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Functional brain network alterations in epilepsy: A magnetoencephalography study

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ABSTRACT

Objective: To test the hypotheses that brain networks of patients with epilepsy differ from that of healthy controls and functional interactions in the brain are correlated to the duration of epilepsy.
Method: The present study recorded Magnetoencephalography (MEG) data from twenty patients with epilepsy and twenty healthy controls, constructed the whole functional brain network based on phase lag index (PLI), compared the differences in functional connectivity and network measures between patients with epilepsy and healthy controls, and analyzed the correlation between network measures and the duration of epilepsy.
Results: The patients with epilepsy showed significant increase in mean functional connectivity in the alpha band, gamma band and ripple band, significant increase in mean clustering coefficient in the theta band, beta band and ripple band, significant increase in average shortest path length in the theta band and alpha band. Only in the alpha band, a significant negative correlation between mean clustering coefficient and the duration of epilepsy was detected.
Conclusions: Our results indicated that the alterations of functional brain network are related to a functional imbalance that resulted from epileptic activity and the brain network of patients with epilepsy become more pathological over time.

1. Introduction

Epilepsy is a neurological disorder characterized by recurrent seizure, which affects more than 50 million people worldwide, according to the World Health Organization (Niso et al., 2015). During the seizures there is abnormal excessive firing of neurons in the brain resulting in diverse symptoms such as staring, muscle stiffness, muscle spasms and impaired consciousness (van Mierlo et al., 2014). The gradual process by which a normal neural network changes into a hyperexcitable one leading to epilepsy is known as epileptogenesis. This hyper-excitability depends on the functional features of the cortical neurons and the organization of the neural networks (Niso et al., 2015).

Research in epilepsy has historically focused on the molecular, anatomical and cellular physiological changes involved in its development and in the initiation of seizures (Kramer et al., 2008a; Kramer and Cash, 2012). More recently, evidences have accumulated that interactions between different regions within the complex brain network not only subserve higher cognitive functions but also are of high relevance to cognitive dysfunctions and pathophysiology (Horstmann et al., 2010). Clinical and anatomical findings, together with invasive electroencephalography and functional neuroimaging now provide increasing evidence for the existence of specific cortical and subcortical epileptic networks in the genesis and expression of not only primary generalized and focal onset seizures (Horstmann et al., 2010; Bettus et al., 2008; Gotman, 2008; Luat, 2008).

The brain is increasingly seen as a complex network of dynamic systems with interactions between local and further remote brain regions. Within this framework, a network (or graph) is considered as a set of nodes and edges. Netoff et al. (2004) indicated that changes in brain network topology might play a crucial role in epilepsy. Ponten et al. (2007, 2009) have proved that functional neural network changes during absence seizures and the network become more regularized in weighted and unweighted analyses,

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when compared to the more randomized pre-ictal network configuration. Recently, several studies have proposed that interictal functional brain networks in epilepsy patients may be characterized by increased connectivity, more regular topology, changes in modular structure and prominent hub-like regions (Niso et al., 2015; Horstmann et al., 2010; Bartolomei et al., 2013; Chávez et al., 2003; Clemens, 2008; Douw et al., 2010).

To characterize the brain network, clustering coefficient and average path length are the most commonly used measures in the graph theory analysis. Mean clustering coefficient represents the average probability that any pair of nodes is linked to a third common node by a single edge and thus describes the tendency of nodes to form local clusters. Average path length represents the average shortest distance between two nodes. However, under some circumstances, clustering coefficient and average path length are not enough to fully characterize the brain network. Therefore, for better understanding, some have tried to use new brain network measures. For examples, Wilke et al. (2011) used betweenness centrality, which was found to correlate with the location of the resected cortical regions in patients who were seizure-free after surgical intervention. Hardmeier et al. (2014) used phase lag index (PLI) and weighted phase lag index (wPLI) and found that global PLI/wPLI and topographic connectivity patterns differed between frequency bands, and all individual networks showed a small-world configuration.

