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Febrile seizures and increased stress sensitivity in children: How it relates to seizure characteristics

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ABSTRACT

Background: Studies suggest that the relationship between seizures and stress starts early in life. However, evidence of long-term altered stress reactivity following early-life seizures is lacking. Our objectives were to assess alterations in stress hormone reactivity in children with past febrile seizures (FS) and investigate how these alterations relate to clinical characteristics.
Method: This case–control study compared a convenience sample of children with simple FS ($n = 24$), complex FS ($n = 18$), and matched healthy controls ($n = 42$). Stress was induced by electrode placement for an electroencephalography (EEG) exam. Salivary cortisol to stress, using three samples collected before and after the stressor, was compared between groups and sex. The relationship between stress reactivity and clinical characteristics (i.e., FS duration, age at first FS, time since the last FS) was investigated.
Results: Cortisol reactivity to stress was significantly different depending on study groups, $F(1, 78) = 6.415$, $p = 0.003$, $\eta_p^2 = 0.141$, but not sex nor was there a significant interaction between group and sex ($p \geq 0.581$). Participants with simple FS showed higher cortisol reactivity to stress ($M = 14.936$, Standard deviation (SD) $= 26.852$) compared with those with complex FS ($M = -4.663$, $SD = 18.649$, $p = 0.015$) and controls ($M = -3.817$, $SD = 18.907$, $p = 0.003$). There was no significant difference between participants with complex FS and controls ($p > 0.999$). Stress reactivity was not linked to clinical characteristics.
Conclusions: Children with past simple FS showed greater changes in salivary cortisol following stress, suggesting enhanced stress sensitivity. As similar results were not found in a population with complex FS, our study shows that stress alterations are not caused by seizure severity. Future studies are needed to investigate whether stress sensitivity may be premorbid to simple FS and may contribute to simple FS incidence.

1. Introduction

Febrile seizures (FS) are associated with fever episodes in young children without a history of spontaneous seizures or neurological insults [1]. These are the most common pediatric seizures, affecting 2 to 5% of children before age 5 years [2,3]. Although FS are common neuropediatric emergencies, they are seen as benign, and seizure frequency is low, with only 30% of patients showing overall seizure recurrence [2]. Nevertheless, FS with complex features (i.e., >1 seizure during the fever episode, and/or focal, and/or ≥10 min seizure duration) have been associated with poorer outcome, including lasting increased anxiety and depressive symptoms [4–6]. Anxiety and depressive symptoms are among the most frequent seizure precipitants reported by people with epilepsy [7,8], consequently, a relationship between anxiety or depressive symptoms and seizures, which would be mediated through physiological stress, has received some support [9]. Incidentally, common underlying mechanisms between seizures and stress have been suggested through familial clustering research [10]. In that context, changes in basal stress hormone and stress reactivity axis found in

Abbreviations: ANOVA, analysis of variance; AUCi, area under the curve with respect to increase; EEG, electroencephalography; FS, febrile seizures; SES, socioeconomical status.

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people with epilepsy [11,12] may be related to higher prevalence of psychiatric symptoms in this population [11,13].

Clear evidences from animal studies suggest that the seizure–stress relationship begins during early infancy, hence, this relationship in early childhood has been suggested in humans as well [14]. More precisely, early-life stress in animals and humans induces alterations in stress hormones secretion, regulation of the stress reactivity axis, and neuroanatomical changes predisposing the brain to seizures [15–17]. Complementarily, animal models show that early-life seizures are associated with changes in stress hormone levels [17–20]. Despite strong evidence in late childhood and adult human studies of a seizure–stress relationship [21,22], we do not know if early-life seizures are associated with altered physiological reactivity to stress in human infants and toddlers. Moreover, it is unknown whether this association is present following seizures of low severity and frequency such as FS.

We aimed to investigate stress reactivity, as measured through salivary cortisol to experimental stress, in children with past FS. Additionally, we assessed how FS characteristics relate to stress reactivity. We hypothesized that stress reactivity differs between children with past simple FS, complex FS, and healthy controls, and may vary depending on clinical characteristics (i.e., FS duration, age at first FS, time since the last FS). Alterations in physiological stress following early-life benign seizures would increase our understanding of the seizure–stress relationship, providing insights into the mechanisms underlying FS prognosis.

