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Original Article

Reduced Interhemispheric Coherence and Cognition in Children with Fetal Alcohol Spectrum Disorder (FASD)—A Quantitative EEG Study

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Neuropediatrics

Abstract

Background Magnetic resonance imaging in fetal alcohol spectrum disorder (FASD) children showed altered connectivity, suggesting underlying deficits in networks, which may be related to cognitive outcome. Functional connectivity has been of interest in neurophysiological research with quantitative electroencephalography (QEEG) as useful tool for measuring pathology, not detectable by normal EEG. The aim of this study was to investigate differences in the EEG interhemispheric coherence (ICoh) in children diagnosed with FASD compared with healthy controls and to relate the results to cognitive scores.

Method Analysis of ICoh in 81 FASD children (4-Digit Code) compared with 31 controls. The children underwent cognitive assessment, and EEG was performed and used for analysis. Group comparisons and analysis of covariance interaction models were used to test for differences between FASD and controls but also to look for differences between FASD subgroups. Significant findings were correlated to cognitive scores.

Results Lower ICoh was found in the frontal and temporal derivations in the FASD group. When comparing FASD subgroups, children with fetal alcohol syndrome had lower ICoh occipital. Reduced ICoh in the temporal alpha band was correlated with lower performance IQ in the FASD group.

Conclusion Our findings could imply hypoconnectivity between the hemispheres with impact on cognition. We suggest that EEG coherence analysis could be a sensitive parameter in the detection of electrophysiological abnormalities in FASD with possible clinical relevance. These results may indicate that QEEG could be used as biomarker for FASD. However, further research is needed to determine the role of QEEG analysis in the diagnosis of FASD.

Keywords
- fetal alcohol syndrome
- fetal alcohol spectrum disorder
- QEEG
- interhemispheric coherence
- epilepsy
- ADHD
- cognition

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Introduction

Fetal alcohol spectrum disorder (FASD) encompasses a spectrum of neurodevelopmental conditions associated with prenatal alcohol exposure.[1,2] The medical diagnosis of fetal alcohol syndrome (FAS) is based on a consensual set of clinical features, including typical facial dysmorphism, prenatal or postnatal growth retardation, and structural (including epilepsy, brain anomalies, reduced head circumference) or functional central nervous system (CNS) pathology. FASD is regarded as a spectrum of clinical conditions with different symptoms.[1–3] Based on the 4-Digit Diagnostic Code, University of Washington, FASD includes four subgroups: full FAS, partial FAS (pFAS), static encephalopathy (SE), and neurobehavioral disorder (ND).[1] Higher score for each diagnostic criteria indicates 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.[4] There is a great variety of possible functioning from the area of mild to moderate mental retardation to normal cognitive functioning. Common to children with FASD, however, is that the impairments of the CNS are lasting, even when intelligence quotient is within the normal range.[4] The role of electroencephalography (EEG) in diagnostics is being debated even if all major FASD diagnostic systems include seizure as expression of brain impairment.[2] An increased incidence of epilepsy and abnormal EEG is documented in several studies with an estimated prevalence of seizures between 3 and 21%.[5] Up to 23% showed abnormalities in the EEG such as slow background activity and interictal epileptiform activity,[5] even among those without epilepsy. There is an overlap in the brain structures that are structurally and functionally impaired by prenatal alcohol exposure and those that are associated with the genesis of epileptiform activity in the brain, including the hippocampus.[6] Pathologic EEG activity may give adverse effects on cognitive functions, concentration, and attention in patients with early cognitive dysfunction.[7] All studies mentioned earlier were limited to qualitative EEG analyses. The quantitative EEG (QEEG) is a different type of analysis that uses mathematical algorithms and has extended the evaluation of the EEG signal.[8] QEEG increases diagnostic options and enlarges the interpretation of neurophysiological analysis because it can show more subtle dysfunctions. QEEG has established its role in neuropsychiatry, for the further evaluation of comorbid neuropsychological deficits in epilepsy, stroke, dementia, depression, encephalopathy, learning and attention disorders.[9] In the field of FASD, there is only one very recent study aimed to investigate the characteristics of the bioelectric activity of the brain using QEEG in 12 FASD children and 12 healthy controls. Bauer et al were able to show the dominance of the alpha rhythm over the beta rhythm and an increased theta/beta ratio among patients with FASD, a typical finding also seen in attention-deficit hyperactivity disorder (ADHD) patients.[10] A different QEEG approach is the coherence analysis. The interhemispheric coherence (ICoh) function quantifies the association between matching pairs of EEG signals in the two hemispheres as a function of frequency. ICoh is useful for measuring changes in EEG topography related to different aspects of brain organization.[11] By analyzing the synchrony between two EEG channels, ICoh can be used as an index of brain connectivity between the brain regions measured by the chosen electrodes. Coherence could be understood as a measure of how effectively two cortical sites are able to link and unlink or to share information. High coherence may represent a measure of strong congruence and an expression of strong structural or functional connection, while low coherence represents rather weak connectivity.[12] Coherence values range from 0 to 1, with 1 meaning perfect agreement in phase difference as a result from complete synchronous activity, and 0 meaning completely no synchronous activity.[13] Deviations in coherence values have been reported in children with ADHD and epilepsy.[14,15] Clarke et al[14] found that ADHD children had reduced coherences in most regions compared with controls, while Varotto et al showed widely reduced local connectivity in children with epilepsy.[15] To our knowledge, no coherence QEEG study has been performed in children with FASD. Looking at ICoh is especially interesting in the FASD group since structural and functional deviations in corpus callosum (CC) have been reported extensively both in animal and clinical studies.[16–18]

