

Altered EEG spectral activity and attentional behavioral deficits following prolonged febrile seizures: a pilot study

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ABSTRACT – The consequences of febrile seizures (FSs) in infants are still a matter of debate. It is important to develop non-invasive tools to determine markers of brain function that could have predictive value for the outcome of FSs in infants. Pattern visual evoked potentials (pVEPs) were recorded in 18 FS infants (mean age of seizure 15.97 months). Spectral density and coherence analyses were performed in infants evaluated at 1.1 month (n = 4), 5.75 months (n = 4) or 30.33 months (n = 6) following a prolonged FS and compared to age-matched healthy controls. The impact of severity of seizures was assessed by comparing the children who had prolonged FSs to 4 infants that had experienced a simple FS. Cognitive tests (Bayley, Stanford-Binet) were administered at the time of testing in FS and control children. Behavioural measures (Achenbach Child Behavior Check List) were administered two years after the FS. pVEP responses and coherence measures failed to yield significant differences between the FS groups and healthy controls. However, spectral density measures showed a significant increase in delta band activity in both FS groups and a reduced high frequency density only in the prolonged FS groups that was seen up to 39 months post-seizure. Behavioural and cognitive measures revealed cognitive development within average, but lower attentional capacities in the FS infants. The persistent changes in spectral density patterns seen in children with prolonged FS may reflect seizure induced alterations in the developing brain or a result of a complex mode of inheritance. Further studies are needed to determine whether these observations can be used as a marker to predict the vulnerability of the child in developing behavioral deficits or epilepsy.

Key words: febrile seizure, development, spectral density, visual evoked potentials, coherence analysis, cognition

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A febrile seizure (FS) is defined as “an event in neurologically healthy infants and children between 6 months and 5 years of age, associated with fever > 38°C, but without evidence of intracranial infection or a defined cause and with no history of prior afebrile seizure” (Knudsen, 2000). Febrile Seizures (FSs) occur in 2-5% of young children living in North-western countries (Nelson and Ellenberg, 1976, Verity *et al.*, 1985). Even though FSs are the most common type of childhood seizures, their significance and their consequences are still a matter of controversy. Most studies concord that the majority of FSs are benign (Shinnar, 1998); (Verity *et al.*, 1998), however, several retrospective and prospective studies have demonstrated a correlation between prolonged complex FS or febrile status epilepticus and brain damage (VanLandingham *et al.*, 1998), neurological sequelae, seizure recurrence (Bessiso *et al.*, 2001, Maytal *et al.*, 1989, Verity *et al.*, 1993) and cognitive deficits. The risk of developing epilepsy, especially temporal lobe epilepsy (TLE) (Sapir *et al.*, 2000, Trinkka *et al.*, 2002, Birca *et al.*, 2005) or Dravet syndrome (Caraballo and Fejerman, 2006) is high in this population. Short generalized FS, on the other hand, have been found to be associated with the development of generalized epilepsy (Trinka *et al.*, 2002). However, according to a British study, the risk of developing epilepsy following simple FS is only 1% compared to 6% after a prolonged FS (Verity and Golding, 1991). Some studies have suggested that complex FSs may differ from simple FSs with respect to origin and outcome (Al Eissa *et al.*, 1992). A genetic predisposition can often be documented. For instance, studying a cohort of 180 children, Shinnar *et al.* (2001) found a higher incidence of family history of epilepsy in children with febrile status epilepticus (FSE) than in children with simple FSs (Shinnar *et al.*, 2001). Furthermore, there are evidences that pre-existing brain abnormalities play an important role in the development of prolonged FSs (Shinnar *et al.*, 2001, VanLandingham *et al.*, 1998). For instance, in animal studies conducted by Scantlebury *et al.* (2004, 2005), a single cortical freeze lesion in neonatal rats was sufficient in creating prolonged hyperthermic seizures and spontaneous recurrent seizures in the majority of animals in adulthood. Currently, there is a lack of prospective data on children that experienced a prolonged FS and there is no general consensus about the impact of prolonged FSs on the immature brain. Electrophysiology is particularly well suited to study brain functions in babies and young children. This technique not only permits the assessment of the impact of FSs at the time of onset, but can also be used to characterize transient or long-term changes in brain physiology that may occur following a FS.

In this study we tested the effects of FSs in children on the following electrophysiological parameters:

- pattern visual evoked potentials (pVEP);
- spectral density measures;
- coherence analysis.

