■ Original article

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Cognitive and behavioural development in children presenting with complex febrile seizures: at onset and school age

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ABSTRACT

Objective. Our goal was to assess development, cognition and behaviour following an initial complex febrile seizure (FS), at onset and school age, in the context of known risk factors for cognitive development.

Methods. Two cohorts were recruited. Thirty-five infants with an initial complex FS were assessed within the first year post-seizure and compared to 30 controls (simple FS) based on measures of cognitive, motor and language development, behaviour and emotions. Additionally, 19 school-age children with previous complex FS (11 multiple, eight prolonged) were assessed and compared to 19 controls (simple FS) based on measures of intelligence, learning/memory, executive functioning, behaviour and emotions.

Results. Within the first year post-onset, infants with complex FS did not significantly differ from controls based on developmental measures. Seizure duration and age at seizure onset did not impact developmental outcome. School-age children with complex FS showed unaltered global intelligence, but lower executive functioning, compared to controls. Children with prolonged FS also showed evidence of a lower level of learning and memory abilities. Neuropsychological scores correlated with seizure duration. Children with complex FS showed more attentional problems and anxious/depressed symptomatology at onset and school age, and more hyperactivity at school age.

Significance. Infants with complex FS seemed to show normal development within the first year post-seizure onset. However, challenges in executive functioning, learning and memory at school age were found in children with a history of FS. Hence, at school age, cognitive challenges cannot be excluded based on undifferentiated early cognitive development, and may occur even in the absence of the most severe form of FS (*i.e.*, FSE). Beyond the limits of this study (*i.e.*, small sample size, use of parental questionnaires for emotional/behavioural outcome, absence of focal cases in the school-age cohort), our results suggest that a follow-up is necessary beyond the early preschool years in order to understand the long-term outcome.

Key words: convulsions; executive functions; attention; memory; learning; behaviour

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Febrile seizures (FS) are defined as a seizure in association with a febrile illness without prior afebrile seizures [1]. They are the most common paediatric seizures [2, 3]. Simple FS (SFS) are characterized by a brief (< 10 minutes), isolated and generalized seizure episode. Complex FS (CFS) represent 20% of cases and are arguably more severe. They are characterized by either a prolonged (15-30 minutes), recurrent within 24h, or focal seizure episode, or a combination of complex features. Febrile status epilepticus (FSE) is a subtype of CFS lasting ≥30 minutes [3]. Although converging evidence has revealed the benign nature of SFS, demonstrating outcomes similar to those in healthy-developing children [4], outcomes subsequent to CFS are less clear.

For instance, infants with FSE have been shown to develop normally within the first month post-onset. However, they demonstrated slightly weaker motor development and receptive language, and accelerated forgetting, which has been associated with hippocampal anomalies, within six weeks to one year post-onset [5-7]. Hence, initial very prolonged CFS (70-90 minutes) are associated with developmental issues. This proposed poor outcome within the first year post-onset requires further investigation, particularly considering other CFS types, in order to better differentiate their impact on development.

Beyond preschool years, population-based studies have demonstrated unaltered global intelligence and scholastic achievement in school-age children following FS [8, 9]. Others have revealed contradictory evidence regarding the impact of CFS on cognition and behaviour, depending on the subtype and the specific measures adopted [10-13]. Studies investigating isolated cognitive functions in CFS have focused on the assessment of hippocampus-dependent cognitive functions, such as learning and memory, given the association between CFS and hippocampal damage [14-17]. In particular, school-age children, having suffered prolonged CFS, demonstrated similar memory skills to controls, although the mechanisms used to achieve these were different, as evidenced by changes in event-related potentials and hemodynamic activity [18, 19].

Given the connections between the hippocampus and frontal areas, known for their involvement in executive functioning, these capacities may also be impacted [20, 21]. Yet, few studies have investigated executive functioning in school-age children with FS. While studies have shown that CFS are associated with increased externalizing issues, attentional difficulties and poor inhibition, as measured by parental questionnaires [10, 22-24], similar studies have demonstrated no impact [25]. Moreover, school-age children with previous FS have been shown to have an increased risk of attentional deficit and hyperactivity disorder (ADHD) and scholastic difficulties [26]. Based on objective measures, evidence has pointed to weaker sustained attention in children who have suffered CFS [27]. Yet, studies have failed to identify executive deficits, although this may be due to lumping together the different FS groups [11, 12, 28]. Still, Billstedt *et al*. [28] have argued that recurrent seizures and a younger age at onset are risk factors for cognitive deficits in children with FS.

