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Electroencephalography based functional networks in newly diagnosed childhood epilepsies

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HIGHLIGHTS

- This is the first study to show that interictal network alterations are already present at an early stage of focal epilepsies and not in generalized epilepsies.
- Network integrity and distribution of hub-nodes are disrupted in focal epilepsy.
- The minimum spanning tree is a new – and more accurate – method to visualize EEG functional networks.

ABSTRACT

Objective: It remains unclear to what extent brain networks are altered at an early stage of epilepsy, which may be important to improve our understanding on the course of network alterations and their association with recurrent seizures and cognitive deficits.
Methods: 89 Drug-naïve children with newly diagnosed focal or generalized epilepsies and 179 controls were included. Brain networks were based on interictal electroencephalography recordings obtained at first consultation. Conventional network metrics and minimum spanning tree (MST) metrics were computed to characterize topological network differences, such integration and segregation and a hub measures (betweenness centrality).
Results: Network alterations between groups were only identified by MST metrics and most pronounced in the delta band, in which a loss of network integration and a significant lower betweenness centrality was found in children with focal epilepsies compared to healthy controls ($p < 0.01$). A reversed group difference was found in the upper alpha band. The network topology in generalized epilepsies was relatively spared.
Conclusions: Interictal network alterations – only identifiable with the MST method – are already present at an early stage of focal epilepsy.
Significance: We argue that these alterations are subtle at the early stage and aggravate later as a result of persisting seizures.

1. Introduction

There is increasing evidence that brain functioning is emerging from a complex interplay of different brain areas, which are organized in a highly efficient manner (Bullmore and Sporns, 2012). A balance between network integration and segregation in combination with the existence of highly interconnected brain areas (so-called 'hubs') are needed to support this normal brain functioning (Stam, 2014).

This balanced network organization of the brain is disturbed in epilepsy (Richardson, 2012; Engel et al., 2013; van Diessen et al., 2013a). Studies have previously shown that network alterations in epilepsy may aggravate with a longer duration of the disease (van Dellen et al., 2009; Liao et al., 2010) eventually resulting in a loss of network integrity that could – at least – partly explain

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the associated behavioral and cognitive deficits in patients (Vlooswijk et al., 2011; Vaessen et al., 2014). As these studies have typically focused on patients with chronic epilepsies, it remains unclear how these networks are altered at an early stage of the disease. This information may be important to improve our understanding on the course of network alterations in epilepsy and their association with recurrent seizures and cognitive deficits.

In this study we investigated to what extent functional network alterations already exist at an early stage of the disease. To avoid possible confounding effects of antiepileptic drugs or recurrent seizures on the construction of functional networks – derived from interictal electroencephalography (EEG) recordings – we focused on a patient cohort of newly diagnosed childhood epilepsies. A second aim of the study was to investigate how focal and generalized epilepsies differ from each other in term of functional network organization. The tendency to generate focal or (primary) generalized seizures may reflect a distinct underlying mechanism (Berg and Scheffer, 2011; Stefan and Lopes da Silva, 2013). Whereas generalized seizures are characterized as fast and diffuse spreading activity in bilateral distributed networks (Meeren et al., 2005) focal seizures are associated with unilateral networks that spread beyond the isolated epileptogenic region (Gotman, 2008).

Conventional network metrics include average (shortest) path length, a measure of integration, and average clustering coefficient, a measure of segregation. These were computed to characterize global network organization (Rubinov and Sporns, 2010). Considering age-related changes in network density (Smit et al., 2012) and its possible influence on the computation of conventional network metrics (van Wijk et al., 2010; Fornito et al., 2013) we also constructed the minimum spanning tree (MST) of the network (Stam et al., 2014). The MST is a relatively new method that is increasingly used to construct brain networks, as it represents a stable network core of the original network and allows an unbiased comparison of networks with a different density. In addition
to global network properties, we were interested if the connectivity of highly interconnected nodes were altered in newly diagnosed epilepsies, as was previously revealed in chronic epilepsies (Wilke et al., 2011; Varotto et al., 2012; van Diessen et al., 2013b).