In the present study, we hypothesized that (1) the functional connectivities of brain network were altered by the epilepsy; (2) the measures of brain functional network were altered by the epilepsy; (3) functional interactions in the brain were correlated to the duration of epilepsy. Based on these hypothesis, we considered that changes in functional connectivity and brain network measures may be a marker of possible progression of epilepsy. We investigated the hypotheses by constructing brain network with Magnetoencephalography (MEG) data from patients with epilepsy and healthy controls. Based on graph theory analysis, we compared the topological properties of brain network to find the brain network alterations caused by epilepsy. In addition, we assessed the correlation between brain network measures and the duration of epilepsy.

2. Materials and methods

2.1. Subjects

Twenty patients with epilepsy (details of the patients can be obtained from Table 1) and twenty healthy controls (10 male and 10 female, age mean 9.00 ± 5.63) were recruited from the Cincinnati Children's Hospital 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.

Table 1
Clinical data of twenty patients with epilepsy.

ID	Age	Gender	Duration (years)	Focal hemisphere	Focal region
1	7	Female	2	Left	Temporal
2	12	Female	3	Left	Mesial frontal
3	9	Female	5	Both	Temporal
4	10	Male	8	Right	Parieto-central
5	11	Male	9	Right	Temporal
6	16	Female	11	Right	Temporal
7	17	Male	13	Left	Central
8	17	Male	13	Right	Parieto-central
9	7	Male	4	Both	Temporal
10	15	Female	12	Left	Mesial frontal
11	14	Female	11	Right	Parieto-central
12	8	Female	6	Both	Temporal
13	9	Female	2	Left	Mesial frontal
14	15	Male	4	Left	Mesial frontal
15	7	Female	5	Left	Temporal
16	15	Female	9	Both	Mesial frontal
17	13	Male	9	Right	Temporal
18	11	Male	10	Left	Parieto-central
19	12	Female	10	Both	Temporal
20	16	Female	8	Right	Temporal

2.2. MEG recordings

The MEG data were recorded using a whole-head CTF 275-Channel MEG system (VSM Medical Technology Company, Canada) in a magnetically shielded room (MSR). Before the MEG recording, three small coils were attached to the nasion, and the left and right pre-auricular points of each subject. The subject's head positions were measured relative to the MEG sensors for every 2 min block using the three coils. A large head movement during MEG recordings might affect the accuracy of source localization. If head movement during a recording was greater than 5 mm, that dataset was indicated as "bad" and an additional dataset was subsequently recorded. MEG signal was acquired at a sampling rate of 6000 Hz with a noise cancelation of third order gradients. To identify system and environmental noise, we routinely recorded one MEG dataset without patient just before the experiment.

Subjects were asked to lie on a bed, keep their eyes closed and stay still (avoid swallowing or teeth clenching). Continuous MEG recordings were completed in 2 min time blocks and were repeated 20 times for a 40 min total recording. The segments of MEG data with artifacts were designated "bad segments", and were automatically excluded from network analysis in our software package.

2.3. Magnetic resonance imaging (MRI) scans

Anatomical image data were recorded for all patients using 3.0 T magnetic resonance imaging (Siemens, Germany). To facilitate co-registration of MEG data and MRI data, three fiducial points were placed at the same locations as the positions of the three coils used in the MEG recordings before MRI scan for each subject.

2.4. MEG data preprocessing

MEG data were analyzed using FieldTrip (an open source MATLAB software toolbox, http://www.fieldtriptoolbox.org/start) and MEG Processor Software (provided by Jing Xiang, Cincinnati Children's Hospital Medical Center, Ohio, USA). Noticeable noise or artifacts were excluded by visual inspection, similar to previous reports (Xiang et al., 2010, 2014). Then, MRI and MEG data were co-registered by using the identification of three pre-arranged landmarks (left and right pre-auricular points and nasion). All data were filtered with band-pass filters at pre-defined bandwidths of delta (1–4 Hz); theta (4–8 Hz); alpha (8–12 Hz); beta (12–30 Hz); gamma(30–80 Hz); and ripple (80–250 Hz) bands.

2.5. Functional connectivity analysis

First, we introduce the basic terminology and quantities of networks (or graph theory). A network is a way to code a set of elements together with their relations. The elements are defined as nodes (or vertices), and their relations are defined as links (or edges). For example, if nodes represent people in a social network, then links can represent friendships between pairs of people. Mathematically, a network is represented by ordered pairs of set $G(N,l)$