2. Material and methods

2.1. Participants

This case–control study compared children with past simple FS, complex FS, and healthy controls. Cases were otherwise healthy children who were admitted to the emergency department of a tertiary care, university affiliated pediatric Hospital (CHU Sainte-Justine), between 10 to 24 months of age, following a simple or complex FS episode meeting the American Academy of Pediatrics criteria [1] from August 2015 to May 2018. A number of control equivalent to the total number of children with FS evaluated was recruited through social media. Children with simple FS, complex FS, and controls had similar age, sex, and socioeconomical status (SES) distribution when tested. Children born before 34 weeks of gestational age, with a history of health problems that could affect neurological development or suspicions of developmental delay were excluded.

The study was approved by the CHU Sainte-Justine Research Ethics Board. Legal guardians gave verbal consent when contacted and gave written informed consent when arriving at the laboratory. They were free to withdraw at any time in the study. Families were given a 30$ compensation for their participation.

2.2. Descriptive measures

Sociodemographic characteristics and personal history were assessed using an in-house questionnaire. Cognitive skills were evaluated using the *Bayley Scales of Infant and Toddler Development — Third Edition* [23], and adaptive behaviors were assessed using the *Adaptive Behavior Assessment System — Second Edition* [24] completed by the parent. Finally, as FS may lead to parental stress, parents of the FS groups were asked to complete the 4-item short form of the *Perceived Stress Scale* [25], measuring the degree to which they appraise their current situation as stressful. Developmental assessment and questionnaires were scored by a Doctoral student in Neuropsychology.

Febrile seizure characteristics were extracted from medical records by a Doctoral student in Neuropsychology specialized in seizure disorders using a standardized report form. Dates, duration, and type of each FS episode were noted. Results of neurological exams, if applicable, were also obtained. According to FS characteristics, children with FS were divided into two study groups: simple (isolated, <10 min, and generalized) and complex FS. For descriptive purposes, complex FS were further classified as multiple (>1 during the fever episode), focal, prolonged (FS duration ≥10 min), and/or febrile status epilepticus (FS duration ≥30 min, or repeated FS ≥ 30 min without regaining consciousness) [5].

2.3. Experimental stress and cortisol assessment

Acute stress was induced using reduced parental support and mild arm restraint during an electroencephalography (EEG) net placement, as this evaluation was required to meet other objectives of the study. Studies in school-aged children show that exposure to novel medical procedures leads to increased stress reactivity, as assessed by significant increase in cortisol levels [26]. However, stressor paradigms in children aged 10–24 months, including EEG net placement and evaluation, have a low success rate [27]. Reviews suggest that supportiveness of adults could be buffering increased cortisol to stress [27]. In that context, threats to parental support may help induce cortisol reactivity to stress in infants and toddlers. Thus, during installation, participants were seated on their parent's lap and, as children tried to pull on the EEG net, parents were asked to immobilize their children's arms and maintain restraint despite fussiness and distress. Saliva sampling for assessment of cortisol levels was taken to measure stress reactivity to the EEG procedure. The first saliva sample was taken before entering the exam room. The second and third saliva samples were collected approximately 20 and 45 min following the stressor, providing cortisol measures during acute stress reactivity [28].

Salivary samples were obtained using sterile synthetic swabs (SalivaBio Children's Swab; Salimetrics LLC, Carlsbad, CA). Cortisol concentration was determined with a high sensitivity enzyme immune assay kit (Salimetrics State College, PA, catalog No. 1-3102). Samples with a reading exceeding the upper limit for detection or significant intra-assay coefficient of variation were rerun at a dilution. All samples for a participant were analyzed in the same batch, and each batch consisted of males and females of all study groups. Comprehensive information regarding cortisol assessment is shown in Supplementary material 1.

Experimental stress was induced during a morning or early-afternoon appointment at CHU Sainte-Justine. Morning and afternoon evaluations were evenly balanced across groups to control for impact of the circadian rhythm on cortisol. Parents were instructed to postpone the evaluation if participants were sick, teething, or had an unusual bad night of sleep. No solid food was given during the testing, and the mouth was thoroughly rinsed prior to saliva samples if participants had liquid food or put an object (e.g., pacifier) in their mouth to avoid contamination.

