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RESEARCH ARTICLE

Frequency of epilepsy and pathological EEG findings in a Norwegian sample of children with fetal alcohol spectrum disorder: Impact on cognition and adaptive functioning

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Abstract

Background: Fetal alcohol spectrum disorder (FASD) comprises a combination of developmental, cognitive, and behavioral disabilities that occur in children exposed to alcohol prenatally. A higher prevalence of epilepsy and pathological electroencephalographic (EEG) features have also been reported in individuals with FASD. We examined the frequency of epilepsy, pathological EEG findings, and their implications for cognitive and adaptive functioning in children with FASD.

Methods: We conducted a cross-sectional study of 148 children with FASD who underwent a multidisciplinary assessment and a 120-min EEG recording. Group comparisons and regression analyses were performed to test the associations between epilepsy and pathological EEG findings, FASD subgroups and neurocognitive test results and adaptive functioning.

Results: The frequency of epilepsy was 6%, which compares with 0.7% in Norway overall. Seventeen percent of children without epilepsy had pathological EEG findings. Attention-deficit hyperactivity disorder (ADHD) was diagnosed in 64% of the children. Children with epilepsy and/or pathological EEG findings had comparable cognitive and adaptive scores to those with normal EEG. However, children with frontal EEG pathology (without epilepsy) had significantly lower scores on the IQ indices *Processing speed* and *Working memory* than FASD children without such findings, irrespective of ADHD comorbidity.

Conclusions: There was a greater prevalence of epilepsy among children with FASD than in the general Norwegian population. A greater frequency of EEG pathology was also evident in children without epilepsy, across all FASD subgroups. Irrespective of epilepsy, ADHD comorbidity, and FASD subgroup, children with frontal EEG pathology, despite having a normal total IQ, showed significantly slower processing speed and poorer working memory, which may indicate specific executive function deficits that could affect learning and adaptive functioning.

KEYWORDS
ADHD, epilepsy, fetal alcohol spectrum disorder, processing speed, working memory

INTRODUCTION

Fetal alcohol spectrum disorder (FASD) describes a group of neurodevelopmental disorders related to maternal alcohol intake during pregnancy. Several diagnostic systems for FASD exist, which differ somewhat in diagnostic criteria and nomenclature (Elliott et al., 2023). In most systems, the most severe subgroup—fetal alcohol syndrome (FAS) requires the combination of typical facial dysmorphism, prenatal, or postnatal growth retardation and structural (brain anomalies, reduced head circumference) or functional brain abnormalities (including epilepsy) (Elliott et al., 2023). Based on the 4-Digit Diagnostic Code, University of Washington, the spectrum includes four subgroups: full fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), static encephalopathy, and neurobehavioral disorder (Astley et al., 2017). Higher scores for each diagnostic criteria in 4-digit diagnostic code indicate a diagnosis toward full FAS. Most children with FASD suffer from comorbidities and a variety of neurological deficits including problems with attention and executive function and learning. Severe behavioral problems, including hyperactivity, reduced impulse control, and arrested social development even with normal intelligence are common (Rasmussen et al., 2006). Epilepsy and seizures have been reported in previous FASD studies with a prevalence of 3–21% (Bell et al., 2010; Boronat et al., 2017; Nicita et al., 2014). Two of the most used guidelines—the IOM (Institute of Medicine) guidelines and the 4-digit diagnostic code both add epilepsy or documentation of recurrent seizures to the potential assignment of children to the diagnostic categories of FAS or pFAS (Astley, 2013; Hoyme et al., 2016). On the other hand, there is little information about specific seizure types or electroencephalography (EEG) findings, and their possible impact on neurocognitive functioning in children with FASD (Boronat et al., 2017). The prevalence of epilepsy in Norwegian children in general is about 0.7% (Suren et al., 2012) and among typically developed children without epilepsy, abnormal EEG findings are registered in 2–3% (Grant et al., 2016). The term "abnormal" refers to changes in background activity as well as more specific findings such as spikes and spike-and-wave activity (Kane et al., 2017). Only a few studies have systematically examined EEGs of children with FASD, and EEG features are poorly described (Bell et al., 2010). Bell et al. examined 425 patients (2–49 years) diagnosed with FASD and found that 6% had epilepsy. A prospective study of 61 adoptive children with FASD reported that 5% had epilepsy, while one patient showed electrical status epilepticus during sleep (Boronat et al., 2017). In the study by Boronat et al. (2017), 14 of 71 children (23%) had abnormal EEG such as slow background activity and inter-ictal epileptiform activity. Several studies report that abnormal EEG may have adverse effects on cognitive functions, concentration, and attention (Riva et al., 2013). Because active epilepsy is much rarer in FASD children compared to abnormal EEG findings, we wished to consider not merely the presence/absence of seizures but rather the role of EEG pathology on neurocognitive and adaptive functioning. To our knowledge, there are no data available on the relationship between specific EEG abnormalities in FASD children without epilepsy and neurocognitive and adaptive functioning. There is one recent study by Pinner et al. finding correlations between decreased magnetoencephalography peak amplitude and neuropsychological test results (Pinner et al., 2023).

