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Children with a history of atypical febrile seizures show abnormal steady state visual evoked potential brain responses

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ABSTRACT

Atypical febrile seizures (FSs) are considered a risk factor for the onset of epilepsy in later life as well as for potential cognitive impairment. However, distinctive characteristics defining the group of children at risk for negative outcomes are not well established. In the following study, children from 6 to 59 months with a history of atypical FSs were investigated using steady state visual evoked potentials (ssVEP), a brain response known to increase with age. Abnormally, low theta and alpha ssVEP brain responses were found in children with a history of atypical FSs.

1. Introduction

Febrile seizures (FSs) are the predominant cause of convulsions in children between 6 months and 5 years of age, affecting 2 to 3% of children [1]. Atypical FSs, characterized by prolonged, repetitive and/or lateralized seizures, occur in roughly 20% of these children [1,2]. Furthermore, children presenting with a history of atypical FSs show greater risk for the onset of epilepsy in later life as well as increased risk for cognitive impairments marked by global developmental delays [3–8]. Although the neuronal mechanisms potentially underlying the risk for epilepsy onset in later life have been investigated, those potentially underlying cognitive impairments in children presenting with atypical FSs have not been well established. In the present study, the low-frequency electrophysiological signal of the steady state visual evoked potentials was used to investigate possible brain activity alterations in children presenting with atypical FSs.

Steady state visual evoked potential (ssVEP) is a method used to test the oscillatory capability of the neuronal networks involved in visual information processing. Alpha and theta range ssVEPs are often used to assess cognitive processes [9–11]. These low-frequency ssVEPs have been extensively studied in clinical populations such as that with schizophrenia, for which smaller ssVEP amplitudes are observed [12,13]. It is hypothesized that this result comes from the inability of the visual neural circuits to synchronize to periodic external stimuli, reflecting abnormal brain responses.

Intermittent photic stimulation (IPS) is a widely used routine EEG test that elicits steady state visual evoked potentials (ssVEPs). Intermittent photic stimulation-induced ssVEPs demonstrate an age-related maturation to adulthood [14–16]. Steady state visual evoked potential studies can shed light onto the mechanisms of imbalance between excitation and inhibition that leads to hyperexcitability in patients with epilepsy [17]. The mechanisms of abnormal contrast gain control were addressed in idiopathic generalized epilepsies, which showed an absence of saturation in the response gain, further supportive of decreased inhibitory control in patients with epilepsy [18]. In the search for potential underlying mechanisms as risk factors for future epilepsy onset in children with FSs, previous studies, including our own data, have focused on gamma (40–120 Hz) activity since gamma oscillations have been shown to precede epileptic discharges. Higher gamma power has been observed in patients with epilepsy during resting state conditions [19]. In children with FSs, we have shown greater magnitude and phase alignment values of IPS-elicited gamma frequency ssVEP components [21]. These increases may be a signature of neuronal excitability.

Since low-frequency ssVEPs (in the range of theta and alpha band frequencies) have been shown to be abnormal in brain diseases associated with cognitive impairments, we aimed to investigate ssVEP responses elicited by low-frequency IPS (5, 7.5, 10, and 12.5 Hz) in

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children with atypical FSs (6 to 59 months of age) and age-matched controls. We hypothesize that children presenting with FSs show less ssVEP phase alignment values compared with controls. We decided to use phase alignment values rather than magnitude measures as the former are not influenced by the individual tissue conductibility properties that change with age. In addition, we used age-appropriate cognitive batteries to investigate cognitive development.

2. Materials and methods

2.1. Subjects

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

Twenty-one patients with atypical FSs followed at the Sainte-Justine Hospital and 26 age-matched controls were included in this study (Tables 1 and 2). They were separated into two age groups of about 25 individuals: (1) 6–34 months of age and (2) 37–59 months of age. Inclusion was based on the following criteria: an uneventful perinatal period, no obvious somatic disease, no previously known neurological disorders except atypical FS episodes in the patient group and no deviation with regard to mental and physical development. Most patients showed between one and five seizures. The median of the number of seizures is two for both groups. The time distance at testing from the FS event was significantly longer for the older atypical FS group ($t = -3.56$, $p = 0.003$). Participants were not taking any form of medication at the time of testing. Additionally, in control children, there was no evidence of any family history of convulsions or epilepsy as extensively discussed with parents via detailed in-house questionnaires. More precisely, parents reported the family history of their first- and second-degree relatives. There was no significant age difference between the atypical FS and control groups.

We considered as atypical FS events those with at least one of the following features: prolonged duration (>15 min), multiple episodes of seizures per 24 h of fever, evidence of focal onset or Todd's postictal paresis. Atypical FS characteristics are described in Tables 1 and 2.