2.4. Statistical analyses

Children with cortisol readings exceeding the upper limit after dilution, significant outlying (± 3 Z score) timing characteristics (i.e., time at first sample, total evaluation duration) or missing samples were excluded. Outlying cortisol values were replaced by plausible values ($|Z\ score| = 3$) [29] to reduce possible bias. To obtain a single value representing stress reactivity, an area under the curve with respect to increase (AUCi) index [30] was calculated using cortisol levels for each sample and time between samples. The AUCi is commonly used to study stress reactivity through changes in cortisol levels. Positive AUCi suggests increased cortisol, and higher absolute values suggest larger changes. Supplemental information on cortisol analysis is shown in Supplementary material 1.

To test our hypothesis, a two-way analysis of variance (ANOVA) with Bonferroni *post-hoc* tests was conducted to compare study groups (i.e., simple FS vs complex FS vs controls), sex, and the sex–group interaction on the AUCi. Sex was added to the analysis as animal testing on

rodents shows that the seizure–stress relationship may depend on sex hormones [19]. To explore how clinical characteristics relate to stress reactivity, the relationships between AUCi and duration of the longest FS, age at first FS, and the time since the last FS of all participants with FS were examined using Pearson's bivariate correlations.

Analyses were carried out using IBM SPSS 25.0 (IBM, Armonk, NY). Normality was examined through visual inspection of histograms and quantile–quantile plots; logarithmic transformations were applied to nonnormally distributed variables. Homogeneity of variance was assessed using Levene's test. Analyses were performed on complete cases; statistical significance was defined as a two-sided alpha level ≤ 0.05. One-way ANOVA and Chi-square tests of independence were computed to examine differences in participants' characteristics and study protocol to ensure group comparability. Pearson's bivariate correlations were conducted between AUCi and participants' characteristics to verify that these variables would not confound our results. Assumptions necessary to conduct all analyses were verified and satisfied.

3. Results

3.1. Descriptive and control results

We identified 108 children with past FS, 54 families declined to participate, and seven children did not meet inclusion criteria, thus, 47 children with FS were recruited and evaluated. The most common reason for refusal was lack of interest. Following exclusion ($n = 5$; 1 out-of-curve reading, 1 missing samples, 3 outlying timing), 42 children with FS were included in our analyses. Prior to analyses, they were classified into two study groups: those with past simple ($n = 24$; *Median* age = 19.07 months, interquartile range (*IQR*) = 15.76–21.99) and complex FS ($n = 18$; *Median* age = 16.52 months, *IQR* = 13.43–20.75). They were compared with 42 healthy controls (*Median* age = 15.03 months, *IQR* = 10.93–25.80), leading to a total sample size of 84 children (*Median* age = 16.65 months, *IQR* = 12.21–21.26).

Febrile seizure types and quantity are shown in Table 2. Children in the complex FS group had their first FS on average 2 months younger than the simple FS group. Overall median seizure duration was 2 min (*IQR* = 1–5), with a bias for shorter duration. Finally, time since the last FS episode and perceived parental stress was similar between FS groups ($p > 0.350$). Parental stress was low, indicating parents "almost-never" experienced feelings of distress in the last month.

Descriptive statistics and comparisons are shown in Table 1. No significant group differences were found regarding descriptive variables, suggesting group comparability. Furthermore, there were no significant differences in study protocol, indicating data collection was comparable across study groups. Cortisol levels varied from 0.0135 to 1.1731 μg/dl. Comprehensive cortisol and evaluation results are shown in Supplementary material 1. Visual inspection of variability in cortisol trajectories (Fig. 1a) shows that stress was not successfully induced in all study participants, despite reduced parental supportiveness. More precisely, increased cortisol reactivity to stress, as defined by an untransformed AUCi >0 was successfully achieved in 49% of study participants. The AUCi was not associated with participants' characteristics ($p \geq 0.080$), thus, these characteristics should not confound our main analysis.

3.2. Stress reactivity and febrile seizures type and clinical characteristics

A two-way ANOVA revealed that cortisol reactivity to stress was significantly different depending on study group, $F(1, 78) = 6.415$, $p = 0.003$ (Fig. 2). The effect size for group differences was large ($\eta_p^2 = 0.141$) [31]. Bonferroni *post-hoc* analyses revealed that the simple FS group showed higher cortisol reactivity to stress ($M = 14.936$, $SD = 26.852$) compared with complex FS ($M = -4.663$, $SD = 18.649$, $p = 0.015$, 95% *CI* = 3.06 to 36.49) and controls ($M = -3.948$, $SD =$

Table 1
Descriptive statistics and group differences.