In summary, few studies have investigated cognitive development following all types of CFS, using objective and standardized measures focusing on specific cognitive domains. Moreover, the impact of seizure characteristics, such as age at onset or complex features, on cognitive development remains unclear in the long-term. Our aim was to investigate cognition and behavioural outcomes at onset and at school age following CFS, compared to children who have had SFS, in the context of known risk factors for poor outcome.

Methods

Participants

Two cohorts were recruited retrospectively for this cross-sectional study. Infants were recruited at seizure onset (i.e., infant cohort), and children were recruited at the beginning of their schooling, between five and six years of age (i.e., school-age cohort). In both cohorts, children with previous CFS were compared to children with SFS (control group) with similar demographics, given their known benign outcome. All recruitment was done through the Mother and Child University Hospital Center Sainte-Justine's Emergency Department. The study was approved by the hospital's research ethics board. All participants' parents provided written informed consent to participate and were free to withdraw at any point.

SFS were defined as a single generalized seizure lasting <10 minutes. CFS were defined either as a seizure with focal onset (i.e., focal), occurring more than once within 24 hours (i.e., multiple), and/or lasting >15 minutes (i.e., prolonged), or a combination of either criterion. FS characteristics were drawn from participants' medical files. Exclusion criteria for all subjects included CNS infection, occurrence of afebrile seizures and known developmental delays. None of the participants were taking medication at the time of testing.

For the infant cohort, infants aged six to 42 months, who had been discharged from the Emergency Department with a diagnosis of a first FS, were flagged by ER physicians and nurses. Parents were contacted by our team for participation within one year post-seizure.

For the school-age cohort, ER physicians provided our team with a list of school-age children who had been discharged with a diagnosis of FS roughly five years previously (i.e., between the ages of six to 42 months). Their medical files were extensively reviewed for eligibility.

Procedures

Parents accompanied their children for the appointment at the hospital. Demographic information was collected through an in-house developmental questionnaire. Neuropsychological testing was completed in one session with one (school-age cohort) or two (infant cohort) examiners who were graduate students in Neuroscience or Clinical Neuropsychology and had received extensive training in the administration of the measures. The order of the measures administered was the same for all participants and several breaks were scheduled during the testing session. Behavioural questionnaires were completed by the parent on the day of the testing. All administration and scoring were overseen by a registered neuropsychologist.

Measures

- ***Infant cohort***

Development was assessed using the Bayley Scales of Infant and Toddler Development, 3rd Edition (BSITD-III), which provided scores in five domains: cognition, receptive and expressive communication and fine and gross motor skills [29]. Scaled scores with a mean of 10 and a standard deviation (SD) of 3 were obtained for each of the abilities, with higher scores representing better performance.

Behavioural and emotional problems were assessed using the Child Behavior Checklist for ages 1.5 to 5 years (CBCL) [30]. Results of this questionnaire are organized according to seven syndrome scales: emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems and aggressive behaviour, and five DSM-oriented scales; affective problems, anxiety problems, pervasive developmental problems, ADHD and oppositional defiant problems. Given the minimum age of 18 months, only a subgroup of our sample was able to complete the assessment (n = 14 CFS and 11 controls). T-scores with a mean of 50 (SD = 10) were provided for all scales; higher scores indicate more problematic behaviours.

- ***School-age cohort***

Intellectual functioning was assessed using the Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (WPPSI-III) [31]. Selected subtests allowed the calculation of a prorated Verbal IQ Index (Information and Vocabulary) and a prorated Performance IQ Index (Blocs and Matrices). The administration of two additional subtests (Comprehension and Object Assembly) allowed for the calculation of a prorated Global IQ Index. Composite scores with a mean of 100 (SD = 15) were provided for each index. Higher scores are representative of better performance.

Learning and memory abilities were assessed using the California Verbal Learning Test for Children (CVLT-C) [32] and selected subtests of the Developmental Neuropsychological Assessment, 2nd Edition (NEPSY-II) [33]. Two scores were derived from the CVLT-C: the Total Trials 1-5, a global index of the child's verbal learning ability, and the Long Delay Free Recall, representing the child's ability to freely recall learned information following a 20-minute delay. T-scores were provided, with higher scores corresponding to better memory abilities. Selected subtests from the NEPSY-II allowed for the assessment of visual memory ("Memory for Designs"), verbal memory ("Narrative Memory"), and working memory ("Sentence Repetition").

Attention and executive functions were evaluated using subtests from the NEPSY-II to assess selective and sustained attention ("Auditory Attention"), inhibition ("Inhibition", "Statue") and generation/planning ("Design Fluency"). Scaled scores were provided for the NEPSY-II subtests. Higher scores represent better performance.