2. Methods

2.1. Patient selection

We included children who visited the outpatient First Seizure Clinic of the University Medical Center Utrecht between January 2008 and May 2013 after one or more suspected epileptic event (s) and had an EEG recording of sufficient quality for the construction of networks (see Section 2.2). Definitive diagnosis of epilepsy was based on ancillary investigations and clinical follow-up. We selected three groups: (1) children who were diagnosed with focal epilepsy; (2) children who were diagnosed with generalized epilepsy and (3) a control group of children in whom the diagnosis of epilepsy was excluded, based on clinical history, EEG report, and at least one year of uneventful follow up. None of the children were taking antiepileptic medication at time of EEG recording. The institutional ethical committee approved the study and concluded that the Dutch Medical Research Involving Human Subjects Act did not apply, and written informed consent was not required.

2.2. Data acquisition and selection

The EEG was recorded at 21 scalp electrodes according to the international 10–20 system (SystemPlus Evolution, Micromed). Impedance of each electrode was kept below 5 kΩ. Data was high- and low-pass filtered at 0.5 and 70 Hz, respectively. The sampling frequency was 512 Hz. Frontoparietal and basal temporal electrodes were excluded (Fp1, Fp2, A1, and A2) from further analyses as these channels are particularly vulnerable to myogenic artifacts that could influence the computation of the functional connectivity and the subsequent construction of functional networks (Douw et al., 2010; van Diessen et al., 2014a). For each patient, the first four artifact-free epochs of 4096 samples (8 s) were selected by on the authors [EvD] and independently re-inspected by a clinical epileptologist [FEJ] on artifacts and epileptiform abnormalities. Before calculating functional connectivity and network metrics, epochs were band-pass filtered into the commonly used frequency bands delta (0.5–4 Hz), theta (4–8 Hz), lower alpha (8–10 Hz), upper alpha (10–13 Hz) and beta (13–30 Hz). The relative spectral power was computed and averaged over all channels, epochs and subjects separately for each group. This was obtained by converting the raw EEG recordings from the time domain into the frequency domain with a fast Fourier transformation with a frequency resolution of 1/8 s = 0.125 Hz. All further analyses were performed for these bands separately. Data acquisition and analyses followed a recent published practical guideline (van Diessen et al., 2015) and were performed in BrainWave [version 0.9.116, authored by CJS, http://home.kpn.nl/stam7883/brainwave.html].

2.3. Functional connectivity

Functional networks were constructed per epoch, based on functional connectivity between each electrode time series' pair. Functional connectivity was quantified between 0 and 1 with the phase lag index (PLI). PLI is a measure of the asymmetry of the distribution of instantaneous phase differences between two time-series. A PLI of 0 indicates no phase coupling between time-series, or coupling with a phase difference centered on $0 \pm \pi$ radians. A PLI >0 indicates the presence of phase coupling. A more mathematical description of computing the PLI can be found elsewhere (Stam et al., 2007).

2.4. Network analytical approach

Network construction for each epoch, we constructed a weighted undirected network, described by the graph $G = (N, W)$, where N is the set of all 17 EEG electrodes and $W = w_{ij}$ is the $N \times N$ symmetric weight matrix, where $w_{ii} = 0$ and w_{ij} the PLI determined between node i and j.

Conventional network metrics two metrics were used to describe global network properties, namely the average clustering coefficient and the average shortest path length. The average clustering coefficient is a global measure of network segregation and reflects the clustered connections around individual network nodes. We computed the weighted clustering coefficient similar to (Stam et al., 2009), and included the PLI as weight for the coupling strength between nodes. The shortest path length is the minimal number of edges that must be traversed to travel from one network node to another. The average path length, a global measure of network integration, is this average minimal number of edges of all possible node connections. The weighted average path length is found by minimizing the sum of weights (that is, PLI coupling strength) assigned to the edges on their path, using Dijkstra's algorithm (Dijkstra, 1959) To reduce the effect of network density, both conventional network metrics were normalized using 50 surrogate networks. This number was sufficient to result in stable surrogate network properties.