With an incidence of 8–11% in children and adolescents, attention-deficit hyperactivity disorder (ADHD) is a common clinical condition (Suren et al., 2012), and also one of the most common comorbidities in FASD (Gerstner et al., 2023). The impact on neuropsychological functions, especially attention and executive function is well-documented (Cook et al., 2018). In children with FASD, the prevalence of ADHD is up to 15 times higher than in the general pediatric population (Lange et al., 2018).

Study aims

The objective of this study was to examine: (1) frequency of epilepsy and pathological EEG findings in a sample of 148 children with confirmed diagnoses of FAS/FASD, (2) the relationship between epilepsy/pathological EEG findings and FASD subgroups, (3) epilepsy/pathological EEG findings and impact on cognitive test results and adaptive functioning, and (4) the relationship between focal EEG pathology and IQ indices adjusted for ADHD as comorbidity. We hypothesize an increased frequency of epilepsy and pathological EEG findings in children with FASD, and that such findings will have an impact on neurocognitive and adaptive functioning regardless of ADHD comorbidity. Additionally, we hypothesize that localization of focal EEG pathology can be associated with different neuropsychological outcomes.

MATERIALS AND METHODS

Study design

In this cross-sectional study, we included children referred to and diagnosed with FASD based on the 4-digit-diagnostic code at the Regional Competence Center for children with prenatal alcohol/drug exposure at the Sørlandet Hospital in Arendal, Norway from 2018 to 2022.

Participants

The study sample consisted of 148 children and adolescents with FASD (mean age = 10.2 years, SD = 3.9 years, age range 3–17 years; 60% males). The distribution of FASD subgroups was full FAS in 7.4%, partial FAS (pFAS) in 15.5%, static encephalopathy (alcohol exposed) in 30.4%, and neurobehavioral disorder (alcohol exposed) in 46.6% of children.

Demographics

Prior to the clinical assessments, we collected demographic information on birth weight, birth length, gestational age, confirmed diagnoses of epilepsy and ADHD, current medication, socioeconomic

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status, and anamnestic data from Child Welfare Services or biological mother on prenatal alcohol exposure.

Clinical assessment

All children underwent a comprehensive standardized cognitive and neuropsychological assessment by a trained neuropsychologist. The children were assessed cognitively with either a complete version of the Wechsler Preschool and Primary Scale of Intelligence—Third or Fourth Edition (WPPSI III or IV), Wechsler Intelligence Scale for Children (WISC III, IV, or 5), Wechsler Adult Intelligence Scale—Fourth edition or Wechsler Nonverbal Scale of Ability (WNV) depending on age. Most of the children were tested with WISC-IV (66 children/46%), followed by WISC-5 (40/29%), WPPSI-III (17/12%), WAIS-IV (11/8%), WPPSI-IV (8/6%) and one child was tested with WISC-III and one with WNV. To evaluate adaptive functioning we used the parent-reported Vineland adaptive behavior scales-II, which is organized within a three-domain structure (indexes) for the age group 2–21 years: Communication, daily living skills, and socialization. Results sum up to an adaptive behavior composite score.

FASD

We used the 4-digit diagnostic code system, which is the standard diagnostic tool In Norway. The diagnostic assessment was performed by a neuropediatrician (growth and facial dysmorphology assessment) and the neuropsychologist (CNS function), both with long experience in assessing children with FASD.

ADHD

The clinical assessment at our center did not include specific diagnostics for ADHD. Information on an ADHD diagnosis was mainly collected prior to admission from the referring Child Psychiatry clinics, which use the Norwegian guideline for diagnosing ADHD (https://www.helsedirektoratet.no/retningslinjer/adhd). However, if ADHD was highly suspected after clinical assessment at our center, the children were referred back to the local Child Psychiatry clinic with the question of a diagnosis of ADHD. The local clinic then informed us about the result of their assessment. Children, who then got a diagnosis of ADHD, were also included in the study.