Study Aims

The aims of this study were: (1) to investigate ICoh differences between children with FASD with and without comorbidities such as ADHD and epilepsy and healthy controls, (2) to examine ICoh differences between FASD subgroups, and (3) to reveal any correlation between reduced ICoh and cognitive scores in the FASD group.

We hypothesized that QEEG deviations indicating reduced ICoh values will be found in children with FASD even in the absence of pathological findings on standard EEG, and that the reduction would be related to FASD subgroup and inferior cognitive scores.

Materials and Methods

Study Design

Children and adolescents (6–16 years, both sexes) referred to our regional competence center for children with prenatal alcohol/drug exposure at Sørlandet Hospital in Arendal, Norway in 2018 to 2022 and fulfilling a FASD diagnosis based on the 4-Digit Code[8] after clinical assessment were included in this cross-sectional case–control study.

Participants

We assessed 148 children whereof 96 (66%) got a FASD diagnosis. Of these 96 children, 81 (84%) gave their consent to participate in this study. The control group consisted of 31 children who were recruited from different schools in the city of Arendal. They had to score below clinical levels on a symptom checklist, and to report no problems at the clinical

interview that could be indicative of psychopathology. Information about any prenatal exposure was not collected in the control group.

Demographics

Demographic information on birth, comorbidities such as epilepsy and ADHD, current medication, socioeconomic status, and anamnestic data on prenatal alcohol exposure were collected prior to the clinical assessment.

Clinical Assessments

All participants in the FASD group underwent a clinical examination by a neuropediatrician with long experience in this field and 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 (WPPSI III or IV), Wechsler Intelligence Scale for Children (WISC IV or V), Wechsler Adult Intelligence Scale, or Wechsler Nonverbal Scale of Ability, depending on age.

EEG Measurement

EEG was recorded using a NicoletOne system (www.natus.com). During fitting of the electrodes, subjects were familiarized with the testing equipment and the procedure. EEG recordings were obtained as part of the clinical and neuropsychological evaluation. EEGs were recorded from 19 Ag/AgCl electrodes fixed on an elastic cap accordingly to the International 10–20 system, referenced to CPz, with the ground in AFz. The 19 recording electrodes were the following: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz. Patients were seated in an armchair, with their arms and legs at rest. All children underwent a standardized EEG examination. Our EEG protocol includes a 2-hour, 19-channel EEG registration (International 10–20 system). Part of this registration was a defined period with closed eyes, open eyes, hyperventilation, and photostimulation. Signals were sampled at 1 kHz and coded on 16 bits. Impedances were kept below 5 kΩ. For the quantitative analysis (QEEG), we chose a segment with minimal presence of artifact and a length of at least 150 seconds from which 10-second epochs were analyzed. In addition, epochs of the filtered EEG with excessive amplitude ($>$100 μV) and/or excessively fast ($>$35 μV in 20–35 Hz band) and slow ($>$50 μV in 0–1 Hz band) frequency activities were automatically marked and excluded from further analysis. Finally, EEG was manually inspected to verify artifact removal.

Coherence Analysis

Coherence analysis was performed for the four frequency bands: delta (0.5–3.99 Hz), theta (4–7.99 Hz), alpha (8–12.99 Hz), and beta (13–21 Hz).These classic fixed frequency ranges allow comparing our data to existing coherence studies, which have used the same ranges. Coherence between a pair of electrodes for a specific frequency band was defined at the cross-spectral power between the sites normalized by dividing by the square root of the product of the power at each site within that band. Coherence estimates were derived for each band for seven interhemispheric electrode pairs (FP1–FP2, F3–F4, F7–F8, C3–C4, T3–T4, T5–T6, O1–O2).

Statistics

Data were processed using the Statistical Package for the Social Sciences (SPSS, IBM, Chicago, Illinois, United States), version 25.0. A one-way analysis of variance was performed where ICoh for three different FASD samples (*model 1*: all with FASD, *model 2*: FASD without those with epilepsy and/or pathological EEG, and *model 3*: FASD without those with epilepsy and/or pathological EEG and ADHD) was compared with controls. A regression model followed significant effects on ICoh within the different FASD subgroups. A subsequent model tested for significant differences between relevant regions/bands and cognitive scores in the FASD group. This was done by dichotomizing the FASD children into one group with ICoh values above and one group with ICoh values $\leq$ two standard deviations (SDs) beneath mean ICoh for the control group in our study. A regression analysis model followed significant effects on correlations between those groups and cognitive scores. Bonferroni correction was performed when looking at significant group differences in ICoh values according to frequency band and location (electrode pairs).