Emotion and behaviour were assessed using questionnaires completed by the parent, including the Conners' Parent Rating Scales-Revised Long Form [34] and the CBCL [30, 35]. Results of the Conners scale, designed to evaluate ADHD, are organized based on seven scales: Oppositional, Cognitive Problems/Inattention, Hyperactivity, Shy/Anxious, Perfectionism, and Psychosomatic. T-scores were provided for each scale, with higher scores indicating more problematic behaviours. Two versions of the CBCL were utilized, depending on age; CBCL 1.5 to 5, which has previously been described in the *Infant Cohort* measures, and CBCL 6 to 18. Results of the latter version are organized according to eight syndrome scales: anxious/depressed, withdrawn, somatic complaints, attention problems, aggressive behaviour scales, social problems, thought problems, and rule-breaking behaviour scales. DSM-oriented scales were the same as for the 1.5 to 5 version. T-scores were provided, with higher scores indicating more problematic behaviours/emotions. This version of the questionnaire was completed by 24 participants (12 CFS and 12 SFS).

Statistical analyses

Statistical analyses were carried out using IBM SPSS for Windows, Version 25.0 (IBM, Armonk, NY). Normality was examined using skewness and kurtosis values (i.e., |0 – 3|). When necessary, variable distributions were logarithmically transformed to normality. Analyses were performed on complete cases. Statistical significance was defined as a two-sided alpha level of ≤ 0.05, and Bonferroni corrections for multiple testing, adjusted for intercorrelation, were applied on all post-hoc analyses. Assumptions necessary to perform our planned statistical analyses were verified and satisfied.
For both cohorts, demographic variables and seizure characteristics were compared between groups using chi-square tests for categorical variables (i.e., sex) and Student's T-tests for continuous variables (i.e., familial income, parental education, age at onset, age at test).
For the infant cohort, multivariate analysis of variance (MANOVA) was used to compare both groups based on developmental measures (i.e., BSITD-III scaled scores). For the school-age cohort, a one-way analysis of variance (ANOVA) was used to investigate group differences based on a composite measure of global intelligence (Full Scale IQ score based on the WPPSI-II). NEPSY-II and CVLT-C scores were pooled and weighted into two cognitive domains: Executive Functioning (Auditory Attention, Inhibition, Design Fluency and Statue subtests) and Memory (Memory for Designs, Narrative Memory, Sentence Repetition subtests and the CVLT-C learning and memory scores). Each domain was compared between groups using a one-way analysis of variance (ANOVA), and performance in both cognitive domains was compared within each group (simple, prolonged and multiple) using paired t-tests. A MANOVA was used to compare scores based on the Conners scale between study groups.
Since the CBCL was administered in both cohorts, the sample was pooled for statistical analysis. Thirty-four children with CFS were compared to 30 children with SFS based on the scales available for both versions of the questionnaire, using a MANOVA. Significant effects were followed using post-hoc ANOVAs.
Lastly, the relationship between our study variables and seizure characteristics known to be risk factors of poor outcome (i.e., age at seizure onset and seizure duration) were investigated in both cohorts using Pearson's bivariate correlation.

Results

Infant cohort

• *Descriptive statistics*

One hundred and ninety-five infants were referred, and 65 parents agreed to participate. Our CFS group included 35 infants (16 males): 19 multiple, 10 prolonged, six focal. These were compared to 30 controls (14 males) with SFS. Mean seizure duration was 27.3 minutes in the prolonged CFS group. No significant group differences were found with regards to demographics or seizure features, other than characteristics defining both groups ($p > 0.09$) (*table 1*). Log transfor-

▼ **Table 1.** Infant cohort sample descriptives for simple and complex FS groups.

	Simple FS group n = 30 Mean (Std)	**Complex FS group n = 35 Mean (Std)**
Seizure type (% per group)		
Simple (n =30)	100%	
Multiple (n = 19)		54.2 %
Prolonged (n = 10)		28.5%
Focal (n = 6)		17.1%
Sex (%)		
Female (Simple n = 16; Complex n = 19)	53.3%	54.2%
Male (Simple n = 19; Complex n = 16)	46.6%	45.7%
Age at test (months)	17.05 (6.30)	20.29 (9.03)
Age at seizure onset (months)	15.23 (5.80)	16.39 (7.47)
Family income ($ CAN)	67 230.76 (23 428.71)	75 375.00 (24 880.03)
Mother's education (years)	15.07 (3.6)	15.91 (2.1)
Father's education (years)	15.23 (5.80)	16.39 (7.47)
Time between last seizure and test (months)	1.7 (1.6)	3.03 (4.11)

▼ **Table 2.** Developmental scores based on the Bayley-III scales for simple and complex FS groups in the infant cohort.