EEG measurement

Of all patients, 147 underwent a 120-min conventional EEG (NicoletOne; 23 channel, 10 KHz sample rate) at the same time in the afternoon after a night with normal sleep in an attempt to obtain wakefulness recordings without any sleep deprivation. Part of this registration was a defined period with hyperventilation and photo-stimulation. EEGs were reviewed independently by a neurophysiologist and a neuropediatrician and consensus was obtained for all examined. Part of the review was an assessment of background activity and the presence of paroxysmal abnormalities. Epileptiform discharges were defined by the presence of spikes or sharp waves. The distribution of these discharges was defined either as focal or generalized. Pathological EEG patterns were defined according to the terminology in the last revised glossary by the International Federation of Clinical Neurophysiology (Kane et al., 2017). Epilepsy and seizures were classified according to the International League Against Epilepsy Classification (Scheffer et al., 2017).

Statistics

Data were processed and analyzed using Statistical Package for the Social Sciences (SPSS, IBM, Chicago, IL, USA), version 25.0. A two-factor mixed analysis of variance (ANOVA) was performed to address whether there were any significant main or interaction effects of the testing parameters (WISC, WPPSI, WAIS, WNV, Vineland) and relevant parameters to interact with test results, such as sex, prematurity, ADHD, epilepsy, intellectual disability, SES, and prenatal alcohol only versus alcohol combined with illegal drugs. A regression analysis model followed significant effects. Correction for interacting factors was implemented. p Values ≤0.05 were considered statistically significant. Due to low percentage of missing data, we used imputation method for developing reasonable guesses for missing data. A statistician assisted with the choice of methods and interpretation of the results.

Ethics

The study was approved by the hospital's local Ethics Committee and by the Regional Committee for Medical and Health Research Ethics (no. 2017/2404). The children's legal guardians agreed to participate in the study by signing the informed consent form. Children older than 16 years signed the consent form together with their guardians. The study adhered to the Declaration of Helsinki (World Medical Association, 2013).

RESULTS

Clinical characteristics of the participants (categorized according to FASD subgroup) are shown in Table 1. The 148 study children included 89 males (60%) and 59 females (40%), ages ranged from three to 17 years (mean age 10.2 ± 3.9 years). All children had confirmed prenatal alcohol exposure. In about two-thirds of the cases (63%), there was a history of prenatal alcohol exposure only, while one-third (37%) were exposed to alcohol and illicit drugs. Full FAS was diagnosed in 11 children (7%), partial FAS (pFAS) in 23 children (16%), static encephalopathy (alcohol exposed) in 47 children (32%), and neurobehavioral disorder (alcohol exposed) in 67

TABLE 1 Overview on background variables in the study group.

	All FASD children ($n=148$)	Neurobehavioral disorder (alcohol exposed) ($n=67$, 45%)	Static encephalopathy (alcohol exposed) ($n=47$, 32%)	pFAS (alcohol exposed) ($n=23$, 16%)	FAS ($n=11$, 7%)
Male	89 (60.1%)	38 (56.7%)	29 (61.7%)	15 (65.2%)	7 (63.6%)
Female	59 (39.9%)	29 (43.3%)	18 (38.3%)	8 (34.8%)	4 (36.4%)
Age/SD (years)	10.2 ± 3.9	9.9 ± 4.2	10.8 ± 3.5	9.6 ± 4.3	10.8 ± 3.6
Alcohol only	93 (62.8%)	43 (64.2%)	26 (55.3%)	16 (69.6%)	9 (81.8%)
Alcohol and illicit drugs	54 (36.5%)	24 (35.8%)	21 (44.7%)	7 (30.4%)	2 (18.2%)
Place of residence					
With biological parents	21 (14.2%)	8 (11.9%)	9 (19.1%)	4 (17.4%)	0
With foster caregivers	97 (65.5%)	47 (70.1%)	27 (57.4%)	14 (60.9%)	9 (81.8%)
With adoptive parents	30 (20.3%)	12 (17.9%)	11 (23.4%)	5 (16.7%)	2 (18.2%)
SES (Hollingshead Four-Factor Index of Socioeconomic Status) ($n=96$)	SES 1: 1(1%)	0	1 (1%)	0	0
	SES 2: 17 (18%)	4 (23.5%)	5 (29.4%)	6 (35.3%)	2 (11.8%)
	SES 3: 30 (31%)	1 (50%)	10 (30%)	3 (10%)	2 (6.7%)
	SES 4: 35 (36%)	14 (40%)	16 (45.7%)	3 (8.65)	2 (5.7%)
	SES 5: 13 (14%)	7 (53.8%)	3 (23.1%)	3 (23.1%)	0
Prematurity	14 (9.5%)	5 (7.5%)	3 (6.4%)	5 (21.7%)	1 (9.1%)

Abbreviations: FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; pFAS, partial fetal alcohol syndrome; SES, socioeconomic status.

children (45%). Most of the study participants were in foster care (65.5%), 20.3% were adopted, while 14.2% were living with their biological parents. Fourteen children (9.5%) were born premature, defined as birth before 37 weeks of gestation with highest percentage in the pFAS (21.7%).

