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Enhanced EEG connectivity in children with febrile seizures

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Summary
Background: Epilepsy is currently conceptualized as a disturbance of neuronal networks with altered connectivity that persists into the interictal phase. Febrile seizures are sometimes a precursor in childhood of lifelong epilepsy. We investigated whether studying functional connectivity in children with febrile seizures could help understand the mechanisms underlying their long-term seizure susceptibility.
Methods: EEG was recorded during rest and intermittent photic stimulation (IPS) in 12 FS patients, 5 siblings and 15 control children between 6 and 36 months of age. Original EEG data were transformed into source space using a multiple regional source model. Source coherence values were calculated for the interfrontal, interoccipital and occipito-frontal connections for the delta, theta, alpha, beta and gamma frequency bands.
Results: Our results suggest enhanced delta and theta frequency EEG source coherence in patients with FSs compared to siblings and control children, both under resting conditions and during IPS, more consistent for the theta band and the occipito-frontal connections.
Conclusions: Enhanced connectivity in patients with FSs could indicate a seizure-prone state and interfere with the maturation of cerebral networks. Further prospective studies are needed to assess whether hyperconnectivity is a risk factor for epileptogenesis and neurodevelopmental disorders.

Abbreviations: FH, family history; FSs, febrile seizures; IGE, idiopathic generalized epilepsy; IPS, intermittent photic stimulation; LORETA, low resolution electromagnetic tomography; SSVEP, steady-state visual evoked potentials.

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Introduction

Febrile seizures (FSs) are the most prevalent type of seizures occurring in 2—5% of children under the age of six years (Verity et al., 1985). While the prognosis is excellent in most of the cases, up to 7% will develop epilepsy by the age of 25 years (Annegers et al., 1987). Moreover, a significant proportion of these children will develop cognitive impairments (Lippe et al., 2009; Verity et al., 1993). Despite the identification of some clinical and genetic risk factors for later epilepsy (Annegers et al., 1987; Birca et al., 2005; Guerrini et al., 2010; Verity et al., 1993), the neural mechanisms underlying seizure liability and potentially affecting cognitive development in patients with FSs are still a matter of debate.

Advances in functional brain imaging have allowed the conceptualisation of the epileptic process as a disturbance of neuronal networks (Laufs, 2012). Abnormal interactions between large populations of neurons have been described during the ictal, but also interictal phase. Thus, increased EEG activity in the delta, theta and gamma frequency bands has been reported in patients with generalized epilepsy (Clemens, 2004; Willoughby et al., 2003). In accordance with these data, our previous studies have shown increased gamma activity evoked by intermittent photic stimulation (IPS) in children with FSs (Birca et al., 2008) and increased delta synchronization in those with atypical FSs (Lippe et al., 2009). Recent functional MRI and quantitative EEG studies have also reported functional brain connectivity alterations, with a differential involvement of the anterior and posterior cortical networks during the interictal phase in patients with idiopathic generalized epilepsy (IGE) and photosensitive epilepsy (Clemens et al., 2011, 2013b; Douw et al., 2010; Maneshi et al., 2012; Varotto et al., 2012). These interictal abnormalities have been suggested to be a sensitive predictor of epilepsy in patients presenting with the first lifetime seizure (Douw et al., 2010) and to interfere with the functioning of the attentional networks in IGE (Maneshi et al., 2012). Hence, studying functional connectivity in FSs could bring new insights into the mechanisms of epileptogenesis and associated neurodevelopmental disorders.

The aim of this study was to investigate the functional connectivity profiles within different frequency bands (delta, theta, alpha, beta and gamma) in patients with FSs compared to age-matched control children and siblings of patients with FSs. More specifically, we used an EEG source coherence model to estimate the intrahemispheric fronto-occipital and interhemispheric interfrontal and interoccipital connectivity patterns during resting state and intermittent photic stimulation (IPS), a functional test applied routinely in clinical electroencephalography to enhance or induce abnormal findings in epileptic patients.

Methods

Subjects

The population included in the study was identical to a previously published article (Birca et al., 2008) and was constituted of twelve patients with FSs, five siblings of FSs patients and fifteen control children between 6 and 36 months of age (see Table 1). To match the age of children with FSs, the subjects termed ''siblings'' were drawn from the brothers and sisters of older or younger patients with FSs, who were not included in this study. Inclusion was based on the following criteria: an uneventful perinatal period, no previously known neurologic disorders except episodes of FSs in the patient group and no deviation with regard to mental and physical development. In addition, in control children, there was no evidence of any family history (FH) of convulsions or epilepsy. No participants were taking any form of medication at the time of testing. All participants were evaluated by a neuropsychologist, and performance scores evaluated according to the Bayley Scale of Infant Development did not show group differences (Bayley, 1993).

Table 1 Demographic data and FSs characteristics.

Control children (*N*)	15
Female gender (*N*/%)	7/47%
Mean age (months/SD)	21.1/9.8
Siblings (*N*)	5
Female gender (*N*/%)	3/60%
Mean age (months/SD)	17.6/4.8
Positive FH of epilepsy (*N*/%)	0/0%
FS patients (*N*)	12
Female gender (*N*/%)	6/50%
Mean age (months/SD)	20.3/9.3
Positive FH of FSs (*N*/%)	9/75%
Positive FH of epilepsy (*N*/%)	3/25%
Time since the last FS episode (months/range)	6.5/1—26
FS characteristics	
Recurrent (*N*/%)	8/67%
Prolonged (*N*/%)	6/50%
Multiple (*N*/%)	5/42%
Focal (*N*/%)	0/0%
Atypical (*N*/%)	10/83%

Table 1 depicts demographic characteristics for participants and FSs description for patients. A positive family history of either FSs or epilepsy was defined as at least one first or second-degree relative being affected. We considered as atypical, FSs with at least one of the following features: more than 15 min duration (prolonged FSs), multiple episodes of seizures per 24 h of fever (multiple FSs) and evidence of focal onset or Todd's postictal paresis (focal FSs). Children who had at least one FS occurring more than 24 h after the initial FS were considered as having had recurrent FSs. This never occurred during the same febrile illness.

This study was approved by the CHU Sainte-Justine Ethics Committee for Human Experimentation. Informed consent was obtained from the parents of all participants.

Procedure

The EEG data were collected while the subjects were alert, with their eyes opened, and quietly sitting in an easy chair