Pattern visual evoked potentials were tested because they are considered to be a robust measure of the functional capacity of the visual system (Roy *et al.*, 1995) and of the nervous system in general (Lippe *et al.*, 2007). Several characteristics of the pVEP provide clues regarding the developmental physiology of the brain. For example, shifts in latencies have been linked to myelination and conductive capacity (Brusa *et al.*, 2001, Eggermont 1988, Emerson 1998, Tsuneishi and Casaer 1997) whereas changes in amplitude are thought to reflect the number of neurons firing together (Scherg and Picton, 1991). Differences in latency and amplitude measurements have been found in other types of childhood pathology, such as prematurity (Atkinson *et al.*, 2002, Lippe *et al.*, 2007, Roy *et al.*, 1995), indicating that this approach constitutes a sensitive tool to study brain development.

Spectral density measures of the developing brain show a pattern characterized by a predominance of slow activity (Matthis *et al.*, 1980, Gasser *et al.*, 1988, Marshall *et al.*, 2002, Stroganova *et al.*, 1999, Lippe *et al.*, 2007). Seizures may cause transient or long-term changes in intra-cortical activity (Schneiderman 1997, Frantzen *et al.*, 1968) which, in turn, may affect the maturational pattern of the spectral density. Moreover, EEG spectral measures reflect awareness and cognitive processing (Cahn 2006, Reid 2007, Uhlhaas et Singer 2006, Canolty 2006) as well as pathological brain states (Kwak 2006, Knyazev 2005, Claus *et al.* 1998), thus providing an index of the brain state during sensory processing. In the present study, we investigated spectral density patterns in three brain areas involved in visual processing (occipital, temporal – what pathway – and parietal – where pathway) (Borowsky *et al.* 2005). Because recordings were carried out when children were visually attentive, these measures should provide a differentiation between the febrile convulsion children and their age-matched peers if the seizure produced any disruption in vigilance or alertness.

Moreover, animal models suggest (Grigonis and Murphy, 1994) that seizures may prevent the normal elimination of exuberant connections, which occurs early in life, thereby interfering with the brain’s ability to generate coherent activity between disparate regions. Given the presumed relationship between FSs and the development of temporal lobe epilepsy (Cendes 2004, Roy *et al.*, 1995, Scantlebury *et al.*, 2005, Shinnar and Glauser, 2002), we expected temporo-occipital coherence to be particularly affected. To study this hypothesis, we explored occipito-temporal (what system) coherence as well as occipito-parietal (where system) and occipital interhemispheric coherence measures in our sample of children.

This constitutes a cross-population study with children tested at three time points, on average one month, 5.75 months and 30.33 months following their first and in most cases the only FS. An additional control group composed of children who had experienced a simple FS was tested 1

month following the episode in order to determine the effect of atypical FS on electrophysiological parameters as compared to simple FS. We also used cognitive and behavioural measures to quantify possible cognitive deficits in the FS group.

Methods

Subjects

A total of 46 infants and children were recruited from the clinical population of the Sainte-Justine University Hospital Center in Montreal. Control infants were recruited in the general population in daycares. Parents filled developmental questionnaires and signed the consent form authorized by the ethics committees of the Hospital's research centre and the University of Montreal. All children were born at term, had no history of neurological or psychiatric illnesses and no abnormalities on the EEG.

Two separate cross population studies were carried out, a prospective and a retrospective one (table 1). The retrospective study allowed the investigation of infants more

than two years post-episode. Infants from the prospective study were recruited at the moment of their first seizure from many health services (emergency, neurology, orthopaedics, paediatrics and ear/throat services) at CHU Ste-Justine in Montreal, whereas infants from the retrospective study were recruited from the hospital medical files. From the 46 participants who originally enrolled in the study, 12 participants (8 FS and 4 controls) were excluded because of substantial amount of artifacts in their electrophysiological recordings. The analyses were conducted on the remaining 34 infants.

Prospective study (n = 22)

Four infants who had experienced a prolonged FS exceeding 15 minutes and four infants who had suffered simple seizures lasting less than 15 minutes were tested one month post-seizure (mean age: 17 and 18.75 months). The two groups were compared to a control group composed of six healthy, age-matched infants (mean age: 18 months). The longitudinal study of these infants was not possible because of withdrawal from participation. Consequently, a second group of four infants who had presented a prolonged FS was tested, on average

Table 1. Experimental subjects description.