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 parents agreed to participate in the study by signing the informed consent form. The study adhered to the Declaration of Helsinki.

Results

Clinical characteristics and comorbidities of the study participants and controls are shown in ►**Table 1**. The 81 children with FASD included 48 boys (59%) and 33 girls (41%) whose ages ranged from 6 to 14 years (mean age 9.8 ± 2.3 years). About two-thirds (62%) of the children with FASD were exposed to alcohol only, while one-third (38%) was exposed to both alcohol and illicit drugs prenatally. Most of the children with FASD (64%) were living in foster care. FAS and pFAS were diagnosed in 17 children (21%), SE with known exposure to alcohol in 25 children (31%), and ND (alcohol exposed) in 39 (48%) of the children. Of the 31 healthy controls, 14 were boys and 17 were girls with a mean age of 10.5 years (± 2.0 years). None of the controls had a history of epilepsy, seizures, ADHD, or other neurodevelopmental disorders. Prenatal alcohol exposure was unknown in the control group. Of the 81 children, 44 (54%) had an ADHD diagnosis whereof 22 (50%) were receiving methylphenidate. Six children had epilepsy (7.4%), four of them treated with lamotrigine, one with valproate, and one with sulthiame. One of the children had generalized and five had focal epilepsy. Epilepsy and seizures were classified according to the International League Against Epilepsy Classification.[19] Pathological EEG was found in 17 (21%) children including the 6 with epilepsy. Pathological EEG patterns were defined according to the terminology used in the last glossary,

Table 1 Overview on background variables and comorbidities in the study population

		All FASD children ($n = 81$)	FASD children without epilepsy or pathological EEG ($n = 63$)	FASD children without epilepsy, pathological EEG, ADHD ($n = 30$)	Control group ($n = 31$)	*p*-Value
Boys		48 (59%)	37 (59%)	10 (33%)	14 (45%)	ns
Girls		33 (41%)	26 (41%)	20 (67%)	17 (55%)	
Age, y (SD)		9.8 (2.3)	9.9 (2.4)	9.2 (2.5)	10.5 (2.0)	ns
Alcohol only		50 (62%)	40 (63.5%)	22 (73.3%)		ns
Alcohol and other illicit drugs		31 (38%)	23 (36.5%)	8 (26.7%)		
Care base						
Biological parents		11 (13.6%)	10 (15.9%)	5 (16.7%)		ns
Foster care		22 (64.2%)	38 (60.3%)	16 (53.3%)		
Adopted		18 (22.2%)	15 (23.8%)	9 (30%)		
SES (Hollingshead four-factor index of SES)	SES 1	11 (16.2%)	9 (17.6%)	5 (21.7%)		ns
	SES 2	21 (30.9%)	16 (31.4%)	6 (26.1%)		
	SES 3	32 (47.1%)	22 (43.1%)	9 (39.1%)		
	SES 4	(5.9%)	4 (7.8%)	3 (13.0%)		
FASD subgroup	FAS/pFAS	17 (21%)	12 (19%)	5 (16.7%)		ns
	SE	25 (31%)	20 (31.7%)	7 (23.3%)		
	ND	39 (48%)	31 (49.2%)	18 (60%)		
Comorbidity		No. of children (%)	Type of epilepsy/epileptiform activity			
ADHD						
Yes		44 (54.3)				
No		37 (45.7)				
Epilepsy						
Yes		6 (7.4)	Generalized epilepsy: 1 (17%)			
No		75 (92.6)	Focal epilepsy: 5 (83%)			
Pathologic EEG						
Yes		17 (21)	Epileptiform activity (IEDs): 14/17 (82%)			
No		64 (79)	Focal slowing: 3/17 (18%)			

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalography; IEDs, interictal epileptic discharges; ND, neurobehavioral disorder; ns, not significant; SD, standard division; SE, static encephalopathy; SES, socioeconomic status.
Note: *t*-test for equality of means.

published by the International Federation of Clinical Neurophysiology in 2017 (epileptiform pattern, background slowing, focal slowing).[20] ►**Table 2** gives an overview on cognitive scores in children with FASD with or without comorbidities. There are no significant differences between groups on cognitive scores.

EEG Findings

Abnormal EEG was found in 17 (21%) children including 6 children with epilepsy, resulting in 11 of 75 (15%) children without epilepsy but abnormal EEG. Epileptiform activity was seen in all children with epilepsy and in 9 (12%) out of 75 children without history of seizures. Generalized paroxysmal activity was present in one case and focal interictal epileptic discharges (frontal, temporal, or posterior) in five. Focal slowing (frontal or posterior) was found in three children. Focal slowing in the EEG indicates cerebral dysfunction. It is generally accepted that focal slowing is common with structural pathology or indicates cerebral dysfunction often caused by structural pathology.

