significantly showed altered patterns of source imaging in the ripple, FRs, and VHFO frequency bands. Arrows point to the significantly altered regions between epileptic patient and healthy control.

Fig. 5.

The typical predominant functional connectivity networks from a healthy control and an epileptic patient. Epileptic patients (18/20) show significantly altered pattern of brain networks in the ripple and FRs frequency bands. Arrows point to the significantly altered regions between epileptic patient and healthy control. Blue lines indicate inhibitory connections, and red lines indicate excitatory connections. An excitatory connection represents a positive connection where the amplitude of signals in two connected nodes are positively correlated. An inhibitory connection represents a negative connection where the amplitude of signals in two connected nodes are negatively correlated.

Fig. 6.

Comparison of brain network measures between patients with epilepsy and healthy controls. (A) Mean functional connectivity was significantly higher in patients with epilepsy in the ripple band ($p = 0.004$), the FRs band ($p = 0.003$) and VhFo band ($p=0.004$), (B) There were no significantly differences of shortest path length in patients with epilepsy in three frequency bands, (C) Mean clustering coefficient was significantly lower in patients with epilepsy in the ripple band ($p = 0.0025$) and the FRs band ($p = 0.003$), (D) Number of modules was significantly higher in patients with epilepsy in the ripple band ($p = 0.001$), the FRs band ($p = 0.001$) and VHFO band ($p=0.001$).

Fig. 7.

Correlations between brain network measures and duration of epilepsy, a significant positive correlation between mean functional connectivity and duration of epilepsy was detected in the ripple band ($R^2=0.21$, $p=0.042$) and VHFO band ($R^2=0.37$, $p=0.004$), and a significant positive correlation between number of modules and duration of epilepsy was detected in the ripple band ($R^2=0.216$, $p=0.039$), FRs band ($R^2=0.253$, $p=0.024$) and VHFO band ($R^2=0.22$, $p=0.037$). The asterisk represents statistically significant differences ($p < 0.05$)

TABLE I

Demographic of twenty epileptic patients

ID	Age	Gender	Epilepsy Subtype	Duration (years)
1	15	Female	CAE	12
2	14	Female	TLE	11
3	17	Male	TLE	13
4	10	Male	n.r.	8
5	11	Male	FLE	9
6	12	Female	CAE	10
7	7	Female	n.r.	2
8	16	Female	FLE	8
9	7	Male	TLE	4
10	8	Female	TLE	6
11	9	Female	FLE	2
12	15	Female	CAE	9
13	13	Male	n.r.	9
14	16	Female	FLE	11
15	17	Male	CAE	13
16	15	Male	TLE	4
17	7	Female	TLE	5
18	11	Male	TLE	10
19	12	Female	CAE	3
20	9	Female	n.r.	5

TLE represents temporal lobe epilepsy, FLE represents frontal lobe epilepsy, n.r. represents not reported, CAE represents children absence epilepsy.

TABLE II

Neuromagnetic source localization from epileptic patients and healthy controls.

	80–250Hz	250–500Hz	500–1000Hz
Healthy controls	superior frontal gyrus	inferior frontal gyrus, temporal-frontal junction	supramarginal gyrus, angular gyrus
Patient 1	parieto-occipito-temporal junction, cingulate gyrus	parieto-occipito-temporal junction, cingulate gyrus	cingulate gyrus, superior frontal gyrus
Patient 2	parieto-occipito-temporal junction	parieto-occipito-temporal junction, supramarginal gyrus	parieto-occipito-temporal junction, angular gyrus
Patient 3	medial frontal gyrus, supramarginal gyrus	medial frontal gyrus, supramarginal gyrus	medial frontal gyrus, parieto-occipito-temporal junction
Patient 4	temporal gyrus	medial frontal gyrus,	medial occipital gyrus
Patient 5	medial frontal gyrus, angular gyrus	medial frontal gyrus, angular gyrus	medial frontal gyrus, supramarginal gyrus
Patient 6	temporal gyrus	medial occipital gyrus, cingulate gyrus	cingulate gyrus, superior frontal gyrus
Patient 7	medial frontal gyrus, cingulate gyrus	superior frontal gyrus, supramarginal gyrus	temporal-frontal junction, medial frontal gyrus
Patient 8	superior frontal gyrus,	supramarginal gyrus, angular gyrus	medial frontal gyrus, angular gyrus
Patient 9	medial frontal gyrus, parieto-occipito-temporal junction	medial frontal gyrus, parieto-occipito-temporal junction	medial frontal gyrus, parieto-occipito-temporal junction
Patient 10	medial frontal gyrus, angular gyrus	temporal-frontal junction, medial frontal gyrus, angular gyrus	medial frontal gyrus, parieto-occipito-temporal junction
Patient 11	temporal gyrus	temporal-frontal junction, medial frontal gyrus	supramarginal gyrus, temporal gyrus
Patient 12	temporal-frontal junction, angular gyrus	temporal gyrus	parieto-occipito-temporal junction
Patient 13	angular gyrus	inferior frontal gyrus, temporal-frontal junction	inferior temporal gyrus
Patient 14	temporal-frontal junction, medial frontal gyrus	superior frontal gyrus, supramarginal gyrus	temporal-frontal junction, medial frontal gyrus
Patient 15	angular gyrus	inferior temporal gyrus	temporal gyrus, angular gyrus
Patient 16	medial frontal gyrus, supramarginal gyrus	cingulate gyrus, parieto-occipito-temporal junction	angular gyms, parieto-occipito-temporal junction
Patient 17	superior frontal gyrus	superior frontal gyrus, angular gyrus	parieto-occipito-temporal junction
Patient 18	supramarginal gyrus, inferior temporal gyrus	inferior frontal gyrus, temporal-frontal junction	middle temporal gyrus
Patient 19	cingulate gyrus, superior frontal gyrus	inferior frontal gyrus, temporal-frontal junction	medial frontal gyrus, supramarginal gyrus
Patient 20	temporal-frontal junction, medial frontal gyrus	cingulate gyrus, superior frontal gyrus	temporal gyrus