	Simple FS ($n = 24$)		Complex FS ($n = 28$)		Control ($n = 42$)		p
	n[a]	$M(SD)$	n[a]	$M(SD)$	n[a]	$M(SD)$	
Participants' characteristics							
Age at testing, months	24	18.80(4.29)	18	16.75(4.25)	42	15.96(5.89)	0.103
Sex							0.543
Male	10		8		23		
Female	14		10		19		
Gestational age at birth							0.987
Term	17		14		34		
Late preterm	1		1		2		
Parental civil status							0.474
Together	19		15		31		
Separated	0		0		3		
Single-parent	1		0		1		
Family income							0.311
<40,000$CA per year	2		0		5		
≥40,000$CA per year	15		14		28		
Maternal education, years	19	16.05(2.68)	15	16.67(2.41)	36	17.86(3.62)	0.116
Paternal education, years	18	15.44(3.58)	15	16.07(1.94)	34	16.79(3.86)	0.399
Cognitive skills, PR	24	57.21(20.43)	18	69.06(22.04)	42	62.12(23.88)	0.248
Adaptive behaviors, PR	17	43.65(23.75)	14	54.29(25.66)	32	47.91(28.68)	0.548
Perceived stress, sum	19	4.16(2.79)	13	4.00(2.80)	n.a.	n.a.	0.876[b]
Study protocol							
Time at 1st sample, hh:mm	24	10:46(1:34)	18	10:49(1:41)	42	10:45(1:49)	0.987
Testing duration, min	24	54.88(5.00)	18	52.17(4.93)	42	53.00(4.13)	0.133
Cortisol 1st sample, μg/dl	24	0.15(0.13)	18	0.23(0.25)	42	0.19(0.18)	0.345
Cortisol 2nd sample, μg/dl	24	0.19(0.13)	18	0.20(0.18)	42	0.17(0.11)	0.703
Cortisol 3rd sample, μg/dl	24	0.19(0.12)	18	0.22(0.21)	42	0.16(0.15)	0.370

Note. Descriptive statistics (Mean, *M*; standard deviation, *SD*) for participants' characteristics (excluding clinical features) and study protocol. Values in the table are following winsorization, prior to transformation. Group differences were computed with one-way ANOVAs and Chi-square tests of independence, *p*-values are included in the table. FS = febrile seizures; PR = percentile rank.

[a] Missing values account for *n* inconsistency.

[b] Controls were not included in this analysis.

Table 2
Clinical characteristics and group differences.

	Simple FS ($n = 24$)		Complex FS ($n = 18$)		p
	n[a]	$M(SD)$	n[a]	$M(SD)$	
Quantity of FS episodes					0.158
1	22		11		
2	1		2		
3	1		2		
4	0		1		
5	0		2		
Complex type					n.a.
Focal	n.a.		4[b]		
Multiple	n.a.		7[b]		
Prolonged	n.a.		5[b]		
FSE	n.a.		5[b]		
Age at first FS, months	24	15.98(4.18)	18	13.34(3.50)	**0.036**
Time between last FS and testing, months	24	2.23(1.65)	18	1.76(1.04)	0.350

Note. Descriptive statistics (Mean, *M*; standard deviation, *SD*) for clinical features. Values in the table are prior transformation. Group differences were computed with one-way ANOVAs and Chi-square tests of independence, *p*-values are included in the table and appear in bold when significant. FS = Febrile seizures.

[a] Missing values account for *n* inconsistency.

[b] Total number adds over 18 because of overlap (one children had both focal and multiple seizures, one both focal and prolonged seizures and one both multiple and prolonged seizures).

18.907, $p = 0.003$, 95% confidence interval (CI) = 4.87 to 32.35). There was no significant difference between participants with complex FS and controls ($p > 0.999$). Visual inspection of participants' distribution (Fig. 2) and variability in cortisol trajectory (Fig. 1b, c, d) suggests that children with past simple FS showed increased cortisol to stress more consistently than complex FS and controls, although the study design was comparable across study groups. Coherently, untransformed AUCi data show that increased cortisol reactivity to stress was achieved in 71% of the children in simple FS group, as opposed to 33% and 43% of the complex FS and healthy control groups, respectively. Significant differences were not found for sex ($p = 0.581$) or the sex–group interaction ($p = 0.661$).

