NeuroImage: Clinical 17 (2018) 739–750

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Identifying neural drivers of benign childhood epilepsy with centrotemporal spikes

Azeez Adebimpe[a,*], Emilie Bourel-Ponchel[a,b], Fabrice Wallois[a,b]

[a] INSERM UMR 1105, Research Group on Multimodal Analysis of Brain Function, University of Picardy Jules Verne, 80036 Amiens Cedex, France
[b] INSERM UMR 1105, EFSN pediatric, Amiens University Hospital, Avenue Laennec, 80054 Amiens Cedex, France

ARTICLE INFO

Keywords:
Benign childhood epilepsy
EEG
Dynamic causal modelling
Interictal activity

ABSTRACT

Epilepsy is a neurological disorder characterized by abnormal electrical discharges in a group of brain cells. Benign childhood epilepsy, which affect children under the age of 12 years, has been reported to contribute to the cognitive impairment of these children, even in the absence of structural abnormalities. Functional connectivity models have been applied to provide a deeper understanding of the processes that control and regulate interictal activity of benign childhood epilepsy. These studies have shown regions of increased connectivity and activity, particularly at the epileptic zone, which is usually the central region around the sensorimotor cortex, and in the immediate regions surrounding the zone and reduced activity in distant regions, such as the frontal lobe and temporal regions. The present study was designed to identify the neural drivers involved in the initiation and propagation of epileptic activity and the causal relationships between brain regions with increased and decreased connectivity and functional activity. We used three different models to identify neural drivers and casual connectivity with dynamic causal modelling (DCM) of EEG data. All models showed that the central region, the source of the epileptic activity, is the major driver of the brain network during interictal discharges. Other regions include the temporoparietal junction and temporal pole. The central region also had influence on the frontal and contralateral hemisphere, which might explain the cognitive deficits observed in these patients.

1. Introduction

Benign childhood epilepsy (BCE) affects 10 to 20% of children with epilepsy (Camfield et al., 2014; Panayiotopoulos, 1999a, 1999b). The risk of cognitive impairment is higher when comparing the cognitive performance of children with BCE with that of healthy children (Danielsson and Petermann, 2009; Datta et al., 2013a, 2013b). Unlike adult epilepsy, such as temporal lobe epilepsy, the brain structure of BCE patients is usually normal (Fountain, 2008). However, epileptic activity can cause various malfunctions between subcortical and cortical regions that may lead to changes not only in resting state activity (Adebimpe et al., 2015a), but also in cognitive performance (Van Bogaert et al., 2012; van Rijckevorsel, 2006; Vingerhoets, 2006). The most common form of BCE is benign childhood epilepsy with central temporal spikes (BCECTS), other type of BCE include benign rolandic epilepsy and Panayiotopoulos syndrome (Panayiotopoulos, 1999a, 1999b). EEG is the essential diagnostic tool for BCE. The appearance of infrequent seizures or focal activity of EEG with biphasic or triphasic interictal epileptic spikes (IES) in rolandic or central brain regions is highly suggestive of benign childhood epilepsy (Bourel-Ponchel, 2013). Further analyses, including normal neurological examination and spike source imaging on high-resolution electroencephalography (HR EEG) with an anteroposterior dipole orientation, confirm the diagnosis of BCECTS (Camfield and Camfield, 2002; Panayiotopoulos, 2005).

BCECTS generally resolves by adulthood, regardless of the frequency of seizures and centrotemporal spikes (CTS), but there are concerns that BCECTS may alter both structural and functional brain properties, as the period during which CTS occur corresponds to the period of rapid brain development (Chugani et al., 1996), as demonstrated by microstructural changes of white and grey matter in the epileptic zone (Kim et al., 2014) and disturbances of grey matter growth in frontal and insular regions (Kanemura and Aihara, 2009; Pardoe et al., 2013). It should be noted that these regions are involved in language and attention processing. Other studies have reported reduced structural and functional connectivity activities, which might delay structural and functional brain development (Besseling et al., 2013a; Kim et al., 2014). Children with BCECTS are reported to perform poorly compared to healthy controls, especially in visuospatial and verbal fluency tests, language and hearing (Besseling et al., 2013b), memory (Lopes et al., 2014) and behavioural problems, such as more

* Corresponding author.
E-mail address: adebimpe@upenn.edu (A. Adebimpe).

https://doi.org/10.1016/j.nicl.2017.11.024
Received 10 August 2017; Received in revised form 23 October 2017; Accepted 30 November 2017
Available online 05 December 2017

Table 1
Patient's clinical characteristics.

patient number	Age (years)	Neuropsychological data	Seizure free	Interictal EEG	Treatment at time of HD EEG
1	12.63	Normal	No	Unilateral IES	Valproate sodium
2	12.64	Normal	Yes	Unilateral IES	Valproate sodium
3	9.25	Attention deficit	No	Unilateral IES	Oxcarbazepine
4	6.03	Normal	No	Unilateral IES	Oxcarbazepine
5	10.47	Attention deficit	Yes	Unilateral IES	Valproate sodium
6	7.16	Normal	Yes	Unilateral IES	Valproate sodium
7	8.51	Attention deficit	Yes	Unilateral IES	No
8	13.16	Normal	Yes	Bilateral[a] independent IES	Valproate sodium
9	9.67	Language Deficit	Yes	Unilateral IES	Lamotrigine
10	7.79	Language deficit	Yes	Unilateral IES	Oxcarbazepine
11	8.2	Normal	Yes	Bilateral[a] independent IES	No
12	7.1	Attention deficit	Yes	Unilateral IES	Valproate sodium