Interhemispheric Coherence Differences in the FASD Group versus the Control Group

Significant differences in ICoh values for each tested region are presented in ►**Table 3**. Bonferroni adjusted significant *p*-value was 0.002. The ICoh values for all children with FASD and controls were compared, showing reduced values for the children with FASD in the frontal delta and beta bands ($p < 0.001$) and the temporal alpha ($p < 0.01$) and theta bands ($p < 0.001$). When comparing ICoh values between children with FASD without EEG pathology and controls, reduced values in the FASD group were reported in the frontal delta

Table 2 Cognitive scores in FASD children with or without comorbidities

	All tested FASD children	FASD children without epilepsy or pathological EEG	FASD children without epilepsy, pathological EEG and ADHD	*p*-Value
Full IQ score (mean score/SD)	*n* = 79 84 (11.6)	*n* = 61 84 (11.2)	*n* = 28 82 (10.1)	ns
Verbal IQ (mean score/SD)	*n* = 73 87 (14.4)	*n* = 55 87 (13.9)	*n* = 26 85 (14.4)	ns
Performance IQ (mean score/SD)	*n* = 72 88 (13.6)	*n* = 55 88 (14.2)	*n* = 26 84.9 (14.4)	ns
Working memory (mean score/SD)	*n* = 68 79 (11.6)	*n* = 52 79 (9.8)	*n* = 24 80 (10.5)	ns
Processing speed (mean score/SD)	*n* = 69 84 (11.6)	*n* = 52 85 (12)	*n* = 24 82 (10.1)	ns

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalography; FASD, fetal alcohol spectrum disorder; ns, not significant; SD, standard deviation.
Note: *t*-test for equality of means.

Table 3 Significant differences in interhemispheric coherence values between the two study groups according to frequency band and location (electrode pairs)

Band and location	FASD group (*n* = 81)	Control group (*n* = 31)	*p*-Value	Cohen's d
Delta F3–F4 (μV^2)/SD	0.34 (0.13)	0.41 (0.08)	<0.001	0.61
Beta F3–F4 (μV^2)/SD	0.29 (0.1)	0.40 (0.07)	<0.001	0.69
Alpha T3–T4 (μV^2)/SD	0.33 (0.09)	0.38 (0.06)	0.01	0.59
Theta T5–T6 (μV^2)/SD	0.30 (0.11)	0.39 (0.1)	<0.001	0.83
Significant differences in interhemispheric coherence values between children with FASD (excluding those with epilepsy/pathological EEG) and controls				
Band and location	**FASD children (*n* = 63)**	**Control group (*n* = 31)**	***p*-Value**	**Cohen's d**
Delta F3–F4 (μV^2)/SD	0.34 (0.13)	0.41 (0.08)	<0.001	0.63
Beta F3–F4 (μV^2)/SD	0.30 (0.1)	0.40 (0.07)	<0.001	1.12
Alpha T3–T4 (μV^2)/SD	0.32 (0.07)	0.38 (0.06)	0.01	0.84
Theta T5–T6 (μV^2)/SD	0.30 (0.12)	0.39 (0.1)	<0.001	0.78
Significant differences in interhemispheric coherence values between children with FASD (excluding those with epilepsy/pathological EEG/ADHD) and controls				
Band and location	**FASD children (*n* = 30)**	**Control group (*n* = 31)**	***p*-Value**	**Cohen's d**
Beta F3–F4 (μV^2)/SD	0.31 (0.12)	0.40 (0.07)	<0.001	0.89
Alpha T3–T4 (μV^2)/SD	0.33 (0.07)	0.38 (0.07)	<0.001	0.82

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalography; F, frontal; FASD, fetal alcohol spectrum disorder; SD, standard division; T, temporal.
Note: *t*-test for equality of means, *p*-value 0.05; adjusted *p*-value 0.002 (Bonferroni correction).

and beta band ($p < 0.001$), and the temporal alpha ($p < 0.01$), and theta band ($p < 0.001$). The comparison of ICoh values between 30 children with FASD without comorbidities (epilepsy, pathological EEG, and/or ADHD) and controls showed reduced values in the FASD group in the frontal beta band ($p < 0.001$) and the temporal alpha band ($p < 0.001$).

Interhemispheric Coherence Differences between FASD Subgroups

ICoh differences between FASD subgroups are presented in ►**Table 4**. An implemented linear regression model with correction for interacting factors (ADHD, epilepsy, pathological EEG) showed significantly lower ICoh values in the occipital alpha band (O1–O2) in children with the more severe subgroups full FAS and pFAS compared with those with SE and ND, according to 4-Digit Code. No significant group differences were found in other frequency bands or locations.

Interhemispheric Coherence Values and Cognitive Scores in the FASD Group

To test for any correlations between the ICoh findings and cognition, we decided to dichotomize the FASD group.

