Epilepsy Research 116 (2015) 79–85

Contents lists available at www.sciencedirect.com

Epilepsy Research

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

Regional homogeneity (ReHo) changes in new onset versus chronic benign epilepsy of childhood with centrotemporal spikes (BECTS): A resting state fMRI study

Hongwu Zeng[a,b], Camille Garcia Ramos[c], Veena A. Nair[b], Yan Hu[d], Jianxiang Liao[d], Christian La[b,e], Li Chen[d], Yungen Gan[a], Feiqiu Wen[d,**], Bruce Hermann[f], Vivek Prabhakaran[b,c,e,f,*]

[a] Department of Radiology, Shenzhen Children's Hospital, Guangdong, China
[b] Department of Radiology, University of Wisconsin, Madison, USA
[c] Department of Medical Physics, University of Wisconsin, Madison, USA
[d] Department of Neurology, Shenzhen Children's Hospital, Guangdong, China
[e] Neurosciences Training Program, University of Wisconsin, Madison, USA
[f] Department of Neurology, University of Wisconsin, Madison, USA

ARTICLE INFO

Article history:
Received 28 January 2015
Received in revised form 11 June 2015
Accepted 23 June 2015
Available online 10 July 2015

Keywords:
Epilepsy
fMRI
Regional homogeneity
Resting state
BECTS
Pediatric

ABSTRACT

Objective: The purpose of this study was to investigate regional homogeneity (ReHo) in children with new-onset drug-naïve Benign Epilepsy with Centrotemporal Spikes (BECTS), chronic BECTS and healthy controls (HC) using the Regional Homogeneity (ReHo) method applied to resting state fMRI data.
Methods: Resting state fMRI data was collected from three groups of children aged 6–13, including new onset drug naïve BECTS, chronic BECTS with medication, and HC; the data analyzed by ReHo method. Mandarin school exams scores were acquired and compared across groups.
Results: There were three main findings. Firstly, compared with HC, abnormally increased ReHo was observed in bilateral sensorimotor regions in new onset BECTS which normalized or even reversed in the chronic BECTS group. Secondly, enhanced ReHo was found in the left frontal language region in the two BECTS groups, with even higher ReHo value in the chronic group. Lastly, decreased ReHo was found in regions of the default mode network (DMN), bilateral occipital lobes and cerebellum in both the new onset and chronic BECTS groups, lower in chronic BECTS. Behavioral analyses of school scores showed the chronic BECTS group presented significantly lower scores compared to HC ($p < .05$).
Significance: The coherence of low frequency fluctuations is disrupted in sensorimotor, language and DMN-related regions in new-onset BECTS. Some of these effects seem to be selectively normalized in chronic BECTS, thus allowing us to explore possible chronicity and AED-induced effects on BECTS. Abnormal ReHo in left language and DMN regions could be responsible for impairments of cognitive function.
Published by Elsevier B.V.

1. Introduction

Benign epilepsy of childhood with centrotemporal spikes (BECTS) is characterized by abnormal nocturnal epileptiform spike activity originating in the rolandic or sensorimotor cortex, without a significant lesion, typically observed in children between 7 and 10 years of age. Although seizure prognosis is good in children with BECTS, growing evidence suggests that BECTS is associated with abnormalities in cognition, specifically language and language dependent abilities, IQ, visuomotor abilities, and reading disorders/dyslexia (Nicolai et al., 2006).

Changes in task-related functional activation patterns, alterations in functional connectivity patterns, and structural brain volumes have been reported in both chronic and new-onset pediatric epilepsies (Bonilha et al., 2014; Datta et al., 2013; Lillywhite et al., 2009; Pardoe et al., 2013). Additionally, functional neuroimaging studies have reported that blood oxygenation level dependent (BOLD) fMRI activity is influenced by epileptiform

* Corresponding author at: UW-Madison, WI, USA.
** Corresponding author at: Department of Neurology, Shenzhen Children's Hospital, Shenzhen, Guangdong, China.
E-mail addresses: homerzeng@126.com (H. Zeng), camille.garcia23@gmail.com (C.G. Ramos), vnair@uwhealth.org (V.A. Nair), 2680224170@qq.com (Y. Hu), liaojianxiang@vip.sina.com (J. Liao), cla.wisc@gmail.com (C. La), chenli2000@126.com (L. Chen), ganyungen@yahoo.com (Y. Gan), fwen62@126.com (F. Wen), hermann@neurology.wisc.edu (B. Hermann), VPrabhakaran@uwhealth.org (V. Prabhakaran).

http://dx.doi.org/10.1016/j.eplepsyres.2015.06.017
0920-1211/Published by Elsevier B.V.

Table 1
Clinical data.