FASD and co-morbidities

Table 2 presents the frequency of comorbidities such as epilepsy and ADHD and the distribution of pathological EEG findings in the different FASD subgroups. Nine children had epilepsy (6.1%); eight of them (89%) were in the static encephalopathy group, and one in the pFAS group. Pathological EEG was found in 33 (22%) of the children including those with epilepsy, without significant differences between the FASD subgroups. Of the 148 children, 94 (64%) had an ADHD diagnosis, whereas 54 (58% of those with ADHD) were receiving methylphenidate. The highest prevalence of ADHD was seen in the static encephalopathy group (70%), but subgroup differences were not significant. A diagnosis of intellectual disability defined as total IQ below 70 was confirmed in 10% of the children (15/144), significantly more common in the pFAS/FAS groups ($p=0.003$).

Epilepsy

Detailed information on the nine children with an epileptic disorder is shown in Table 3. Eight of them (89%) were boys and mean age was 9.5 years, range 5–14 years. Two of the children had generalized epilepsy with tonic–clonic seizures and seven children had focal epilepsy with focal seizures with impaired awareness and motor onset in four and focal seizures with impaired awareness and non-motor onset in three. Focal epileptic activity (e.g., spike, spike, and wave) was recorded in the seven patients with focal seizures, while two showed generalized paroxysmal discharges fitting the diagnosis of generalized epilepsy. Only one of the children with epilepsy had mild developmental delay. Six (67%) of the children with epilepsy were treated with lamotrigine, two received valproate and one sulthiame; none needed polypharmacy. All were considered seizure-free on medication, which in all cases was the first anti-seizure medication offered.

EEG findings

Details on EEG findings are listed in Table 4. Abnormal EEG was found in 33 children (22%) including nine children with epilepsy, resulting in 24/138 (17%) children without epilepsy but with abnormal EEG. Epileptiform activity was seen in all children with epilepsy and in 11 (8%) out of 138 children without a history of seizures. Generalized paroxysmal activity was present in nine cases and focal interictal epileptic discharges in 11 (3 frontal, 7 temporal, 1 posterior). Generalized slowing of background activity was detected in two patients. Focal slowing was registered in 11 children (7 frontal, 4 posterior). Focal slowing in the EEG indicates cerebral dysfunction. It is generally accepted that focal slowing indicates structural dysfunction and/or an underlying epileptiform dysfunction (Britton et al., 2016). Superficial sleep or drowsiness was registered in 25 children accidentally. In none of these cases did sleep or drowsiness add any abnormal findings on EEG.

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TABLE 2 Co-morbidities and FASD subgroups (4-Digit-Code).

	All FASD children ($n=148$)	Neurobehavioral disorder (alcohol exposed) ($n=67$)	Static encephalopathy (alcohol exposed) ($n=47$)	pFAS (alcohol exposed) ($n=23$)	FAS ($n=11$)	p-Value NBD/SE versus pFAS/FAS
Epilepsy						
Yes	9 (6%)	0[a]	8 (17%)	1 (4%)	0	0.39
No	139 (94%)	67 (100%)	39 (83%)	22 (96%)	11 (100%)	
Pathological EEG ($n=147$)						
Yes	33 (22%)	16 (24%)	9 (21%)	7 (30%)	1 (9%)	0.37
No	114 (78%)	51 (76%)	38 (79%)	16 (70%)	10 (91%)	
ADHD						
Yes	94 (64%)	41 (61%)	33 (70%)	13 (57%)	6 (55%)	0.26
No	54 (36%)	26 (39%)	14 (30%)	10 (43%)	5 (45%)	
ADHD treatment (methylphenidate)	$n=94$	$n=41$	$n=33$	$n=13$	$n=7$	
Yes	54 (58%)	23 (56%)	30 (64%)	6 (46%)	3 (43%)	0.28
No	40 (42%)	18 (44%)	17 (36%)	7 (54%)	4 (57%)	
Intellectual disability (IQ < 70)	15/144 (10%)	3/66 (5%)	4/44 (9%)	6/23(26%)	2/11 (18%)	**0.002**

Note: Bold values are those with significance due to the statistics.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalography; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; IQ, intelligence quotient; NBD, Neurobehavioral disorder (alcohol exposed); pFAS, partial fetal alcohol syndrome; SE, Static Encephalopathy (alcohol exposed).

[a]By definition. Confirmed epilepsy will give CNS rank 4 in 4-Digit Diagnostic Code, excluding subgroup Neurobehavioral disorder as an option.

TABLE 3 Clinical and neurophysiological findings in nine children with FASD and epilepsy.