	Simple FS group n = 30 Mean (Std)	Complex FS group n = 35 Mean (Std)	*F*	*p*
Cognition	10.66 (1.7)	10.42 (2.42)	0.20	0.65
Receptive communication	9.63 (2.14)	10.11 (3.30)	0.46	0.49
Expressive communication	10.03 (1.9)	9.48 (2.68)	0.86	0.35
Fine motor	11.03 (2.60)	10.88 (2.70)	0.05	0.82
Gross motor	9.8 (2.56)	9.9 (3.39)	0.01	0.89

Results are presented as scaled scores for each of the five scales.

mations were applied to the time between last seizure and test and seizure duration.

● ***Group differences***

Mean performances across all BSITD-III scales for both groups fell within the average range (*table 2*). All children from both groups showed cognitive development within average range (standard scores from 80 to 119) or above. Seven and 20% of children with SFS and CFS, respectively, showed below average (standard scores from 70 to 79) verbal development, while 3% (SFS) and 11% (CFS) showed below average motor development. No significant differences between CFS and SFS were found for mean developmental scores within the first year following seizure onset.

● ***Associated risk factors***

Correlational analyses between study variables and risk factors revealed no significant relationships between developmental scores and age at onset, seizure duration or time between last seizure and test within the first year following seizure onset.

School-age cohort

● ***Descriptive statistics***

Based on the medical files, 223 children were eligible to participate, and 40 parents agreed. Our CFS group included 21 children (12 males): 13 multiple CFS and 10 prolonged CFS. Children with multiple and prolonged CFS were studied separately, given the similar sample size. Two children were excluded due to a complex presentation, hence final groups were composed of eight prolonged CFS and 11 multiple CFS. No participants with focal features were identified based on the medical files. Participants were compared to 19 children (eight males) with SFS. Mean seizure duration in the prolonged CFS group was 19.5 minutes, ranging from 1 to 45 minutes. No significant group differences were found with regards to demographics or seizure characteristics, other than characteristics defining both groups ($p > 0.14$) (*table 3*).

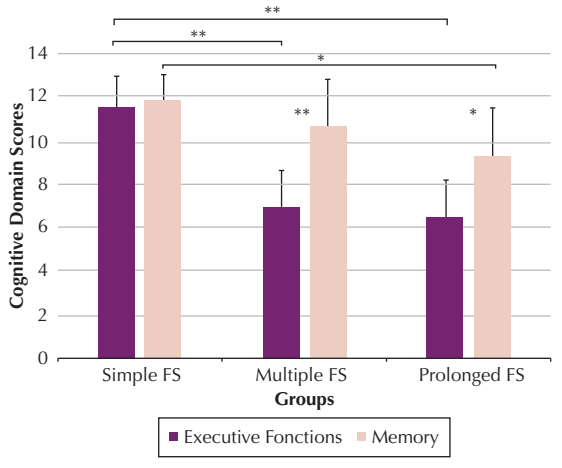
▼ **Table 3.** Sample descriptives for simple, multiple and prolonged FS groups in the school-age cohort.

	Simple FS group n = 19 Mean (Std)	Complex Multiple FS group n = 11 Mean (Std)	Complex Prolonged FS group n = 10 Mean (Std)
Sex (%)			
Female	57.8%	18.1%	70%
Male	42.1%	81.8%	30%
Age at test (years)	6.00 (0.44)	6.00 (0.32)	6.04 (0.23)
Age at seizure onset (years)	1.33 (0.33)	1.04 (0.46)	1.27 (0.62)
Family income ($ CAN)	79 368.4 (26 179.3)	90 454.5 (42 629.5)	77 500.0 (23 717.1)
Mother's education (years)	16.5 (2.0)	15.0 (2.0)	15.0 (2.6)
Father's education (years)	15.2 (2.6)	14.8 (2.9)	15.3 (2.4)