Table 4 Regression analysis on alpha O1–O2 as dependent factor in FASD subgroups

Clinical factors	Alpha O1–O2					
	Covariates	Mean coherence value (SD)	Estimate	*p*-Value	Lower bound	Upper bound
FAS/pFAS ($n = 17$) SE/ND ($n = 64$)		0.42 (0.07) vs. 0.50 (0.1)	7.42	**0.007**	−0.16	−0.03
	ADHD		0.15	0.71	−0.24	0.17
	Epilepsy		3.80	0.09	−0.03	0.28
	Pathologic EEG		0.14	0.71	−0.21	0.14

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalography; FASD, fetal alcohol spectrum disorder; ND, neurobehavioral disorder (alcohol exposed); pFAS, partial fetal alcohol syndrome; SE, static encephalopathy (alcohol exposed).
Note: General linear model. Alpha = 0.05. R squared = 0.117.

A mean value of ICoh within the control group was calculated (mean 0.38, SD 0.07). An ICoh value of less than/equal to −2 SDs from the mean was chosen as cutoff point. When testing for any significant effects on correlations between those groups and cognitive scores (full IQ, verbal and performance IQ and the IQ indices *working memory* and *processing speed*), we found significant correlations for the temporal (T3–T4) alpha band and performance IQ ($p = 0.04$) and *processing speed* ($p = 0.02$), respectively (►**Table 5**). Those with ICoh values beneath two SDs from mean had significantly lower cognitive scores, also after covarying for comorbidities. For other cognitive scores, no significant relationships were found.

Discussion

The main aim of this study was to explore any EEG ICoh differences between children with FASD and a group of healthy children. Additionally, we wanted to explore whether reduced coherence indicating poor connectivity would have clinical correlates in the FASD group. The EEG coherence as dependent variable of interest was derived from systematically deartifacted EEG data for different frequency bands. In children with FASD, there was a significantly lower coherence in both delta, beta, and alpha bands in the frontal and temporal regions compared with healthy controls. Reduced values were still present when FASD children with comorbidities (ADHD, epilepsy) were excluded. The children in the FASD group with the lowest coherence values in the temporal alpha band had reduced performance IQ and inferior *processing speed*, indicating clinical implications.

FASD and Comorbidities

Only few studies have focused on epilepsy among persons with FASD and most of them with relatively small samples of subject with FAS only. These studies reported epilepsy as comorbidity in 3 to 21% of patients with FAS.[5] We found a frequency of epilepsy of 7.4% ($n = 6$) in our children with FASD, compared with the general prevalence of 0.7% in Norwegian children.[21] Even if this is not a prevalence study, our findings do confirm prevalence data published before.[5,22] The frequency of children with pathological EEG findings with or without epilepsy was significantly increased with 21% ($n = 17$) compared with 2 to 3% in the general population.[23] Findings in studies with animals prenatally exposed to alcohol showed permanent neuropathological and functional alteration in the physiology of brain structures promoting epileptic activity and enhancing kindling associated with the genesis of epileptiform activity in the brain.[24] However, to determine the true cause–effect relationship between alcohol exposure and the increased risk of seizures, larger clinical studies are required.

Interhemispheric Coherence Differences between the FASD Group and Controls

In contrast to the many studies on QEEG coherence in children and adults with different psychiatric and neurological diseases, to our knowledge, there is no such study on individuals with FASD. As both epileptic disorders and ADHD may have impact on ICoh, we compared the controls not only to the whole sample of children with FASD but also to a subpopulation where those with epilepsy and/or confirmed ADHD were excluded. The obtained results showed significantly lower coherence for delta, beta, and alpha waves in frontal and temporal regions in the FASD group. Different regions of the brain have to communicate with each other in networks to enable a basis for the integration of sensory information, sensory–motor coordination and other functions that are important for perception, learning, memory, information processing, and behavior.[25] To interpret our results, it might be helpful to look at coherence studies on other diseases. The group investigated mostly in coherence research is children with ADHD. An Australian group[26] found that ADHD children had lower alpha ICoh compared with controls in frontal and temporal regions, suggesting reduced cortical differentiation and specialization in ADHD, particularly in corticocortical circuits.[27] Our results with decreased ICoh in the frontal and temporal areas in the FASD group without ADHD could be interpreted in the same direction. Another group that has been analyzed with ICoh is children with cerebral palsy (CP). Kułak et al showed that children with hemiplegic CP had lower ICoh in the temporal, parietal, and occipital derivations for the alpha band, suggesting hypoconnectivity between the right and left hemispheres, due to the hemistructural brain lesion.[25] Decreased EEG coherence has also been reported in children with such anatomic disconnection as agenesis of the CC.[28]

Several animal and clinical studies have confirmed that intrauterine alcohol exposure can lead to reduction of size of

Table 5 Regression analysis with performance IQ and processing speed index as dependent factors

	Performance IQ					Processing speed				
	Covariates	Estimate	*p*-Value	Lower bound	Upper bound		Estimate	*p*-Value	Lower bound	Upper bound
Alpha T3–T4 ≤ or > 0.24 μV^2		8.52	**0.04**	0.50	16.54	Alpha T3–T4 ≤ or > 0.24 μV^2	12.2	**0.02**	4.75	19.61
	ADHD	0.03	0.99	−10.37	10.42		0.78	0.87	−8.53	10.01
	Epilepsy	3.61	0.57	−9.22	16.43		2.99	0.60	−8.37	14.36
	Pathologic EEG	8.51	0.13	−2.46	19.62		7.1	0.10	−0.77	18.78

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalography; T, temporal.
Note: General linear model. Alpha = 0.05. R squared = 0.24.