Sex	Age	FASD sub-group	Classification	EEG findings	Age of debut	Developmental delay (severity)	Seizure evolution at follow-up	ASM
Male	8 y	SE	Focal	Focal IEDs (right temporal)	11 y	Mild	Seizure free	LTG
Male	5 y	SE	Focal	Focal IEDs (left parietal)	4 y	No	Seizure free	LTG
Male	12 y	SE	Focal	Focal IEDs (left temporo-posterior)	11 y	No	Seizure free	LTG
Male	6 y	pFAS	Focal	Focal IEDs (right fronto-temporal)	6 y	No	Seizure free	SUL
Male	14 y	SE	Generalized	Generalized nonspecific paroxysms	10 y	No	Seizure free	VPA
Male	14 y	SE	Generalized	Generalized nonspecific paroxysms	12 y	No	Seizure free	LTG
Male	5 y	SE	Focal	Focal IEDs (right parietal)	3 y	No	Seizure free	LTG
Female	11 y	SE	Focal	Focal IEDs (right posterior)	9 y	No	Seizure free	LTG
Male	10 y	SE	Focal	Focal IEDs (right posterior)	9 y	No	Seizure free	VPA

Abbreviations: ASM, anti-seizure medication; EEG, electroencephalography; FASD, fetal alcohol spectrum disorder; IEDs, inter-ictal epileptic discharges; LTG, lamotrigine; pFAS, partial fetal alcohol syndrome; SE, Static Encephalopathy (alcohol exposed); SUL, sulthiame; VPA, valproic acid.

Cognitive and adaptive scores in FASD children with and without epilepsy/pathological EEG findings

Table 5 gives an overview of cognitive and adaptive functioning scores in children with FASD with or without epilepsy and in those with normal or pathological EEG findings. Mean full IQ was the same (83) for those with and without epilepsy and for those with and without pathological EEG findings. No significant differences in verbal and performance IQ were found between the different groups. Vineland adaptive behavior scales (VABS) showed poor results (about 20 points lower than the IQ results) on all domain scores and composite score without any significant differences between clinical groups (Table 5).

Frontal EEG pathology and cognition

The 10 children without epilepsy but with frontal pathology on EEG (focal slowing or focal spikes) had normal full IQ (84 SD 19), verbal IQ (87 SD 21), and performance IQ (88 SD 15), but significantly reduced

TABLE 4 Details on EEG findings in the study group ($n = 147$).

EEG findings	Number (*n*)	Percentage	Type of epileptiform activity	*n* / %
Pathological (awake)	33/147	22%		
Epileptiform activity	20/33	61%	Generalized epileptic discharges	9/20 (45)
			Focal IEDs	11/20 (55)
			Frontal	3/11 (27)
			Temporal	7/11 (64)
			Posterior	1/11 (9)
Generalized slowing	2/33	6%		
Focal slowing	11/33	33%		
Frontal	7/11	64%		
Posterior	4/11	36%		

Abbreviations: EEG: electroencephalography; IEDs: inter-ictal epileptic discharges.

scores on the IQ indices *processing speed* (68 SD 12) and *working memory* (69 SD 10). A general linear model adjusted for several covariates (ADHD, prematurity, sex, neurobehavioral disorder/static encephalopathy vs. pFAS/FAS) still showed significantly reduced results for these IQ indices in those with frontal EEG pathology (Tables 6 and 7).

DISCUSSION

We found an increased frequency of epilepsy among children with FASD. A high number of children in all FASD subgroups had pathological EEG findings, even in the absence of epilepsy. Children with epilepsy and/or pathological EEG findings did not have lower cognitive and adaptive scores than the total FASD group. However, irrespective of epilepsy, ADHD comorbidity, and FASD subgroup, children with frontal EEG pathologies showed significantly reduced scores on IQ indices *processing speed* and *working memory*.

Epilepsy and EEG findings

Several neurodevelopmental disorders such as cerebral palsy and autism lead to increased chance for epilepsy (Suren et al., 2012). Only a couple of studies have reported epilepsy among persons with FASD, but with relatively small study samples and including only subjects with FAS. These studies reported epilepsy as co-morbidity in 3–21% of patients with FAS (Bell et al., 2010; Boronat et al., 2017). We found a total frequency of epilepsy of 6.1% in our children with FASD, compared to the general prevalence of 0.7% in Norwegian children (Suren et al., 2012). Most of these children with epilepsy (89%) were within the FASD subgroup Static encephalopathy (alcohol exposed) and none in the FAS subgroup. In the 4-digit diagnostic code, manifest epilepsy entails the FASD subgroups static encephalopathy (alcohol exposed) or FAS/pFAS because it reflects a confirmed affection of the CNS (CNS rank 4) and excludes the subgroup neurobehavioral disorder (alcohol exposed). Our findings differ from those reported by Boronat et al. (2017) and Nicita et al. (2014) where most of the children with epilepsy had a diagnosis of FAS or pFAS, noting that they used different classifications and different study samples. In a study by Bell et al. (2010), epilepsy was diagnosed in 25 (5.9%) of 425 patients with FASD, which is in agreement with our findings. The frequency of epilepsy in that study did not differ between several diagnostic groups of FASD (FAS, pFAS, and alcohol-related neurodevelopmental disorder). The limitation of the study was the lack of EEG data.