• ***Group differences based on cognitive and behavioural measures***

One-way ANOVA revealed no significant differences in global intelligence (*table 4*). All children with SFS and prolonged CFS showed global intelligence within average range or above, while 9% of children with multiple CFS showed below average global intelligence. One-way ANOVA revealed significant differences between groups based on executive functions ($F(2, 35) = 46.37$, $p = 0.0000000001$) and memory ($F(2, 35) = 6.45$, $p = 0.004$). Post-hoc analyses revealed lower executive functioning scores in both CFS groups ($p < 0.00000001$) and lower memory scores in the prolonged CFS group ($p = 0.004$), compared to the SFS group (*table 4*). Paired t-tests showed a significant difference in performance between cognitive domains in both CFS groups (multiple, $t(10) = -8.34$, $p = 0.000008$; prolonged, ($t(7) = -5.02$, $p = 0.002$), but not in the SFS group ($t(18) = -0.71$, $p = 0.486$). Children with multiple and prolonged CFS showed worse performance in executive functions ($M = 6.93$, $SD = 1.72$; $M = 6.5$, $SD = 1.72$, respectively) compared to memory ($M = 10.67$, $SD = 2.16$; $M = 9.31$, $SD = 2.20$, respectively) (*figure 1*).

Average scores across behavioural scales were below clinical cut-offs for all groups. MANOVA, based on a



■ **Figure 1.** School-age group differences according to cognitive domain.

▼ **Table 4.** Neuropsychological scores for simple, multiple and prolonged FS groups in the school-age cohort.

	Simple FS group n = 19 Mean (Std)	Complex Multiple FS group n = 11 Mean (Std)	Complex Prolonged FS group n = 8 Mean (Std)
WPPSI-III Global IQ	106.05 (15.12)	94.56 (11.36)	106.25 (16.47)
Executive Function	11.60 (1.37)	6.92 (1.72) **	6.5 (1.72) **
Auditory Attention	10.84 (2.46)	6.36 (1.50)	5.13 (1.36)
Inhibition	11.45 (2.33)	6.50 (2.52)	6.88 (1.91)
Statue	13.00 (1.25)	6.27 (2.65)	5.38 (3.29)
Design Fluency	11.26 (2.02)	9.00 (2.32)	8.25 (2.96)
Memory	11.89 (1.18)	10.67 (2.16)	9.31 (2.20) *
Memory for Designs	10.32 (2.63)	11.18 (4.07)	10.00 (3.30)
Narrative Memory			
Free Recall	13.05 (2.30)	10.73 (3.69)	8.75 (2.25)
Recognition	11.16 (1.68)	9.36 (2.84)	7.88 (3.48)
Sentence Repetition	11.74 (2.05)	9.73 (1.56)	10.63 (2.26)
CVLT-C			
Total Trials 1-5	12.74 (2.42)	11.55 (2.98)	11.61 (3.03)
Long Delay Free Recall	12.32 (2.43)	11.45 (1.75)	9.63 (2.50)

Results of the Global IQ are presented as standard scores. Results of the cognitive domains (i.e. Memory and Executive Functions) and their subtests are presented as weighted scaled scores.

* $p < 0.001$

* $p < 0.01$

▼ **Table 5.** Behaviour/emotion scores based on the Conners scale for simple, multiple and prolonged FS groups in the school-age cohort.

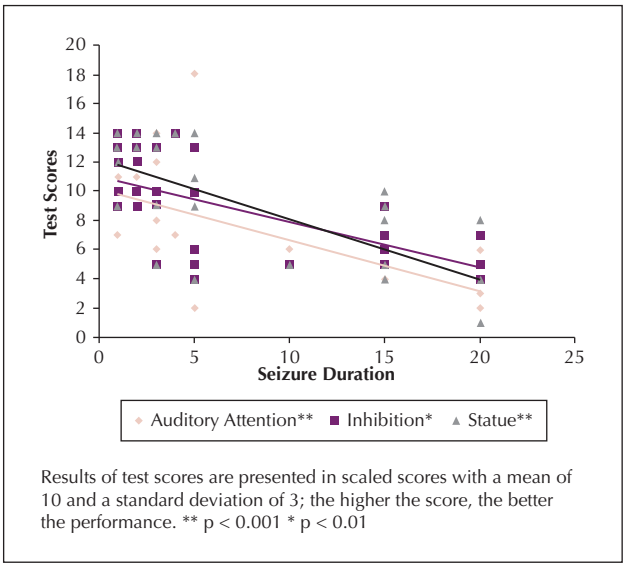
	Simple FS group n = 19 Mean (Std)	Complex Multiple FS group n = 11 Mean (Std)	Complex Prolonged FS group n = 8 Mean (Std)
Conners			
Hyperactivity	50.9 (6.7)	63.2 (12.9)*	59.3 (11.3)
Oppositional	50.1 (9.2)	56.6 (13.0)	54.4 (9.1)
Cognitive problems	49.9 (6.5)	59.5 (14.7)	48.4 (10.5)
Shy/Anxious	48.6 (6.9)	56.6 (9.3)	53.3 (12.9)
Perfectionism	52.9 (8.6)	55.1 (12.5)	60.2 (12.5)
Psychosomatic	50.2 (4.8)	54.4 (13.5)	51.4 (5.4)

Results are presented as t-scores; the higher the score, the worse the performance.
* p < 0.0001
* p < 0.01

comparison of Conners subscales between groups, revealed a significant effect of FS type ($F(10, 62) = 2.05$, $p = 0.043$). Post-hoc ANOVAs revealed a significant difference on the hyperactivity scale ($F(2, 34) = 5.72$, $p = 0.007$); children with multiple CFS scored worse than those of other groups ($p = 0.008$) (*table 5*).