Diagnoses	Age at onset (mths)	Age at testing (mths)	Duration (min)	Mother's scolarity (years)	Family history
Prospective study					
<i>1 month post</i>					
Pt # 1. FSE	18	19	60	11	
Pt # 2. FSE	8,5	10	90	10	FS mother
Pt # 3. FSE	21	22	50	11	
Pt#4. PFS	14	15	15	11	
<i>1 month post</i>					
Pt # 5. SFS	16	17	2	14	
Pt # 6. SFS	16	17	< 1	< 11	
Pt # 7. SFS	13	14	1		
Pt#8. SFS	26	27	< 1	21	Epilepsy mother
<i>4,5-8 months post</i>					
Pt # 9. FSE	21	26	50	11	
Pt# 10. PFS	10, 12, 14, 22	26,5	20	19	Epilepsy aunt
Pt# 11. CFS	10	18	3 seizures in 2 hours	11	
Pt# 12. PFS	14	20	15	11	
Retrospective study					
<i>21-39 months post</i>					
Pt# 13. FSE	14, 24	44	60, 10	16	
Pt# 14. FSE	18, 24	63	45, 15	11	
Pt# 15. FSE	11 m 17 d	41	60	8	
Pt#16. FSE	18 m 11 d	52	45	11	
Pt#17. FSE	18	56	40	16	
Pt#18. PFS	21	42	15	16	

FSE: febrile status epilepticus; CFS: complex febrile seizure; PFS: prolonged febrile seizure; SFS: simple febrile seizure.

at 5.75 months post-seizure (mean age: 22.6 months) was compared to four healthy, age-matched controls (mean age: 22 months).

Retrospective study (n = 12)

The clinical sample consisted of six children who had a prolonged FS, on average, 30.33 months prior to the evaluation (mean age: 50 months). Six age-matched neurologically-intact children (mean age: 51 months) served as controls.

Apparatus and stimuli

Pattern-reversal visual evoked potentials (pVEP) were recorded in response to a black and white checkerboard stimulus subtending a visual angle of 2 degrees. The stimuli were generated by a Dell GX 150 PC using E-Prime 2000 software (Pittsburg, USA) and had a luminance of 40 cd/m². They were presented binocularly at a reversal rate of 1 Hz at a distance of 70 cm from the child's eyes and subtended 38.5 x 38.5 degrees of visual angle. Young infants were seated on their parent's lap. Their fixation on the monitor was assured by a small, attractive object held by the experimenter in the lower middle part of the screen. Following a procedure widely used in developmental VEP experiments (Roy *et al.*, 1995), the EEG was recorded only when the children were sitting still and their gaze was focused on the centre of the screen. Recording was carried out using the 128 electrodes Electrical Geodesic Inc. System (Eugene, USA) with Cz as reference and an impedance kept below 40 K Ohms, as suggested by Tucker *et al.*, (1993). The 0.1 Hz to 100 Hz bandpass filtered signal was digitized at 250 Hz.

Data analysis

Off-line analyses were conducted by means of the Brain Vision Analyser software from Brain Products (Munich, Germany). The data were digitally filtered with a 0.5 to 50 Hz bandpass filter, and re-referenced to an averaged reference. The EEG was subjected to algorithmic artefact rejection of voltage exceeding $\pm 100 \mu\text{V}$. Eye movement artefacts were corrected using the Gratton and Coles algorithm (Gratton *et al.*, 1983). Visual examination of the segmented (0-1 000 ms) data was also performed, and segments containing artefacts were manually rejected.

Visual evoked potentials analyses

A mean of 127 (SD 39) artefact-free segments were averaged and baseline-corrected. Due to the non-stationary nature of EEG signals in infants, standard peak to baseline analysis was replaced by a new technique of visual evoked potential (VEP) peak detection. Rather than defining positive and negative peaks as global minima and maxima of each lobe, we first visually established a specific time window for each component (N70, P100,

N145) at the central occipital electrode. Following this, the position where the sum of all points in the interval reached 50% was determined. The time value of this position constituted the latency for each component. The amplitude was defined as the difference in magnitude (measured in μV) between this point and a 100 ms pre-stimulus baseline.