CC, which is the tract of nerve fibers bridging the two brain hemispheres.[18] The CC participates in learning and interhemispheric transfer of sensory–motor habits, as well as contributing to language processing and cognitive functions.[29] Coben et al[30] found low interhemispheric delta and theta coherences across the frontal region as well as decreased delta, theta, and alpha coherence over the temporal regions in children with autistic disorders, interpreted as neural underconnectivity. Another study on children with Asperger's syndrome found reduced frontal ICoh in the beta and alpha bands, construed as the existence of frontal lobe abnormalities in these children, possible due to abnormal CNS maturational processes.[31] We found similar ICoh results in our children with FASD and the interpretation might be the same. Network connectivity deficits occur in children with FASD and functional magnetic resonance imaging (MRI) studies have shown aberrant frontal–parietal connectivity.[32] Network abnormalities positively correlate with white matter microstructural integrity and with the extent of prenatal alcohol exposure, resulting in functional impairments of the brain's communication network in children with FASD.[33] Neuroanatomical connectivity refers to structural links such as synapses or fiber pathways of neurons, and different MR modalities may reveal the brain structural connectivity with a relatively high spatial resolution. EEG cannot directly reveal structural connections and it is applied to estimate functional and effective connectivity.[34] However, ICoh could represent as a measure of how effectively the two hemispheres are able to link and share information,[27] and high coherence between two signals may therefore be interpreted as expression of strong structural and functional connectivity.[12]

Interhemispheric Coherence between Different FASD Subgroups According to 4-Digit Code

We divided the FASD children in two groups, those with full FAS or pFAS and those with nonsyndromic forms (SE and ND).[3] We found significantly lower alpha ICoh at the occipital pair, even after correction for comorbidities with known impact on ICoh. Some of the subgroup analysis resulted in small sample sizes, and this should be taken into account when interpreting the results. Similar results were shown by Koeda and Takeshita with lower ICoh at the occipital region for the alpha band in preterm children with CP, suggesting that these findings could correspond neuroanatomically to the posterior callosal thinning often seen on MRI in preterm born children.[35] Children with FASD tend to have not only a smaller brain but also a disproportional reduction in specific brain structures, including CC, detectable with MRI, even if no specific neuroanatomical criterion has been added to the diagnostic guidelines.[3] CC, being the largest commissural white matter bundle in the human brain, is the main route for interhemispheric transfer of information and is involved in a large number of cognitive processes.[36] Already in 1995, Riley et al described a significant reduction in size of the anterior region and the two posterior regions of the CC by measuring photographic slice of the CC.[18] Recent MRI research by Fraize et al demonstrated bimodal damage mostly in the posterior

half of the CC, more frequently and sensitively observed than the reduction in the whole section area in children with FASD.[17] Within the callosal structure, it appeared that the size reduction affected the posterior region more severely, which correlated to the amount of prenatal alcohol consumption.[16–18] Independent of CC abnormalities, increased ICoh in occipital lobe networks have been reported for children with ADHD.[37] Our results may be describing functional and anatomical hypoconnectivity between posterior brain regions in the more severely affected FASD children. However, because we have not done MRI to confirm, this remains speculative.

Interhemispheric Coherence Reduction and Cognitive Scores in the FASD Group

Finding differences in interhemispheric communication, we wanted to investigate whether this could be reflected in cognitive scores. We did find a relationship between lower coherence values for the temporal (T3–T4) alpha band and lower scores on performance IQ ($p = 0.04$) and the *processing speed* index ($p = 0.02$). Performance IQ provides a measure of an individual's overall nonverbal or visuospatial intellectual abilities and comprises fluid reasoning, spatial processing, attentiveness to details, and visual-motor integration. The *processing speed* index provides a measure of a person's ability to process visually presented information quickly in terms of reaction time; the time required to complete a series of operations, or the number of items answered correctly in a set period of time.[38] Deficits in these areas contribute to executive function problems, including initiation, inhibition, mental flexibility, novel problem solving, planning, and regulation of emotions.[38] Such deficits may be partly explained by reduced interhemispheric transfer.[28] White matter abnormalities, including deviations in CC are among the most well-replicated neuroimaging findings in FASD and are thought to contribute to impaired functional connectivity and prominent deficits in executive function.[39] We speculate that the decreased ICoh seen in the FASD group could be related to impaired transcallosal pathways, a hypoconnectivity between the right and left hemispheres partly due to reduction in CC[18] and our findings of reduced cognitive functioning may indicate that this hypoconnectivity has clinical consequences.