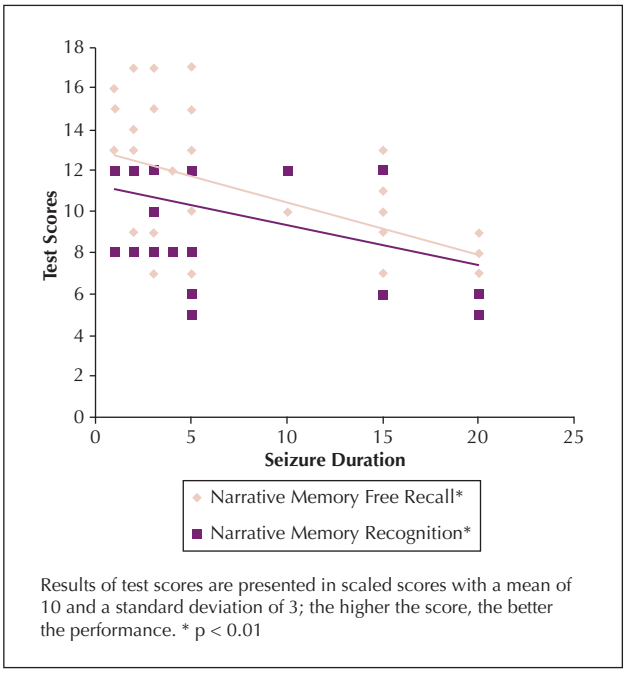
● ***Associated risks factors***

Significant negative correlations were found between seizure duration, executive functions ($r = -0.560$, $p = 0.0002$) and memory ($r = -0.542$, $p = 0.0004$). Follow-up correlations between seizure duration and specific subtests revealed significant relationships between seizure duration and measures of attention and executive functioning, notably Auditory Attention ($r = -0.612$, $p = 0.0001$), Inhibition ($r = -0.407$, $p = 0.009$), and Statue ($r = -0.686$, $p = 0.0001$) (*figure 2*), as well as on measures of learning and memory, namely Narrative Memory Free Recall ($r = -0.495$, $p = 0.001$) and Narrative Memory Recognition ($r = -0.481$, $p = 0.002$) (*figure 3*). These results suggest that as seizure duration increased, performance decreased. There was no



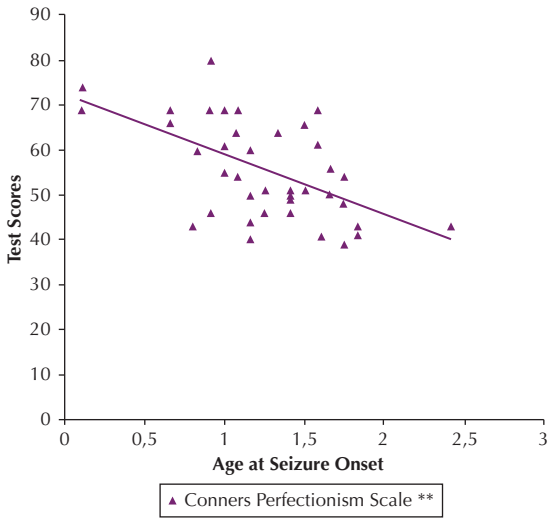
Results of test scores are presented in scaled scores with a mean of 10 and a standard deviation of 3; the higher the score, the better the performance. ** p < 0.001 * p < 0.01

■ **Figure 2.** Correlations between executive functioning measures and seizure duration.