Spectral density and coherence analyses

Spectral density and coherence analyses were performed on the visual evoked potential artefact-free EEG data. At least 85 artefact-free EEG epochs of 1000 ms, time-locked to stimulus onset, were collected for each subject. All epochs were re-sampled at 256 Hz and submitted to Fast Fourier Transformation (FFT) with a 10% Hanning window yielding a frequency resolution of 1 Hz. The sum of the spectral power values (μV^2), were averaged for the following EEG bands: delta: 1 to 3 Hz; theta: 3 to 7 Hz; alpha: 7 to 13 Hz; beta1: 13 to 20 Hz; beta2: 20 to 32 Hz and gamma: 32 to 50 Hz. The data were averaged between five electrodes per brain region: temporal, parietal and occipital. In parallel, coherence, representing the cross-spectrum/auto-spectrum ratio, was obtained from the same EEG epochs and computed for the following pairs of electrodes: intra-hemispheric leads: occipito-temporal: O1-T7, O2-T8, occipito-parietal: O1-P3, O2-P4 and interhemispheric occipital leads: O1-O2.

Developmental data and cognitive testing

Developmental data were gathered for all participants of all experimental groups through medical files, interviews with the parents and a developmental questionnaire completed by one of the parents. We evaluated these data for the age of acquisition of developmental milestones to ensure normal development. All children also underwent cognitive testing. Participants, aged 10-24 months, were assessed on the Mental subscale of the Bayley Scales of Infant Development (Bayley 1993). For children older than 24 months, the Stanford Binet Intelligence Scale (Thorndike *et al.*, 1994) was used (*table 2*). These assessments were performed by one experimenter and one observer, and an inter-judge agreement was established. Two years post-evaluation, the parents of both experimental groups were invited to complete the Achenbach Child Behaviour questionnaire (CBCL) (Achenbach 1991) to assess their child's adaptive capacities.

Statistical analysis

Data were transferred to SPSS software. A logarithmic transformation was applied to non-gaussian distributions, when applicable. Analyses of variance were performed separately on the spectral density, coherence, and pVEP measures. One-way anovas were performed on each study, *i.e.* the prospective (one-month and 5.75 months

Table 2. Clinical subjects description.

Prospective study					CBCL scores		
Diagnoses	Age at onset (months)	Age at testing (months)	Duration (min)	Mental Scale	Attention scores	Internalizing	Externalizing
<i>1 month post</i>							
Pt#1. FSE	18	19	60	92	62	39	59
Pt#2. FSE	8,5	10	90	90	62	53	67
Pt#3. FSE	21	22	50	104	50	47	43
Pt#4. PFS	14	15	15	92			
<i>1 month post</i>							
Pt#5. SFS	16	17	2	100	70	49	58
Pt#6. SFS	16	17	< 1	77			
Pt#7. SFS	13	14	1		53	60	57
Pt#8. SFS	26	27	< 1	64	50	41	37
<i>4,5-8 months post</i>							
Pt#9. FSE	21	26	50	104	50	47	43
Pt#10. PFS	10,12, 14, 22	26,5	20		57	60	55
Pt#11. CFS	10	18	3 seizures in 2 hours	94	57	69	58
Pt#12. PFS	14	20	15	92			
Retrospective study							
<i>21-39 months post</i>							
Pt#13. FSE	14, 24	44	60, 10	110	55	50	47
Pt#14. FSE	18, 24	63	45, 15	60	57	45	57
Pt#15. FSE	11 m 17 days	41	60	97	51	45	40
Pt#16. FSE	18 m 11 days	52	45	96			
Pt#17. FSE	18	56	40	91			
Pt#18. PFS	21	42	15		69	68	63

FSE: febrile status epilepticus; CFS: complex febrile seizure; PFS: prolonged febrile seizure; SFS: simple febrile seizure.

post-FS) and the retrospective (30.33 months post FS) ones. Regarding the spectral density measures, the dependent variable was the mean spectral density values (μV^2) per frequency bands. The dependent variables for the coherence measures statistics and the pVEP measures statistics, were respectively the coherence values per electrode pairs and the amplitudes and latencies values of the three components (N70, P100, N145). In both designs, the between-subject factor was the groups (sFS, pFS, controls). Two separate one way anovas were conducted for the latency and amplitude VEP data.

Results

PVEPs analyses

The pVEPs results of the prospective (one-month, 5.75-months post-seizure) and the retrospective (30.33-months post FS) studies are illustrated in *figure 1*. As can be seen in this figure, the groups did not differ with regard to the latency of the responses. The amplitudes of the group with prolonged FSs were elevated at one month

(N70) and at 5-6 months (P100) and depressed at 2 years (P100) compared to controls, but these differences were not statistically significant.