Finally, Pearson's bivariate correlations conducted on participants with past FS only ($n = 42$) suggest that neither duration of the longest FS episode, age at first FS, nor time since the last FS were significantly associated with AUCi ($p \geq 0.150$).

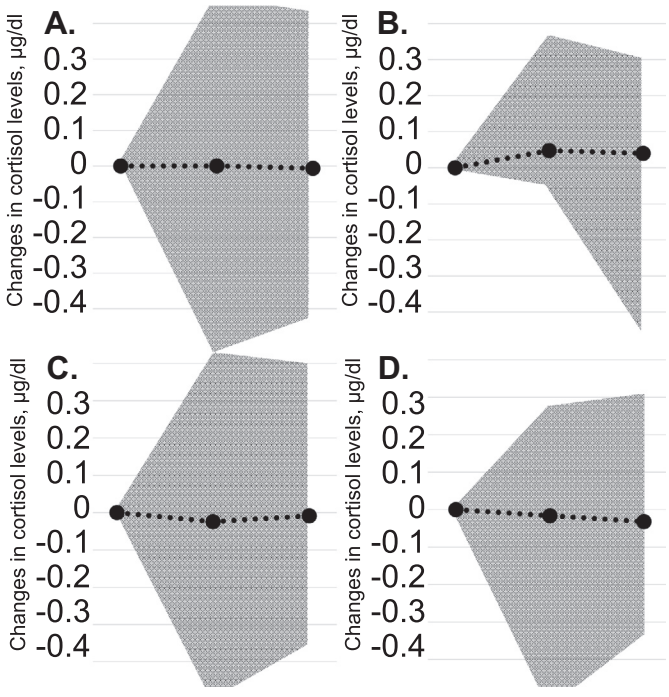

Fig. 1. Title: changes in cortisol levels throughout the experiment. Description: Dotted black line represents mean cortisol trajectory per group; shaded area represents overall variation in cortisol trajectory throughout the experiment. Models were baseline-adjusted and show changes in cortisol levels between measurement times ($X_1 = 0$; $X_2 = Sample_2 - Sample_1$; $X_3 = Sample_3 - Sample_1$). Models built using untransformed and winsorized cortisol values. A. All participants; B. Simple FS group; C. Complex FS group; D. Control group. The figure shows that the Simple FS group has less variation in cortisol trajectory than the other study groups and overall study sample.

4. Discussion

We found that children with a history of simple FS show changes in salivary cortisol to experimental stress that are significantly different from children with complex FS and controls. Meanwhile, no significant difference was found between children with complex FS and controls. While average AUCi was positive for the simple FS group, it was negative for those with complex FS and controls. Furthermore, variability in cortisol trajectories shows that participants in the simple FS group display increased cortisol to stress more consistently, while participants with complex FS and controls exhibited more diverse patterns of response in cortisol reactivity to experimental stress. Thus, our results indicate that only our simple FS group was, on average, stressed during our experiment, suggesting children with simple FS may have a lower threshold for stress reactivity than their peers. Importantly, this difference cannot be explained by group differences in developmental characteristics, parental stress, or study protocol. Our results did not support sex as a contributive factor to the FS–stress model and did not show stress reactivity to be associated with parental stress, duration of the longest FS, age at first FS, or time since the incident.

While previous studies have shown increased cortisol immediately following FS in young children [32,33], which may reflect an acute postictal stress response, this is the first study supporting long-term alterations in physiological stress sensitivity in young children with common and harmless seizures. These results may help to improve our understanding of the relationship between early-life seizures and stress in humans. Specifically, animal studies show that seizures may lower the stress threshold and increase stress reactivity [11,12]. Our study cannot fully support this hypothesis in populations with FS, as the threshold for stress reactivity in children with complex FS did not significantly differ from healthy controls'. However, it has been widely suggested through animal studies that early-life stress can lead to reduced seizure threshold, increased seizure severity, and reduced therapeutic response to antiepileptic drugs [16–18]. Furthermore, while human studies of physiological stress in relation to seizures during early childhood are lacking, longitudinal human studies show that perinatal maternal self-reported stress is linked to early life seizure severity and younger age at first simple FS [34,35]. Thus, although our data do not support changes in stress sensitivity in all children affected by early-life seizures, they do suggest that enhanced stress sensitivity can be associated with seizure vulnerability in some children, notably those with simple FS.