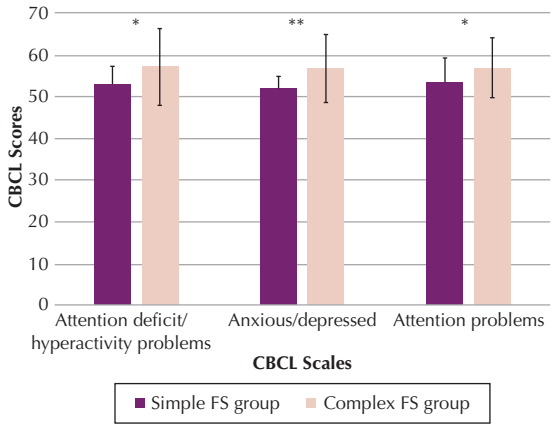
Results of test scores are presented in scaled scores with a mean of 10 and a standard deviation of 3; the higher the score, the better the performance. * p < 0.01

■ **Figure 3.** Correlations between learning and memory measures and seizure duration.



Results of test scores are presented in t-scores; the higher the score, the worse the performance. ** p < 0.001

■ **Figure 4.** Correlation between Conners Perfectionism Scale and age at seizure onset.



Scores are presented in T-scores; the higher the value, the worse the performance. ** p < 0.01 * p < 0.05

■ **Figure 5.** Significant CBCL group differences accross both cohorts.

significant association between neuropsychological scores and age at seizure onset.

However, significant negative correlations were obtained between age at seizure onset and the Conners' Perfectionism scale (r = -0.565, p = 0.0001), suggesting that a younger age at onset was associated with more pronounced perfectionism traits (*figure 4*). There was no significant association between behavioural/emotional scales and seizure duration.

The combined cohorts

Mean group scores across all CBCL scales for both cohorts fell below clinically significant cut-offs (*table 6*). A MANOVA revealed a significant effect of seizure type on CBCL scales (F(9, 52) = 2.4, p = 0.023). No effect of age group or association between age and FS type was found. Post-hoc analyses were significant for ADHD symptomatology (F(1, 60) = 4.81, p = 0.032), anxiety/depression (F(11, 60) = 8.08, p = 0.006) and

▼ **Table 6.** Behaviour/emotion scores based on the CBCL for simple and complex FS groups across both cohorts.

	Simple FS group n = 30 Mean (Std)	Complex FS group n = 34 Mean (Std)	*F*	*p*
Affective problems	52.80 (5.06)	55.76 (7.31)	2.15	0.14
Anxiety problems	53.13 (4.86)	57.20 (8.71)	3.45	0.06
Attention deficit/ hyperactivity problems	53.23 (4.24)	57.20 (9.17)	4.81	0.03
Oppositional defiant problems	53.50 (5.96)	56.82 (7.44)	3.50	0.06
Anxious/ depressed	51.96 (2.95)	56.88 (8.07)	8.08	0.006
Somatic Complaints	52.76 (5.46)	54.20 (6.94)	0.44	0.51
Withdrawn	53.76 (4.95)	54.20 (5.86)	0.01	0.90
Attention problems	53.33 (6.04)	57.00 (7.02)	4.44	0.03
Aggressive behaviour	53.33 (6.79)	56.50 (8.25)	1.80	0.18

Note. Results are presented as t-scores; the higher the score the more problematic the behaviours.

attentional problems ($F(1, 60) = 4.45$, $p = 0.039$), with the CFS group presenting higher scores than those of the SFS group (*figure 5*). Correlational analysis revealed no significant association between CBCL scores and age at seizure onset or seizure duration.

Discussion

Our aim was to examine cognition and behaviour following an initial CFS, including non-prolonged CFS, at school age, using standardized measures for specific cognitive domains which have rarely been explored. Additionally, we aimed to evaluate the association between FS and seizure characteristics that may influence the cognitive prognosis.

Our results reveal no differences in developmental outcomes within the first year post-seizure onset. Lower sensitivity of tools for cognitive measures in infants due to high variability may have obscured differences. Our results are consistent with previous findings one year post-FSE showing mean scores within the average range, however, they do not mirror the slightly weaker developmental usually reported [6, 7]. The longer seizure duration of FSE could explain, at least in part, the discrepancy in findings regarding the impact on developmental performances.

At school age, our results reveal no significant differences in global intellectual capacity between CFS types and children with SFS, a finding consistent with the existing literature [8, 36]. However, both CFS groups demonstrated weaker executive functioning and the prolonged CFS group showed weaker learning and memory, compared to the eSFS group. Moreover, our data are consistent with previous research revealing sustained attention difficulties after FS [27]. Regarding learning and memory, our results corroborate previous findings by Martinos *et al*. [5], demonstrating a negative impact of prolonged FS or FSE on memory. In their study, those deficits were observed a few weeks as well as a year after onset and were associated with a smaller hippocampal volume. In a more recent study, Martinos *et al*. [37], however, demonstrated preserved global memory scores in children within 10 years following FSE. This discrepancy with our results could possibly be due to the time elapsed since the episode or differences in the tests selected to assess memory skills.