Spectral density values

The mean spectral densities (in μV^2) for the prospective studies and the retrospective study are presented in *figures 2A, 2B, 2C, 2D*. The power spectra obtained in the temporal, parietal and occipital regions were summed and one-way ANOVAs were conducted for each study set (prospective and retrospective).

Prospective study

Significant increases in the delta frequency band were observed in the simple FS group and the prolonged FS group at 1 month post-episode ($p = 0.004$) and in the prolonged FS group tested at 5.75 months-post-episode ($p = 0.004$) (*figure 2A*). No significant differences between the FS infants and the controls were found in the theta and alpha bands at any time point.

As shown in *figure 2B*, beta1 frequency band density was significantly reduced 1 month post prolonged FSs

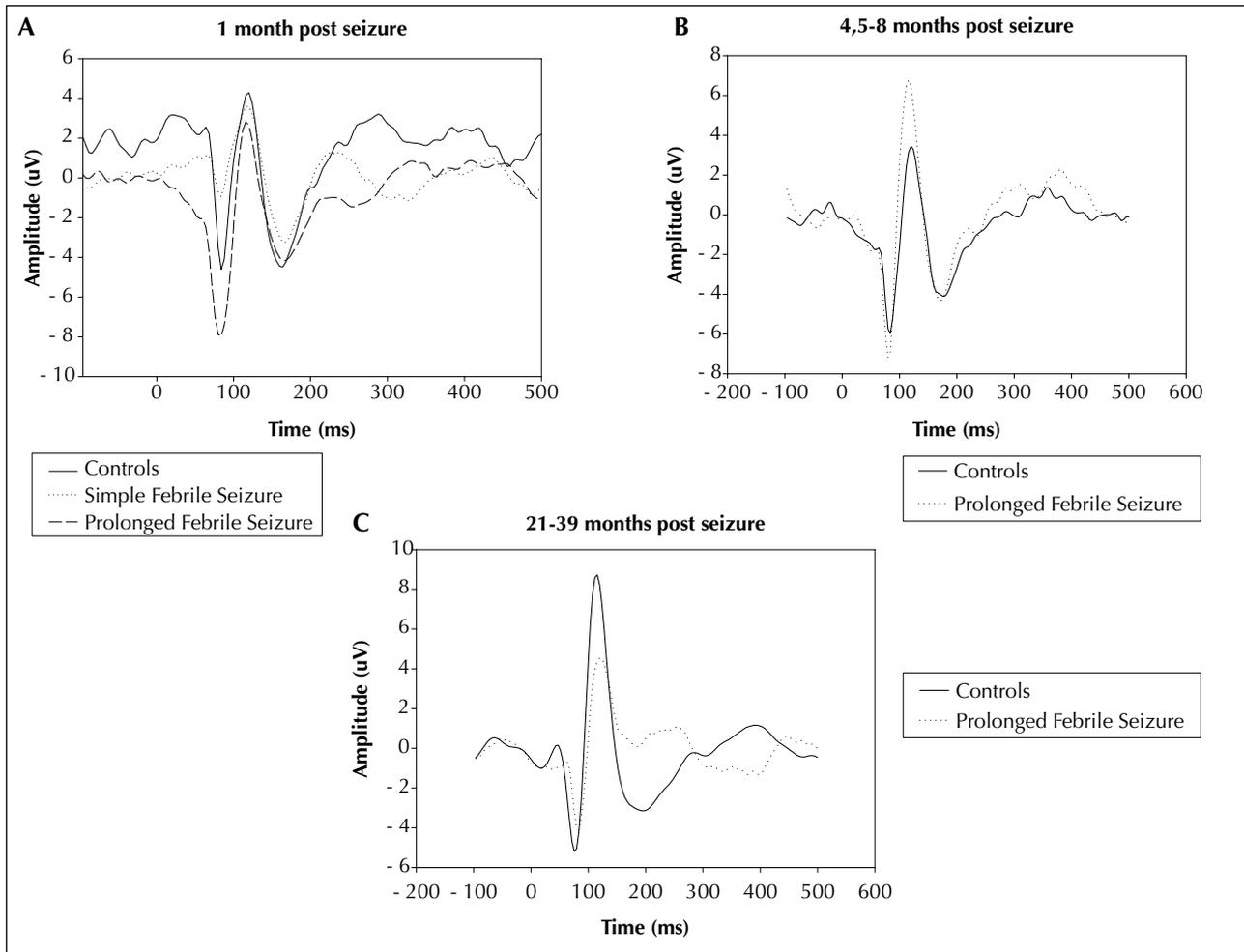


Figure 1. Group averages of the pattern visual evoked potentials (pVEPs) for: prospective study: **A)** children tested on average at 18 months; **B)** children tested on average at 22 months and the retrospective study; **C)** children tested on average at 51 months of age. Within all graphs, the first negative deflection is the N70, the first positive deflection is the P100 and the last negative deflection is the N145.