Although various animal studies show that stress may be associated with increased seizure severity [36–41], children in our study with arguably more severe seizures, as a group, did not show altered stress reactivity. These results are coherent with multiple human studies suggesting that stress may impact seizure genesis [35,42–44] and increase seizure occurrence [7,8], but not necessarily seizure severity. Notably, one study showed that children with a first seizure provoked by stressful events tended to have more controlled epilepsies than those with a first seizure unprovoked by stress, suggesting that premorbid stress exposure may affect epileptogenesis rather than prognosis [42]. As children with complex FS in our study did not significantly differ from healthy controls, our study may further support altered early-life stress reactivity as being mostly associated with a low seizure threshold and not enhanced seizure severity. Thus, seizure occurrence in children

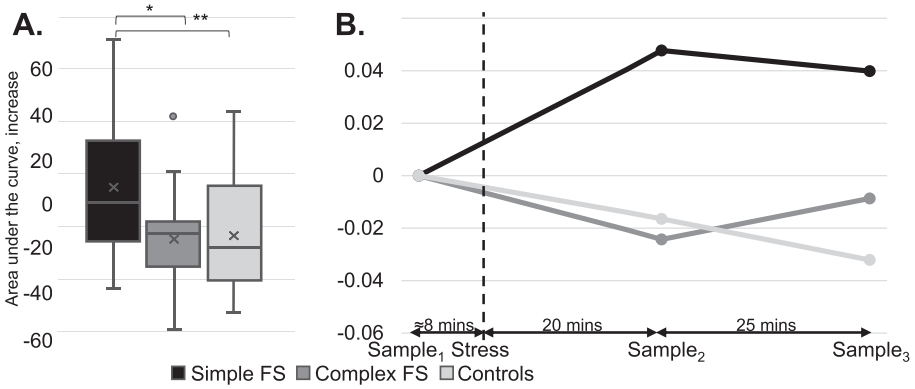

Fig. 2. Title: differences in cortisol levels between study groups. Description: A. Main difference between study groups in mean AUCi ("x"). Second quartile is represented by the boxes, whiskers indicate outside variability, and group outliers are plotted. * = $p < 0.05$; ** = $p < 0.01$. B. Mean cortisol trajectory separated per study groups. Trajectories are baseline-adjusted and show changes in cortisol levels between measurement times ($X_1 = 0$; $X_2 = Sample_2 - Sample_1$; $X_3 = Sample_3 - Sample_1$). Model built using untransformed and winsorized cortisol values. The figure suggests that only the simple FS group show increased cortisol reactivity to experimental stress.

with complex FS as a group may signal abnormal network connectivity in the developing brain or premorbid brain insults [10,45], rather than reduced seizure threshold that induced by stress.

As a result, an important, novel aspect of our study is the disparity in stress sensitivity according to seizure type, suggesting that differences between simple and complex FS may go beyond clinical features. More precisely, we argue that the distinction between children with past simple and complex FS may include differences in environmental exposure, notably to stress, and genetic predisposition to stress sensitivity. Divergences in environmental and genetic origins between FS types have already received some support [46]. Additionally, familial clustering of epilepsy and behavioral disorders in humans suggest a greater role of genetics and environmental influences in uncomplicated epilepsies whereas more severe seizures would be influenced by preexisting neurological insults [10]. With regard to environmental factors, acute exposure to psychological stress in humans leads to changes in gene expression of polymorphisms [47] associated with increased incidence of simple but not complex FS in humans [48], and lower FS resistancy in rodents [49]. Thus, we suggest that in the context of simple FS, fever could be enhancing neuronal excitability in already hyperexcitable children. Whether hyperexcitability was present in these children, and was due to premorbid stress, genetic predisposition, or a combination of both is beyond the scope of this study and should be the subject of future research. Studies of children and teenagers with epilepsy have shown altered stress reactivity only in patients with stress sensitive epilepsy [22], further supporting that the seizure–stress relationship may depend on patients' stress sensitivity.

Descriptive analyses did not show group differences regarding cognition nor could they support a relationship between cognition and stress reactivity. These results might be explained by the unspecific nature of instruments available to evaluate cognition during early childhood. Still, as stress may exacerbate seizures' consequences on cognition [50], future longitudinal studies are needed to show how enhanced stress reactivity may relate to prognosis following simple FS.