In our study, seizure control was easy to obtain by using common anti-seizure drugs (ASDs) at standard dosages in all children with epilepsy, while other studies have shown an increased percentage of children with FASD with difficult-to-treat epileptic syndromes (Bell et al., 2010; Boronat et al., 2017; Nicita et al., 2014). In addition, the authors have identified some risk factors for developing seizure disorders in children with FASD, like preterm birth (Bell et al., 2010). Preterm birth may be a consequence of prenatal alcohol exposure and increases the risk of abnormal brain development, which may increase the risk of epilepsy (Bell et al., 2010). In our sample, prematurity was not associated with an increased risk of epilepsy. In fact, the only possible risk factor of epilepsy identified in our study was male gender (8/9 children, 89%; $p = 0.01$).

There is an overlap in brain structures that are neuropathologically and functionally impaired by prenatal alcohol exposure and those that are associated with the genesis of epileptiform activity in the brain (Bonthius et al., 2001). One of the most frequently reported focal brain abnormality occurs in the corpus callosum (Astley et al., 2009; Fraize et al., 2023), but findings in studies with rats exposed to alcohol during early brain development showed also permanent alteration in the physiology of the hippocampus, thus promoting epileptic activity and enhancing kindling. However, whether there are specific types of seizure disorders that are linked to prenatal alcohol exposure require larger clinical studies, to determine the true cause–effect relationship between alcohol exposure and the increased risk of seizures. The frequency of children with pathological EEG findings without epilepsy in our study group was clearly increased (17%) compared to 2–3% in the general population, in line with previous studies in children with FASD (Bell et al., 2010; Kaneko et al., 1996). In contrast to former studies, we were able to give detailed information on

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TABLE 5 Cognitive and adaptive scores in FASD children with or without epilepsy/pathological EEG.

	FASD children without epilepsy ($n=136$)	FASD children with epilepsy ($n=9$)	FASD children with normal EEG ($n=113$)	FASD children with pathological EEG ($n=33$)	p-Value
Full-IQ score (mean score/SD)	83 (11.9)	83 (14.8)	83 (11.5)	83 (12.1)	ns
Verbal IQ (mean score/SD)	86 (14.2)	88 (18.7)	86 (13.9)	88 (11.4)	ns
Performance IQ (mean score/SD)	88 (13.9)	89 (13)	88 (14.1)	87 (13.26)	ns
Vineland Composite Score (mean/SD)	63 (12.8)	59 (9.5)	63 (12.5)	60 (13)	ns
Vineland Socialization (mean/SD)	71 (12.5)	68 (12.6)	71 (12.4)	69 (12.8)	ns
Vineland, Daily Living Skills (mean/SD)	69 (14)	66 (11)	70 (13.7)	65 (14)	ns
Vineland Communication (mean/SD)	61 (10.8)	57 (8.5)	61 (10.8)	58 (9.7)	ns

Note: *t*-test for equality of means.

Abbreviations: EEG, electroencephalography; FASD, fetal alcohol spectrum disorder; ns, not significant; SD, standard deviation; Vineland, Vineland Adaptive Behavior Scales.

TABLE 6 Regression analysis on working memory as dependent factor.

	Working memory index					
Clinical factors	**Covariates**	**Mean**	**Estimate**	***p*-Value**	**Lower bound**	**Upper bound**
Frontal EEG pathologies (epilepsy excluded)						
Yes (10)		69	−9.4	**0.02**	−17.5	−1.3
No (121)		79				
	ADHD		−2.3	0.32	−6.8	2.3
	Prematurity		1.1	0.78	−5.9	8.1
	Sex		1.5	0.49	−2.8	5.9
	NBD/SE versus pFAS/FAS		−2.4	0.15	−5.5	1.1

Note: *General linear model*. Alpha = 0.05. *R* Squared = 0.116. Bold values are those with significance due to the statistics.

Abbreviations: ADHD: attention-deficit hyperactivity disorder; EEG: electroencephalography; FAS: fetal alcohol syndrome; NBD: Neurobehavioral disorder (alcohol exposed); pFAS: partial fetal alcohol syndrome; SE: Static Encephalopathy (alcohol exposed).

the type of EEG abnormalities and we were able to relate pathological EEG findings to cognitive and adaptive test results.