($p = 0.018$) but not following simple FSs. *Figures 2C and D* also depict a significant reduction in beta2 and gamma bands density 1 month post prolonged FSs compared to the controls (respectively $p = 0.032$, $p = 0.033$). Children with simple FSs did not show significant changes in spectral density in the beta and gamma range.

Retrospective study

Infants with FSs also showed significant increases in delta ($p = 0.046$) and a decrease in beta1 ($p = 0.0018$) frequency bands density. Although not statistically significant, infants who had suffered a prolonged FS also showed a reduction in beta2 and gamma bands spectral density 5.75 months and even up to 30.33 months post-seizure (*figure 2C, D*). It is noteworthy that the exclusion of the only child in the prolonged FS group, who scored below average on the cognitive measures (*table 2*), did not affect the electrophysiological results.

Coherence analyses

Analyses of variance with repeated measures performed on the six EEG bands and the three pairs of leads, did not yield significant differences between the controls and FS infants in the prospective study (one month: $F = 0.911$, $p = 0.473$; 5.75 months: $F = 1.977$, $p = 0.132$) nor the retrospective study (30.33 months post-seizure $F = 1.046$, $p = 0.406$).

Cognitive/behavioural measures and follow-up

The results of cognitive and behavioural measures are presented in *table 2*. Most FS children performed in the normal range (90.87, SD 13.99) on the mental scale of the Bayley or the Stanford Binet Intelligence scales (*table 2*). Only one child in the retrospective FS group performed one standard deviation below the mean, and two children with simple FSs scored two standard