Strength and Weaknesses

There are limitations in the current study that are worth mentioning. Our results are limited to 81 Norwegian children. As many other publications on children with FAS/FASD, our research relies on clinically referred samples. This may limit generalization of results since children referred to a specialist center as ours are more likely to be more severely impaired, are more often from foster care and have crossed a threshold where parents or caretakers are seeking help. However, the distribution of FASD subgroups in our study is comparable with the largest sample of FASD patients from the Washington State Fetal Alcohol Syndrome Diagnostic and Prevention Network.[40] The small sample size in some of the subgroup analyses in our study is a weakness and makes interpretation more uncertain. Strength of study is that our patients underwent a clinical assessment done by professionals within the field of FASD and all the children had a confirmed diagnosis of FASD by the use of the 4-Digit Code, the preferred diagnostic system used in Norway. All EEG examinations were analyzed by the same neuropediatrician. Even though the EEG recording was performed at the same time of the day and after a good night sleep to minimize the impact on EEG recording, it is possible that the children's performance was still affected by for instance tiredness.

Conclusion

In this study, we found significantly reduced ICoh values in both temporal and frontal frequency bands in children with FASD compared with controls. This could imply reduce connectivity between the two hemispheres through CC. Those with poorest interhemispheric connectivity in the FASD group had lower scores on performance IQ and *processing speed* index, indicating possible clinical consequences. We speculate that the reduced connectivity could be explained by neuropathological alterations in gray and white matter caused by prenatal alcohol exposure. Our study supports the idea that QEEG might be a useful biomarker in the diagnosis of FASD. However, further research is needed to determine the role of QEEG analysis in diagnosis and follow-up of children with FASD.

Conflict of Interest
None declared.

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References

1 Astley SJ, Bledsoe JM, Davies JK, Thorne JC. Comparison of the FASD 4-Digit Code and Hoyme et al. 2016 FASD diagnostic guidelines. Adv Pediatr Res 2017;4(03):13
2 Hoyme HE, Kalberg WO, Elliott AJ, et al. Updated clinical guidelines for diagnosing fetal alcohol spectrum disorders. Pediatrics 2016;138(02):e20154256
3 Kent N, Hayes N, Young S, et al. Exploring resource implications and models of care for assessment and diagnosis of fetal alcohol spectrum disorder: A scoping review. Alcohol Clin Exp Res 2023; 47(11):2022–2032
4 Rasmussen C, Soleimani M, Pei J. Executive functioning and working memory deficits on the CANTAB among children with prenatal alcohol exposure. J Popul Ther Clin Pharmacol 2011;18 (01):e44–e53
5 Boronat S, Vicente M, Lainez E, et al. Seizures and electroencephalography findings in 61 patients with fetal alcohol spectrum disorders. Eur J Med Genet 2017;60(01):72–78