Cognitive and adaptive scores in children with FASD with and without epilepsy

Several studies have shown that abnormal EEG activity may lead to adverse effects on cognitive function, attention, and possibly emotional functioning in children (Riva et al., 2013), some of these studies refer to patients with active epilepsy or so-called ESES (electrical status epilepticus in sleep) (Pal et al., 2016). It is also assumed that absence of seizures with generalized spike-waves of frontal onset cause a suspension of working memory as part of frontal functions (Niedermeyer & Naidu, 1997). Numerous researchers have documented diminished intellectual functioning in children with FASD (Mattson et al., 2019). Past research also indicates that children with different epilepsies without reduced full IQ may display specific cognitive weaknesses, as deficits in memory and executive functioning, even in mild epilepsies with good seizure control (Kernan et al., 2012). In our study, the mean full IQ score of 83 was similar in children with FASD with or without epilepsy, not surprisingly highest score in the "mildest" FASD subgroup Neurobehavioral disorder (alcohol exposed) (IQ 87), with significantly lower scores (IQ 78) in the pFAS and FAS subgroups ($p=0.002$). Results on the VABS were even lower (composite score 59–63, SD 8.5–14) than expected based on the IQ scores for the children in our study. This is in agreement with several studies that show a mismatch between cognition and adaptive functioning in children with FASD (Astley, 2013; Fagerlund et al., 2012). Carr et al. (2010) argue that reduced adaptive functioning is found regardless of FASD subtype and even if they could not be observed using IQ testing. Estimates consistently find that about 25% of people with epilepsy have an intellectual disability if all types of epilepsies and epileptic encephalopathies are included (Kerr et al., 2014). In our sample, none of the children with FASD with epilepsy had a total IQ below 70 and all of the epilepsies were considered as "mild" forms with quick seizure-free response to medication. Recent research describes epilepsy as a disease which can present with a highly variable phenotype with genetic mutations thought to be the underlying cause in 70–80% of patients (Dunn et al., 2018). In the nine children with epilepsy in our sample, and this might be the case in all studies on epilepsy in FASD, it is not possible to make any statement about causality. The epileptic disorder may be related to the intrauterine exposure to alcohol or of genetic origin, or to the combination of those.

TABLE 7 Regression analysis on processing speed as dependent factor.

	Processing speed index					
Clinical factors	**Covariates**	**Mean**	**Estimate**	***p*-Value**	**Lower bound**	**Upper bound**
Frontal EEG pathologies (epilepsy excluded)						
Yes (10)		68	−16.7	**<0.001**	−25.1	−8.3
No (123)		86				
	ADHD		−4.4	0.11	−8.3	0.15
	Prematurity		−1.1	0.77	−8.3	6.2
	Sex		−3.6	0.13	−8.1	0.89
	NBD/SE versus pFAS/FAS		−2.0	0.12	−4.3	0.41

Note: *General linear model*. Alpha = 0.05. *R* Squared = 0.117. Bold values are those with significance due to the statistics.

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; EEG, electroencephalography; FAS, fetal alcohol syndrome; NBD, Neurobehavioral disorder (alcohol exposed); pFAS, partial fetal alcohol syndrome; SE, Static Encephalopathy (alcohol exposed).

Involvement of the frontal lobe

Apart from their well-known involvement in motor function and language, the frontal lobes play important roles in a multitude of cognitive processes, such as executive function, attention, memory, and language, additionally to processes underlying emotions, mood, and personality (Chayer & Freedman, 2001). In our study, we found associations between *frontal* EEG pathology in children without epilepsy and reduced scores on the two IQ indices *processing speed* and *working memory*, irrespective of the presence or absence of ADHD comorbidity. Executive functions typically include inhibition, working memory, switching, and updating (Engelhardt et al., 2016). Additionally, processing speed, which is how quickly an individual can perceive and process information and/or initiate a response (Shanahan et al., 2006), could also be seen as a component of executive functioning (Sabhlok et al., 2021). The association between *frontal* EEG pathologies without epilepsy and reduced scores on the two IQ indices *processing speed* and *working memory* in our study may indicate clinical significance. Processing speed and working memory are fundamental components to general intellectual functioning. Importantly, both functions are highly susceptible to disruption in cases of brain injury, neurological diseases, and even in normal aging (Hillary et al., 2006). The concept of a disturbed functioning of the frontal cortex was first developed in the severe Rett Syndrome with smallness of the frontal lobe, and with EEG abnormalities in the frontal region (Niedermeyer & Naidu, 1997). Accordingly, what is due to structural damage in Rett syndrome was considered as a neuronal dysfunction in ADHD under more benign circumstances. This functionally impaired frontal lobe results in affected motor activity and also in disturbed attention (Niedermeyer & Naidu, 1997). Studies on patients with left or right frontal damage confirm these results; and implicate that the frontal lobe is exertional in the manifestation of impaired response inhibition and working memory deficits (Chamberlain et al., 2007). O'Hare et al. report alterations in frontal processing in children and adolescents with heavy prenatal alcohol exposure. Working memory tasks were less efficient suggesting functional recruitment abnormalities (O'Hare et al., 2009). Reductions in the frontal lobe volume were demonstrated on MRI by Astley et al. (2009) showing that the mean relative volume of the frontal lobe decreased incrementally across the study groups from controls to FASD subgroups of increasing severity. Prenatal alcohol exposure is associated with microscopic impaired neuronal and glial migration, including heterotopias. Heterotopias are associated with seizures or abnormal EEG (Boronat et al., 2017). Additionally, a recent study showed a mispositioning of GABAergic interneurons in the frontal cortical plate persisting throughout fetal life of 17 fetal and infant brains prenatally exposed to alcohol. An impaired GABAergic signaling is known to trigger various forms of epilepsy (Marguet et al., 2020).