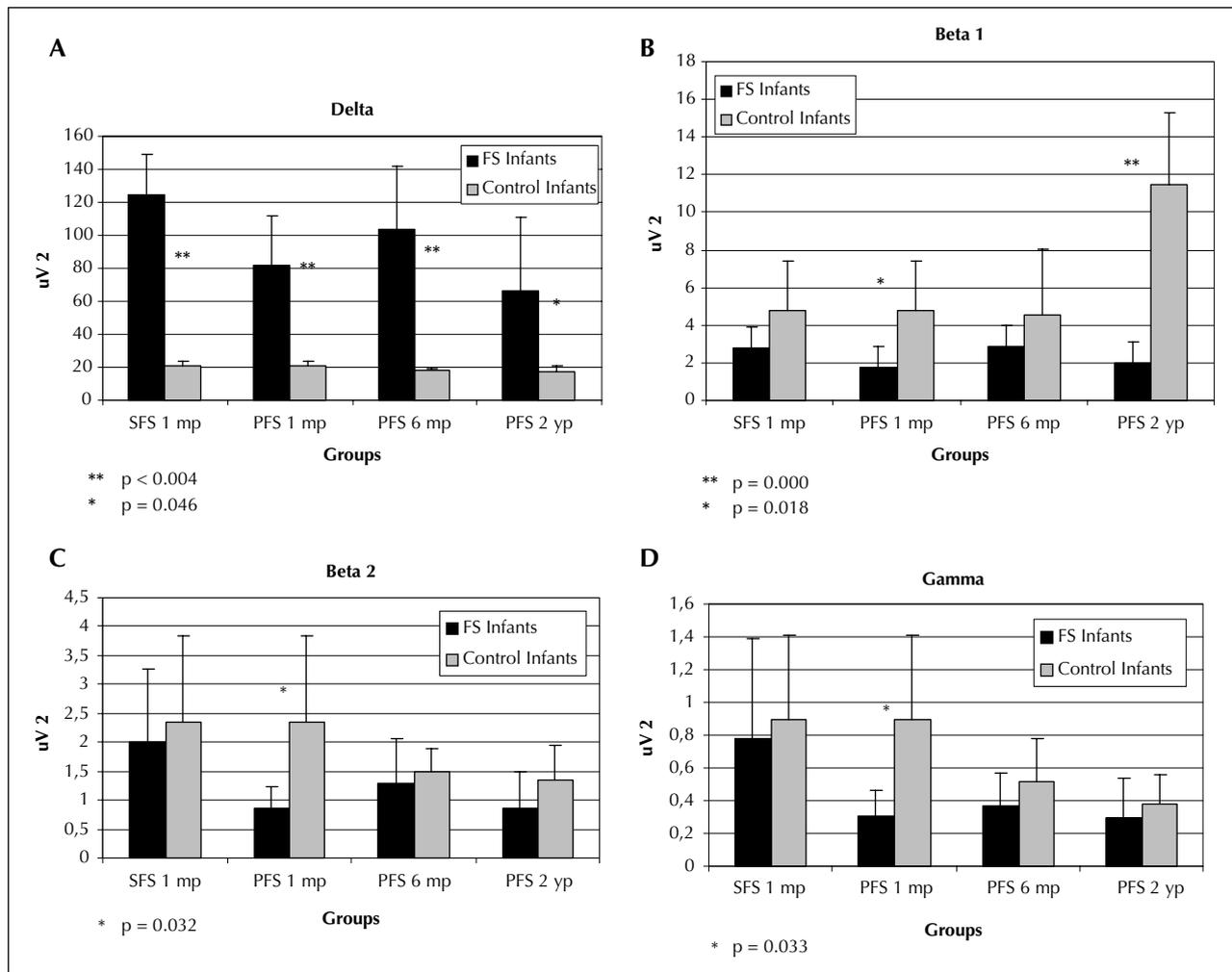


Figure 2. Sum of spectral densities for each group in the occipital, parietals and temporals regions. **A)** delta band (1-3 Hz); **B)** beta1 band (13-20 Hz); **C)** beta2 band (20-32 Hz) and **d)** gamma band (32-50 Hz). Note the increase in delta density and the decrease in beta1, beta2 and gamma density up to two years post seizure.

deviations below the mean. No correlations between cognitive and behavioural scores and the mother’s scolarity (p values from 0.3 to 0.9) were found.

Two to three years after the electrophysiological evaluation (and up to 7 years post-seizure), an interview was carried out with the parents from the clinical sample. Six out of 14 (43%) children with prolonged FS had presented at least another FS and 6/18 (33%) of children with either simple or prolonged FSs were receiving behavioural or academic intervention by professionals. Thirteen parents agreed to fill out the Child Behavior Checklist, which yielded, on average, normal results on both the internalizing (T score: 51.77 ± 9.68) and externalizing (T score: 52.61 ± 9.39) subscales. However, on average, children with simple or prolonged FSs showed scores close to 1 standard deviation above the mean (T = 59.23, min 50 max 77) on the attentional index. The removal of the

child from the simple FS group who had scored in the deficient range during the cognitive assessment did not affect the attentional index results (T = 58.33 min 50 max 77). The averaged scores of the aggressiveness index (T = 57.1, min 50 max 72) was also high, whereas the somatisation (T = 55.61 min 50 max 72), anxiety (T = 53.31 min 50 max 70) and withdrawn (T = 51.46 min 50 max 56) indices were, on average, within normal limits.

Discussion

Our results indicate that FS infants present electrophysiological alterations that can be measured by quantitative EEG. All FS infants showed a persisting increase in delta band spectral density in response to visual stimulation but

only the infants with prolonged FSs also showed a significant reduction in beta 1, beta 2 and gamma bands spectral density one month post-seizure. Furthermore, although not statistically significant, reduced spectral density within high frequency bands (20-50 Hz) was still present two years after the first and, in most cases, only episode. This spectral density pattern was observed both in primary visual and extra-visual regions, a finding that may reflect a global characteristic of cerebral processing.

We report here that infants suffering a prolonged FS had an increased delta band density and a reduced density of 13-50 Hz activity. While slow bands are typically associated with lack of awareness, beta and gamma frequency bands are characteristic of the waking state (Bazhenov *et al.*, 2002), which is associated with cognitive processes, such as perception and attention (Bertrand and Tallon-Baudry 2000, Tallon-Baudry *et al.*, 1999, Csibra *et al.*, 2000, Tamas *et al.*, 2004). Yet, the infants with prolonged FSs obtained normal scores on the mental scale of the Bayley or the Stanford-Binet. Furthermore, the removal of the only infant with prolonged FS who obtained a below average score did not affect the spectral results. Thus, while the spectral density results obtained in the present study do not reflect alterations in global cognitive development, they may, however, reflect changes in alertness or attention states. Indeed, two years post-evaluation, reduced attentional capacities, measured by the attention index of the Child Behavior Check List, were reported by the parents of the FS group. In addition, one third of the FS children had required special clinical intervention (e.g. speech therapy, occupational therapy).