Importantly, our results show that memory was affected to a lesser degree than executive functions, which can be surprising given the suspected role of the hippocampus in FS, as highlighted by animal models and early human imaging studies [14]. However, these studies mostly restricted their clinical sample to very prolonged FS or FSE, in contrast to participants included in the current study, and focused on hippocampal anatomy and hippocampal-dependent cognitive functions. Anatomical analysis beyond the mesial temporal lobe should be the focus of future studies, given the numerous connections between the hippocampus and other brain structures. Nevertheless, based on the current results, it can be speculated that early damage to the hippocampus may result in faulty connections in this network, hindering functions beyond those that are strictly dependent on the hippocampus. Moreover, attentional and executive networks are also highly sensitive to brain function alterations in children and young persons with epilepsy [38].

Regarding behavioural and emotional problems, our results indicate significant parental concern with regards to attention, ADHD, and anxious/depressed symptomology in children with CFS from onset to school age. Heightened hyperactivity was also identified in school-age children with CFS. These results corroborate previous findings demonstrating weaker attentional abilities and increased behavioural problems through parental questionnaires [22, 23]. However, scores remained within normal ranges, consistent with previous studies showing normal functioning following recurrent FS [25]. Other studies revealed significant behavioural problems eight years post-onset, however, these were found in the context of CSE only [39]. Given the subjective nature of our questionnaire measures, we cannot rule out the possible impact and influence of parental stress on our results. It is possible that parents who are stressed as a result of CFS [40] have a biased perception of their child, although childhood problems could also lead to parental stress. Results on the questionnaire may reflect this bidirectional relationship. Hence, the nature of behavioural and emotional challenges following FS remains unclear and requires further research.

In considering known risk factors, our results reveal no impact of age at seizure onset or seizure duration on developmental outcome within the first year post-onset. This may be explained by the relatively short mean seizure duration in our prolonged CFS infant group (27.3 minutes), which is contrast to that of previous studies (70-90 minutes). It is possible that prolonged CFS that do not meet the criteria for FSE are not sufficiently severe to alter development within the first year post-onset. At school age, however, seizure duration, although still short on average (19.5 minutes), was associated with cognitive functions. Previous studies have not revealed a relationship between seizure duration and cognitive deficits in children with prolonged FS, although these children show altered development compared to healthy controls. Thus, it is

possible that seizure duration in the long-term may be reason for concern even before meeting the criteria for FSE, however, this does not further explain cognitive development once the threshold for FSE has been reached. On the other hand, we did not identify a link between seizure duration and behavioural measures.
Overall, our results show that deficits in early development are not detected in infants with CFS within the first year post-onset. It is possible that infants with CFS do not present sequelae within this timeframe or are still too young for any to be detected by objective measures, as cognitive capacities have yet to be differentiated at that point. Of note, an altered functional signal has been found in young children with CFS, suggesting that the mechanisms underlying cognitive sequalae are already at play [41]. As such, school-age participants with CFS demonstrate weaknesses in executive functioning, and to a lesser extent, learning and memory abilities, which worsen as a function of seizure duration, despite normal global intelligence. Our results thus indicate that children presenting with all types of CFS, not limited to FSE, may have impairments in specific cognitive domains within the first six years of their life, when cognitive functions begin to specialize in the developing brain.
Limitations of our study include a small sample size which could have hindered our statistical power and masked some effects. Results of this study will therefore have to be replicated in larger cohorts. Moreover, behavioural/emotional outcome was assessed using parental questionnaires, which inherently limits our interpretation, as previously discussed. Administering a parental stress questionnaire could help disentangle the nature of these results. For school-age children, using teacher questionnaires would also be a relevant way to assess behaviour and emotion outside the influence of parental stress. In the school-age cohort, no children with focal seizures could be identified, limiting our results to complex multiple and prolonged FS.

Conclusion

Our results suggest that development appears to be normal within the first year post-CFS, although specific cognitive domains may be affected at school age, depending on complex features and seizure duration. Additional research is required to shed light on the heterogeneity of FS, as well as to better understand the interplay between genetic and environmental factors and their impact on cognition. Follow-up regarding the impact of CFS on cognition is necessary, beyond the early preschool years and into adulthood, in understanding their long-term outcome. ■

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TEST YOURSELF

(1) Did children with complex febrile seizure show altered development during the first year post-onset?

(2) Which cognitive domains were impacted in children with complex febrile seizures from the school-age cohort?

(3) Which febrile seizure characteristics may influence febrile seizure prognosis?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".