6 Bonthius DJ, Pantazis NJ, Karacay B, Bonthius NE, Taggard And DA, Lothman EW. Alcohol exposure during the brain growth spurt promotes hippocampal seizures, rapid kindling, and spreading depression. Alcohol Clin Exp Res 2001;25(05):734–745
7 Riva D, Franceschetti S, Erbetta A, Baranello G, Esposito S, Bulgheroni S. Congenital brain damage: cognitive development correlates with lesion and electroencephalographic features. J Child Neurol 2013;28(04):446–454
8 Nuwer M. Assessment of digital EEG, quantitative EEG, and EEG brain mapping: report of the American Academy of Neurology and the American Clinical Neurophysiology Society. Neurology 1997;49(01):277–292
9 Livint Popa L, Dragos H, Pantelemon C, Verisezan Rosu O, Strilciuc S. The role of quantitative EEG in the diagnosis of neuropsychiatric disorders. J Med Life 2020;13(01):8–15
10 Bauer W, Dylag KA, Lysiak A, et al. Initial study on quantitative electroencephalographic analysis of bioelectrical activity of the brain of children with fetal alcohol spectrum disorders (FASD) without epilepsy. Sci Rep 2023;13(01):109
11 Shaw JC. An introduction to the coherence function and its use in EEG signal analysis. J Med Eng Technol 1981;5(06):279–288
12 Fein G, Raz J, Brown FF, Merrin EL. Common reference coherence data are confounded by power and phase effects. Electroencephalogr Clin Neurophysiol 1988;69(06):581–584
13 Nunez PL, Silberstein RB, Shi Z, et al. EEG coherency II: experimental comparisons of multiple measures. Clin Neurophysiol 1999;110(03):469–486
14 Clarke AR, Barry RJ, McCarthy R, et al. Effects of methylphenidate on EEG coherence in attention-deficit/hyperactivity disorder. Int J Psychophysiol 2005;58(01):4–11
15 Varotto G, Franceschetti S, Caputo D, et al. Network characteristics in benign epilepsy with centro-temporal spikes patients indicating defective connectivity during spindle sleep: a partial directed coherence study of EEG signals. Clin Neurophysiol 2018;129(11):2372–2379
16 Astley SJ, Aylward EH, Olson HC, et al. Magnetic resonance imaging outcomes from a comprehensive magnetic resonance study of children with fetal alcohol spectrum disorders. Alcohol Clin Exp Res 2009;33(10):1671–1689
17 Fraize J, Convert G, Leprince Y, et al. Mapping corpus callosum surface reduction in fetal alcohol spectrum disorders with sulci and connectivity-based parcellation. Front Neurosci 2023;17:1188367
18 Riley EP, Mattson SN, Sowell ER, Jernigan TL, Sobel DF, Jones KL. Abnormalities of the corpus callosum in children prenatally exposed to alcohol. Alcohol Clin Exp Res 1995;19(05):1198–1202
19 Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(04):512–521
20 Kane N, Acharya J, Benickzy S, et al. A revised glossary of terms most commonly used by clinical electroencephalographers and updated proposal for the report format of the EEG findings. Revision 2017. Clin Neurophysiol Pract 2017;2:170–185
21 Surén P, Bakken IJ, Aase H, et al. Autism spectrum disorder, ADHD, epilepsy, and cerebral palsy in Norwegian children. Pediatrics 2012;130(01):e152–e158
22 Nicita F, Verrotti A, Pruna D, et al. Seizures in fetal alcohol spectrum disorders: evaluation of clinical, electroencephalographic, and neuroradiologic features in a pediatric case series. Epilepsia 2014;55(06):e60–e66
23 Smith SJ. EEG in the diagnosis, classification, and management of patients with epilepsy. J Neurol Neurosurg Psychiatry 2005;76 Suppl 2(Suppl 2):ii2–ii7
24 Bonthius DJ, Woodhouse J, Bonthius NE, Taggard DA, Lothman EW. Reduced seizure threshold and hippocampal cell loss in rats exposed to alcohol during the brain growth spurt. Alcohol Clin Exp Res 2001;25(01):70–82
25 Kułak W, Sobaniec W, Boćkowski L. EEG spectral analysis and coherence in children with hemiparetic cerebral palsy. Med Sci Monit 2005;11(09):CR449–CR455
26 Barry RJ, Clarke AR, Hajos M, Dupuy FE, McCarthy R, Selikowitz M. EEG coherence and symptom profiles of children with attention--deficit/hyperactivity disorder. Clin Neurophysiol 2011;122(07):1327–1332
27 Markovska-Simoska S, Pop-Jordanova N, Pop-Jordanov J. Inter- and intra-hemispheric EEG coherence study in adults with neuropsychiatric disorders. Pril (Makedon Akad Nauk Umet Odd Med Nauki) 2018;39(2-3):5–19
28 Marco EJ, Harrell KM, Brown WS, et al. Processing speed delays contribute to executive function deficits in individuals with agenesis of the corpus callosum. J Int Neuropsychol Soc 2012;18(03):521–529
29 Innocenti GM, Schmidt K, Milleret C, et al. The functional characterization of callosal connections. Prog Neurobiol 2022;208:102186
30 Coben R, Clarke AR, Hudspeth W, Barry RJ. EEG power and coherence in autistic spectrum disorder. Clin Neurophysiol 2008;119(05):1002–1009
31 Clarke AR, Barry RJ, Indraratna A, Dupuy FE, McCarthy R, Selikowitz M. EEG activity in children with Asperger's syndrome. Clin Neurophysiol 2016;127(01):442–451
32 Wozniak JR, Mueller BA, Bell CJ, et al. Global functional connectivity abnormalities in children with fetal alcohol spectrum disorders. Alcohol Clin Exp Res 2013;37(05):748–756
33 Wozniak JR, Riley EP, Charness ME. Clinical presentation, diagnosis, and management of fetal alcohol spectrum disorder. Lancet Neurol 2019;18(08):760–770
34 Cao J, Zhao Y, Shan X, et al. Brain functional and effective connectivity based on electroencephalography recordings: a review. Hum Brain Mapp 2022;43(02):860–879
35 Koeda T, Takeshita K. Electroencephalographic coherence abnormalities in preterm diplegia. Pediatr Neurol 1998;18(01):51–56
36 Treble A, Hasan KM, Iftikhar A, et al. Working memory and corpus callosum microstructural integrity after pediatric traumatic brain injury: a diffusion tensor tractography study. J Neurotrauma 2013;30(19):1609–1619
37 Saunders A, Kirk IJ, Waldie KE. Hemispheric coherence in ASD with and without comorbid ADHD and anxiety. BioMed Res Int 2016;2016:4267842
38 Lange RT. Performance IQ. In: Kreutzer JS, DeLuca J, Caplan B, eds. Encyclopedia of Clinical Neuropsychology. New York, NY:: Springer New York;; 2011:1907–1908
39 Ware AL, Long X, Lebel C. Functional connectivity of the attention networks is altered and relates to neuropsychological outcomes in children with prenatal alcohol exposure. Dev Cogn Neurosci 2021;48:100951
40 Astley SJ. Profile of the first 1,400 patients receiving diagnostic evaluations for fetal alcohol spectrum disorder at the Washington State Fetal Alcohol Syndrome Diagnostic & Prevention Network. Can J Clin Pharmacol 2010;17(01):e132–e164