Group	Enrolled participants					Number of subjects for whom final results are reported (after excluding for scanner motion)				
	N	Gender (M/F)	Age (m ± std/y)	Age at onset	School Grade	*N*	Gender (M/F)	Age (m ± std/y)	Age at onset	School Grade
BECTS New onset	24	15/9	8.9 ± 2.1	8.7 ± 2.06	2.8 ± 1.7	16	9/7	9.2 ± 2.2	8.9 ± 2.27	2.9 ± 1.8
BECTS Chronic	30	22/8	10.9 ± 1.9	7.8 ± 2.32	3.9 ± 1.7	17	13/4	11.1 ± 2.1	7.7 ± 2.78	4.2 ± 1.7
HC	30	17/13	10.2 ± 1.8			18	11/7	10.5 ± 1.7		

activity (Detre, 2006; Mankinen et al., 2011; Salek-Haddadi et al., 2006). There is sparse but growing evidence that BECTS is also characterized by alterations in functional connectivity (Besseling et al., 2013; Oser et al., 2014). However, all studies to date have examined children with chronic BECTS with or without antiepileptic treatment, thus confounding seizure frequency and severity, chronicity, and cumulative medication exposure which could affect brain activation and network connectivity patterns in neuroimaging studies (Datta et al., 2013; Lillywhite et al., 2009).

Our objective in this study was to investigate alterations in brain connectivity patterns comparing new-*onset drug-naïve* children with BECTS to children with chronic BECTS treated with antiepilepsy drugs (AEDs) and healthy controls (HC). As children with BECTS have been reported to have a significantly increased history of need of language-based services antecedent to seizure onset and diagnosis, it is possible that brain connectivity patterns may be abnormal at the time of seizure onset and diagnosis, and may further evolve over time with chronicity of epilepsy and treatment with AEDs. To address these issues we focused on resting state functional connectivity using a novel measure known as regional homogeneity.

Functional connectivity is defined as the temporal correlation or synchronization of low frequency oscillations between anatomically separate brain regions (Biswal et al., 1995; Constable et al., 2013; Friston, 2011; Negishi et al., 2011). Resting state functional connectivity is increasingly recognized as a useful tool to investigate brain connectivity patterns in patients as no exogenous task demands are made on the subject. This is particularly useful in young children who may or may not comprehend a task well enough to perform reliably in the scanner.

Regional homogeneity (ReHo) analysis evaluates the degree of synchronization between the time-series of a voxel and its neighboring voxels (Liu et al., 2010; Zang et al., 2004) and can be computed from a five minute 'resting-state' functional MRI scan when the children are lying in the scanner with eyes closed or fixating on a plus sign. It requires no a priori definition of regions of interest and provides information about the local activity of regions throughout the brain. It is a data-driven method and has been widely used in the literature to characterize changes in the functional integrity of brain regions with aging and disease (Mankinen et al., 2011; Paakki et al., 2010; Wu et al., 2007; You et al., 2011). We have previously used this technique in a study with adult epilepsy patients and found increased ReHo in a network of regions that may be responsible for seizure genesis and propagation (Zeng et al., 2013).

In the current study we applied this technique to children with new-onset drug-naïve BECTS, children with chronic BECTS on AEDs, and healthy controls. We applied the ReHo method to resting state fMRI data to characterize differences among these groups to provide information regarding the natural history of alterations in brain connectivity patterns.

2. Methods

2.1. Participants

Participants were 84 children, aged 8–12, including 24 children with new-onset drug naïve BECTS, 30 with chronic BECTS, and 30 healthy controls (HC). Children with BECTS were recruited from the Shenzhen Children's Hospital, Guangdong, China and met the following inclusion criteria: (1) EEG showing classic centrotemporal spikes arising from a normal background, (2) clinical history of at least one seizure that was consistent with the diagnosis of BECTS, and (3) no other clinically diagnosed neurologic disorder. Exclusion criteria were: (1) epilepsy other than BECTS, (2) any parenchymal pathology, for example, pathologic abnormality revealed by magnetic resonance imaging (MRI); and (3) other accompanying neurological disorders such as cerebral palsy, brain tumor, or neurometabolic diseases. Table 1 provides demographics for the three groups of children. All children were diagnosed by the attending pediatric neurologist and all were native Mandarin speakers.

The HC were recruited via local primary schools and hospital staff. All controls had acquired Mandarin as their first language and were screened for medical and developmental disorders and had normal structural MRI at the time of recruitment. Middle and final semester Mandarin exam scores (an academic achievement test considered related to language ability, in which lower scores represent lower language ability) for each participant was recorded (Total raw score = 100) and the means per group were calculated. This study was approved by Institutional Review Board of both Shenzhen Children's Hospital and University of Wisconsin-Madison. Written informed assent (from the child) and consent (from the parents) was obtained for each participant.

One way ANOVAs showed statistically significant differences in age represented in Table 1 between new onset BECTS and chronic BECTS group ($p = 0.009$) as well as a trend toward significant difference between new onset BECTS and HC ($p = 0.056$). No statistically significant difference in age was noted between chronic BECTS and HC ($p = 0.41$). There is no significant difference in age of onset between the new onset and chronic BECTS groups ($p = 0.17$, $t = 1.407$).

2.1.1. Medication usage

10 of 17 chronic BECTS took single anti-epileptic drugs (Lamotrigine, $n = 3$; Oxcarbazepine, $n = 4$; levetiracetam, $n = 2$; Depakene, $n = 1$), 2 of the 17 were switched from one drug to another (one from Tegretol to Topiramate, the other from Lamotrigine to Oxcarbazepine). The remaining 5 patients took multiple (2–3) antiepileptic drugs. The average medication period was 2.73 ± 1.76 years.