4.1. Study design and limitations

Our study was conducted on a total sample size large enough to find a large effect size given our main hypothesis. Still, sample size for the complex FS group was small, and unequal sample size could lead to loss of statistical power. Furthermore, small sample size and large variance in cortisol data led to large confidence interval. Nevertheless, assumptions necessary to conduct our analyses were satisfied, and our study design led to pertinent, statistically significant findings. Comparisons with healthy controls only could have biased interpretation of the results, as it is possible that increased stress sensitivity had been induced by minor illnesses or hospital visits. However, this seems unlikely as children were seen on average months following FS, and neither minor illnesses nor repeated hospital visits for mild childhood illnesses are associated with long-term enhanced stress in children [51,52]. Furthermore, significant differences between participants with simple and complex FS provided interesting results on stress sensitivity in children with simple FS, while controlling for these variables.

While FS may be associated with neurodevelopmental disorders such as autism, our exclusion criteria may limit the generalizability of our results to neurotypical children. High SES in our studied families and recruitment in a large metropolitan area may limit generalizability as well. Personality and environmental factors may have led some families to decline to participate or fail to complete the questionnaires. These factors cannot be assessed, may have an impact on data interpretation, and led to missing data in descriptive statistics, but not studied variables.

The use of salivary cortisol as our stress measure provides multiple advantages in early childhood studies as a noninvasive, easy to use method for assessing cortisol levels [28]. The efficiency of stressor paradigms in early childhood has been a concern of developmental researchers [27,53], yielding only a 20% success rate in children aged 10–24 months [27]. As school-aged children show increased cortisol reactivity to medical procedures and novelty [26], it has been suggested that adult supportiveness may act as a buffer to increased cortisol to experimental stress in infants and toddlers. Thus, precautions were systematically taken while evaluating all participants in order to increase chances of inducing a physiological stress reaction (i.e., arm restraint, reduced parental support). Still, increased cortisol reactivity to stress was not successfully induced in all participants of the current study. Hence, mild arm restraint and parental unresponsiveness might be insufficient to induce cortisol reactivity to experimental stress in developmental research. In addition, studies have shown that parents preventing their children to interact with novel stimulus leads to enhanced cortisol reactivity to novelty [54]. In that context, children of parents who agreed to participate in a research-EEG, which is a novel situation, might show greater stress regulation to novelty. Nevertheless, our study design led to significant results regarding stress in children with FS. More precisely, as controls and complex FS did not show a significant increase in mean cortisol levels following the stressor, increased cortisol reactivity to stress in children with past simple FS revealed increased sensitivity to experimental stress in this population. Moreover, developmental studies have previously suggested that increased cortisol reactivity to stress in single groups or individuals, while the overall study sample does not show such responses, may reveal individual characteristics, such as unsecure attachment or anxious predisposition, that could affect development [55,56]. Still, future studies aiming to

investigate stress reactivity in children with FS should incorporate multiple stressor paradigms that may represent a threat to parental supportiveness, as well as multiple measures of stress reactivity and stress regulation. For instance, autonomic nervous system responses may be less likely to be buffered by parental support behavior [53].

5. Conclusion

Stress is the most frequent seizure precipitant for people with epilepsy and is considered a burden for patients and their caretakers [7]. A growing body of literature suggests that the seizure–stress relationship starts in early infancy [14]. Our study supports the existence of neuroendocrine alterations in children with common, benign seizures but shows that the relationship between early-life seizures and stress may depend on seizure type. These results add to previous studies suggesting that the relationship between stress and seizures, in humans, acts mainly on seizure genesis not severity and may depend on patients' stress sensitivity. While results from our study clarify this relationship, they raise questions about the link between stress and seizure severity in early childhood. Furthermore, although simple FS are considered benign, our study supports a reduced stress sensitivity threshold in this population. As animal studies suggest that stress in the context of seizure disorders may have an impact on neurological and behavioral outcome [50,57,58], the relationship between stress and development in children with simple FS should be the subject of future studies. Thus, the next steps would involve studying early-life stress, seizures, and cognitive or neurological outcome longitudinally, preferably combining multiple measures of stress reactivity and regulation. Findings of such studies would result in further clarifying the relationship between early-life stress and seizure, potentially leading to noninvasive interventions targeting stress, which are still rare in seizure disorders.

Declaration of interests

None.

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Appendix A. Supplementary material

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