Power spectral density measures have been extensively studied in ADHD populations (Clarke *et al.* 2002, Clarke *et al.*, 2003, Barry *et al.*, 2003). An increase in absolute delta and a reduction in beta power density have been observed over posterior regions (Hobbs *et al.*, 2007). Prolonged FSs at young age have also been found to be a risk factor for developing ADHD in school-aged children with normal global cognitive abilities (Pineda *et al.*, 2007). Although the relationship between the cognitive-behavioural profile and electrophysiological patterns seen in our FS infants has yet to be confirmed in larger samples, our findings suggest that the EEG of infants who showed an episode of prolonged FS is sufficiently altered to produce a behavioural and electrophysiological profile comparable to that described in older ADHD children.

It is noteworthy that the infants with simple FSs, who were tested one month post-episode, demonstrated an increase in delta band density but failed to show significant changes in spectral density in the high frequency bands (a reduction in beta 1, beta 2 and gamma bands spectral density as seen in the prolonged FS group). This "in between" response pattern seen in children with simple FS may be an indicator of the degree of severity of this FS type. In fact, many studies have reported a deleterious

effect of prolonged or complex FS on brain functioning and cognitive behaviour compared to the favourable outcome of simple FS (Al Eissa, 1995, Annegers *et al.*, 1987, Bessiso *et al.*, 2001, Berg and Shinnar, 1996). The present results suggest that changes in high frequency density may be a better indicator of the severity impact of the seizures or a better marker of FS infants' functioning. However, its predictive value regarding the long-term prognosis of prolonged FSs still has to be evaluated in a longer prospective study.

The significance of the persistently increased low frequency spectral density seen one month to more than two years post prolonged FSs in regards to brain development and risk of developing epilepsy remains unknown. Recently it has been proposed that seizures in the developing brain may delay or interrupt its maturation leaving certain networks in a persistent immature state (Cohen *et al.* 2002) and reviewed in Scantlebury *et al.* (2007). It is noteworthy that in our study the spectral activity pattern seen in the children with prolonged FSs mimicked a pattern found in younger children as described in our larger study of visual electrophysiological development (Lippe *et al.*, 2007); findings consistent with a delay in maturity. It is nonetheless not clear if prolonged FSs themselves will delay the maturation of the brain making it more susceptible to seizures than the adult brain (Moshe *et al.*, 1983) or if this electrophysiological response pattern reflects the consequences of a complex mode of inheritance. Again, a larger multicentre trial using the tests we describe here will be helpful in answering these questions.

Although a widely used method in paediatric research, the pattern visual evoked potentials in the present study failed to reveal significant differences between the groups in terms of amplitude and latency. Since visual evoked potentials are the result of the averaged responses time-locked to the stimulus, differences in electrophysiological activity may not be evident because of hidden information resulting from the averaging process. Furthermore, the failure to reach statistical significance may be attributable to the high variability in amplitude, which is frequently observed in normal and abnormal developmental cohorts.

With respect to coherence analysis, the latter is thought to indicate the degree of correlated changes between the signals of disparate brain regions, thus reflecting the functional connectivity between neuronal networks (Thatcher, 1992, Andrew and Pfurtscheller, 1995). Considering the presumed relationship between FS and the development of temporal lobe epilepsy, we expected temporo-occipital coherence to be particularly affected. On the contrary, no differences in coherence values were found between the groups in any of the paired regions. We have recently shown that coherence values undergo important developmental changes which are most marked at the age interval addressed in the present study (Lippe *et al.*, 2007). These

changes could have masked any alteration in connectivity in our FS patients. This explanation is all the more plausible for interhemispheric coherence as it is well established that callosal connections develop gradually and do not reach their functional maturity before puberty (Lassonde *et al.*, 1991). Therefore, any changes in coherence would more likely be demonstrable in adult patients with a history of prolonged FSs.

Conclusion

In children, both prolonged and to a lesser extent, simple FSs alter the electrophysiological response pattern and cognitive-behavioural outcome even after a single episode. Although these results still have to be replicated in a larger cohort, their persistence over time suggests that this abnormal pattern is stable, supporting the notion that prolonged FS infants show altered development leading to long-term behavioral deficits. These findings emphasize the necessity of closely following children with atypical FSs using relatively inexpensive and non-invasive electrophysiological and behavioural testing to better determine their longterm outcome and to identify risk factors for developing TLE and behavioral abnormalities following FSs. □

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