[a] Bilateral: patients with bilateral IES occurring independently from one to the other hemisphere.

aggressive behaviour, social problems, depression and attention deficits (Dunn, 2014; Pąchalska et al., 2012). Antiepileptic drugs (AEDs) might reduce CTS by suppressing the amplitude of the spikes, but some studies have indicated that some AEDs might worsen language and cognitive functions, raising a concern about the trade-off of benefits and risks related to AEDs (Camfield and Camfield, 2002; Park and Kwon, 2008). A few studies have reported that some deficits can persist throughout adulthood, even when the patients no longer experience BCECTS (Camfield and Camfield, 2002). Considering these altered functional properties, EEG studies on BCECTS have reported that patients present increased delta and theta power and increased synchronization, which can be related to the disorganization of electrical activity related to epileptic activities occurring during brain development (Adebimpe et al., 2015a, 2015b).

A large number of studies have tried to assess the functional connectivity pattern of BCECTS, especially in comparison with healthy controls (Adebimpe et al., 2016; Adebimpe et al., 2015b; Besseling et al., 2013b). The brain network of these patients has been reported to be disrupted. In particular, reduced connectivity in the default mode network, increased functional connectivity in the sensorimotor region and abnormal functional connectivity between language network and frontal regions have been reported (Adebimpe et al., 2015b; Clemens, 2004; Clemens et al., 2016; Oser et al., 2014). EEG functional connectivity studies have also reported higher theta synchronization, notably during epileptic activity and decreased alpha and beta functional connectivity in the occipital regions (Adebimpe et al., 2015b; Clemens et al., 2016). However, a better understanding of the directionality of connectivity is essential to determine whether epileptic regions have a direct or indirect influence on other distant regions, especially those related to language and cognitive networks.

To study these aspects, the dynamic causal modelling (DCM) (Kiebel et al., 2008) was applied as a measure of effective connectivity, to accurately track and quantify CTS dynamics and its impact on certain selected regions of interest (ROI). Dynamic causal modelling (DCM) is an established procedure for the analysis of both functional magnetic resonance imaging (fMRI) and electrophysiological recordings (Friston et al., 2003) and provides a generative spatiotemporal model for EEG and MEG responses with dynamic input and output (David et al., 2006). DCM is a Bayesian model scheme with competing hypotheses that identifies directional connectivity patterns and connection strengths of neuronal activity. DCM has been used to study neural drivers and to identify epileptic foci of IES with both EEG/MEG and fMRI; and with simultaneous EEG-fMRI recordings (Murta et al., 2012). More specifically, it has been used to study the seizure activity with EEG and ECOG (Cooray et al., 2016; Papadopoulou et al., 2017).

The primary objective of this study using DCM on scalp HR EEG data was to investigate the main neural drivers and causal relationships or coupling between identified interictal epileptic region of BCECTS patients and other distant ROI that have been reported to be affected by the presence of IES by previous studies from our laboratory (Adebimpe et al., 2015a, 2015b; Bourel-Ponchel et al., 2017) and the literature (Clemens, 2004; Clemens et al., 2010; Yeom et al., 2014).

2. Methods

2.1. Data

This study was conducted in 12 BCECTS patients (age: 9.38 ± 2.39 years, 5 females) with right centrotemporal spikes. All patients had IES in the right hemisphere. Patient selection was based on criteria concerning common source location at the central region, anteroposterior dipole orientation (Camfield and Camfield, 2002), similar interictal epileptic patterns and no evidence of any structural brain damage based on magnetic resonance imaging (MRI). BCECTS was diagnosed on the basis of a typical clinical history and the presence of characteristic IES on standard EEG, according to ILAE criteria (Berg et al., 2010). Clinical diagnostic criteria of BCECTS included children presenting sensorimotor seizures with inconsistent secondary generalization, with an age of onset between 4 and 10 years (Beaumanoir et al., 1974) and typical diphasic spikes either isolated or occurring in clusters, unilaterally or bilaterally, in the centro-temporal areas on a standard normal background EEG (Beaumanoir et al., 1974). Patients with an abnormal neonatal history, intellectual deficit (IQ < 70), neurological abnormalities on physical examination, and/or any lesions in brain neuroimaging were not included in the study.

To define a homogeneous sample of patients for both single subject and group analyses, twelve patients with right centro-temporal spikes have been selected. This includes two patients with bilateral IES occurring independently from one to the other hemisphere. Table 1 lists the patient's clinical characteristics. Fig. 1 provides the EEG sample of one patients.

2.2. Ethical considerations

The study was approved by the local ethics committee (CPP Nord-Ouest No. A00782-39) Written informed consent to participate in the study was obtained from the parents and all patients before inclusion.

2.3. EEG recordings and pre-processing

All patients underwent at least a 14-minute 64-channel EEG recording (ANT, Netherlands) with electrodes placed on the scalp in accordance with the international 10-10 system (EasyCap®) at 512 Hz sampling rate. Only a notch filter (50 Hz) was applied. A mastoid reference was used for acquisition. HD EEG recordings were performed during quiet arousal. The electrode impedances were kept below 5 kΩ. The signals were re-referenced to an average reference for further analysis. Patients were monitored for movements during acquisition to