Our results could suggest an altered frontal functioning shown by lower scores on IQ indices *processing speed* and *working memory* in children with FASD with focal frontal EEG pathology. These specific cognitive deficits could not be explained by other risk factors such as ADHD comorbidity or prematurity.

Strength and weaknesses

As many other studies on children with FAS/FASD, our research relies on a clinically referred sample. This may be problematic given that children referred to a specialized third-line center are likely to be more severely clinically impaired, have experienced more placements in foster care and have crossed a threshold where parents or caretakers are seeking help. Therefore, the data cannot and were not intended to be used as prevalence data for Norway. On the other hand, our sample is quite similar to the samples used in other studies regarding FASD subgroups, frequency of ADHD, and epilepsy. The same applies to the results of the IQ testing and Vineland scores. This strengthens the generalization of the results. Another strength is that our study presents data from a rather large sample size where all participants underwent a multidisciplinary assessment done by experienced professionals well trained in FASD diagnostics and the use of the 4-digit diagnostic code, the standard and preferred diagnostic instrument I Norway. However, several diagnostic systems exist and there is no evidence that one diagnostic system is better or more valid for diagnosing FASD than any other (Astley, 2013; Coles et al., 2016). In a study by Peadon et al. (2008), they received information about diagnostic system in use at 34 Centers diagnosing FASD, 24 in USA, five in Canada, and five in

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other countries (UK, Italy, Chile, South Africa). Twenty-three used only one diagnostic system, while 11 centers used elements from several systems. Of those using one system, 14 used the 4-digit code, while nine used the IOM system. Age-appropriate full-version Wechsler tests were used for cognitive assessment and VABS scores were validated in Norwegian children. An experienced neuropediatrician and neurophysiologist evaluated EEG. Weaknesses included the inability to make any statement about whether the increased frequency of epilepsy seen in our sample is causally related to the intrauterine exposure to alcohol or to other causes. However, this uncertainty applies to all comparable studies. The study lacks a comparison group due to the design of the study. Frequencies of epilepsy and pathological EEG findings have therefore been compared to known prevalence in the general (Norwegian) child population. When looking at the relationship between EEG findings and cognition, we have tried to adjust for possible confounders like ADHD and prematurity. Cognitive scores in the FASD subgroups have been compared to norms. However, further study on this topic should include a comparison group, and especially a group of children with ADHD not related to FASD would have been interesting to compare to our study population.

Clinical implications

We report an increased frequency of epilepsy and abnormal EEG findings in children with FASD. The frequency of epilepsy in our sample is comparable to other studies, but the correlation of subclinical EEG pathology to specific cognitive scores has not been reported before. Although EEG pathology did not seem to influence total IQ and adaptive functioning, it was associated with neuropsychological deficits in processing speed and working memory, representing important aspects of executive functioning. We speculate that such deficits may increase the chance of learning disorders. Based on this concern, we suggest a rather low threshold for considering EEG examination in children with FASD regardless of age and FASD subgroup. Children with FASD and focal frontal EEG pathology need special attention and one could speculate that antiepileptic drug treatment could lead to an improvement in frontal functioning, especially if cognitive tests show reduced scores on processing speed and working memory. A different, but interesting, non-invasive and recently published approach is repetitive transcranial magnetic stimulation (rTMS) in children with FASD (Melder et al., 2023). However, any beneficial effects of medication on cognitive/executive functioning should be balanced against any side effects from medication in children without clinical epilepsy. Larger samples and further research on this topic is needed before medical intervention should be decided.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interests related to this publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author.

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