2.2. Procedure

Each participant came to the laboratory during the morning hours for a visit lasting about 2 h. The EEG data were collected while the subjects were alert and quietly sitting in a chair next to their parents in a sound-proof, electrically shielded, and dimly lit room. Electroencephalography was recorded during intermittent photic stimulation (IPS) that consisted of white flickers at 5, 7.5, 10, and 12.5 flashes/s with a flash energy of 0.7 J, which were given in a random order for 30 s, three–four times for each frequency, with an interval of at least 10 s between the flash periods. Stimulation was delivered by a photostimulator and a stroboscopic lamp (Astro-Med, Inc.), placed 30 cm from the subject's eyelids, and triggered by a TTL pulse controlled by a PC computer. In order to render the participants more comfortable with the IPS, children of the younger age group always kept their eyes open while the older children kept theirs closed during the recording.

Table 1
Descriptive statistics for patients and controls 6–34 months old.

	Patients (N = 10)	Controls (N = 15)
Age (months)	20.2 (13–35)	20.68 (6–34)
Gender (female; %)	5 (50%)	10 (46.66%)
Cognitive scores		
Bayley score	87.14 (57–114)[a]	92.66 (77–113)
Febrile seizures		Patients (N = 10)
Type (%)		Atypical (100%)
Average number of seizures		2.4 (1–5)
Age at 1st episode (months)		12.4 (8–16)
Prolonged seizures		N = 6
Multiple seizures in the same episode		N = 6
Focal seizures		N = 1
Time since the last FS episode (months)		6.10 (10.23)

[a] Two children with atypical FSs could not undergo the Bayley Scale of Infant Development.

Table 2
Descriptive statistics for patients and controls 37–59 months old.

	Patients (N = 11)	Controls (N = 11)
Age (months)	48.81 (39–57)	47.58 (37–57)
Gender (female; %)	6 (72.7%)	9 (56.2%)
Cognitive scores		
EVIP	100.9 (12.24)	117.54 (10.66)
WPPSI-R		
Object assembly	11.54 (2.29)	12.5 (3.2)
Block	9.72 (2.53)	12.33 (4.8)
Information	10.54 (2.20)	13 (2.09)
Comprehension	8.36 (1.96)	11.3 (2.5)
Similarities	8.54 (1.29)	9.63 (1.1)
Febrile seizures		Patients (N = 11)
Type (%)		Atypical (100%)
Average number of seizures		3 (1–7)
Age at 1st episode (months)		11.63 (7–20)
Prolonged seizures		N = 8
Multiple seizures in the same episode		N = 3
Focal seizures		N = 2
Time since the last FS episode (months)		25.0 (13.1)

2.3. EEG recording and data processing

Electroencephalography data were acquired from 128 electrodes with an Electrical Geodesic, Inc. (EGI) system (sampling rate of 500 Hz, bandpass of 0.1–200 Hz, Cz reference). Further analyses were done using Brain Vision software (Brain Products, GmbH). All EEG records were rated by a neuropediatrician. Three children with atypical FSs showed paroxysmal generalized slow waves (PSWs) induced by IPS. Paroxysmal generalized slow-wave segments were excluded. The EEG records of control children were judged as being normal.

2.3.1. Quantitative EEG analyses

The recording was re-sampled at 512 Hz, digitally filtered (0.1- to 100-Hz bandpass, 60-Hz notch), and re-referenced (average reference). Data acquisition with the EGI systems occurred at 500 Hz. The resampling at 512 Hz is necessary when using frequency spectrum data and Fast Fourier Transform. As such, it is performed in most studies using an EGI system [22]. An increase of 12 data points per second by interpolation will not affect the results since we investigated the low-frequency spectrum. Electroencephalography sections containing PSWs or artifacts associated with eye movements, blinking, muscle activity, etc. were rejected subsequent to a combined visual and automatic inspection of the record. Specifically, the EEG was subjected to algorithmic artifact rejection of voltages exceeding ± 100 μV. Eye movement artifacts were further corrected using the Gratton and Coles algorithm [20]. Then, the EEG results were inspected by a neurologist who identified and extracted PSWs and residual artifacts.

Fast Fourier Transform was then applied to around 30 to 60 two-second artifact-free epochs locked to the stimulus separately for each frequency of the IPS. As previously used in Birca et al. [21], phase alignment values were estimated by normalizing the phase vectors by their lengths (i.e. by dividing both the real and imaginary parts of the FFT components by the magnitude of the complex numbers) and then averaging them. These values are known to represent the degree of phase consistency of oscillations across the epochs at a given frequency