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Thorsten Gerstner

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Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
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Department of Clinical and Molecular Medicine

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Søvnforstyrrelser, epilepsi, EEG-funn og klinisk funksjon hos norske barn med føtalt alkohol spektrumforstyrrelse (FASD)

Vi har utført en omfattende undersøkelse av barn og ungdom med diagnosen FASD som har vært til diagnostisering og utredning ved Regional Kompetansetjeneste – Medfødte Russkader (RK-MR) ved Sørlandet Sykehus HF. Fokus har vært å sammenligne det kliniske bildet av FASD med testing av barnets evnenivå og vurdering av adaptiv atferd, dvs. daglige aktiviteter som kreves for å klare seg på egen hånd. Samtidig ble det undersøkt for søvnvansker, og det ble tatt et EEG (elektroencefalogram) som ble analysert med tanke på epilepsitypiske avvik og med en kvantitativ metode som måler hjernens evne til å kommunisere mellom høyre og venstre halvdelen.

I studien fant vi at barn og ungdom med FASD har økt forekomst av forstyrret søvn (79%) og at denne søvnproblematikken rammer barn med FASD uavhengig av alvorlighetsgraden av FASD. Søvn ble kartlagt ved at foresatte fylte ut en norsk versjon av skjemaet Sleep Disturbance Scale for Children. Barn med oppmerksomhetsforstyrrelse (ADHD) i tillegg til FASD, hadde økt forekomst av søvnforstyrrelser sammenlignet med de uten ADHD. Barna med forstyrret søvn hadde dårligere skårer på tester som måler eksekutive funksjoner, altså evnen til problemløsning, planlegging, gjennomføring av oppgaver og regulering av atferd. Funnene våre understreker viktigheten av screening for søvnforstyrrelser hos alle barn med FASD siden søvnproblemer kan behandles. Vi kartla også hvor mange av barna med FASD som i tillegg har epilepsi. I vår gruppe med 148 barn og ungdom i alder 6-17 år var det 6% med epilepsi sammenlignet med 0,7% i generell barnepopulasjon i Norge. I tillegg hadde 17% av barna med FASD avvik på EEG (elektroencefalogram) uten å ha epilepsi, noe som også er mye høyere enn det som ses hos friske barn. De med unormale EEG-funn hadde ikke lavere intelligenskvotient (IQ) sammenlignet med de med normalt EEG, men de med EEG avvik i de fremre deler av hjernen (uten epilepsi) hadde signifikant lavere skårer på tester som måler prosesseringshastighet og arbeidsminne. Dette er noe som også sees hos barn med ADHD, men vi fant det uavhengig av en ADHD-tilstand. En svekkelse på disse to kognitive områdene kan ha stor betydning for barnet evne til å lære. I en fortsettelse av dette fant vi også avvik i en kvantitativ EEG koherensundersøkelse, som sier noe om hvordan de to hjernehalvdelene kommuniserer seg imellom. Sammenlignet med en gruppe friske barn fant vi redusert interhemisfærisk kommunikasjon (ICoh) i spesifikke hjerneområder korrelert med lavere eksekutive funksjoner. Funnene kan tyde på svekkede forbindelser mellom de to hjernehalvdelene med innvirkning på hjernens funksjon. Våre resultater kan tyde på at en slik EEG-undersøkelse kan være en mulig biomarkør for FASD.

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List of papers

1. Gerstner T, Saevareid HI, Johnsen AR, Løhaugen G and Skranes J. Sleep disturbances in Norwegian children with fetal alcohol spectrum disorders (FASD) with and without a diagnosis of attention-deficit hyperactivity disorder or epilepsy. *Alcohol Clin Exp Res*. 2023 Mar;47(3):589-599. doi: 10.1111/acer.15009. Epub 2023 Feb 21. PMID: 36811179

2. Gerstner T, Henning O, Løhaugen G, Skranes J. Frequency of epilepsy and pathological EEG findings in a Norwegian sample of children with fetal alcohol spectrum disorder: Impact on cognition and adaptive functioning. *Alcohol Clin Exp Res.* 2024 Feb;48(2):309-318. doi: 10.1111/acer.15247. Epub 2023 Dec 26. PMID: 38105112

3. Gerstner T, Henning O, Løhaugen G, Skranes J. Reduced Inter-hemispheric coherence and cognition in children with Fetal Alcohol Spectrum Disorders (FASD) - a quantitative EEG study. *Neuropediatrics*. 2024 Feb 6. doi: 10.1055/a-2262-7781. Online ahead of print. PMID: 38320603

4. Abbreviations

ADHD	Attention deficit hyperactivity disorder
ASM	Anti-seizure medication
CC	Corpus callosum
CNS	Central nervous system
CP	Cerebral palsy
DA	Disorders of arousal
DIMS	Disorders of initiating and maintaining sleep
DOES	Disorders of excessive somnolence
EEG	Electroencephalography
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorder
GABA	Gamma Aminobutyric Acid
ICoh	Inter-hemispheric coherence
IEDs	Inter-ictal epileptic discharges
IQ	Intelligence quotient
LTG	Lamotrigine
pFAS	Partial Fetal Alcohol Syndrome
MRI	Magnetic resonance imaging
ND/AE	Neurobehavioral Disorder/Alcohol-Exposed
PAE	Prenatal alcohol exposure
PSG	**Polysomnography**
QEEG	Quantitative Electroencephalography
RK-MR	Regional kompetansetjeneste - medfødte russkader
SBD	Disorders of sleep-related breathing
SE/AE	Static Encephalopathy/Alcohol-Exposed
SES	Socioeconomic status
SUL	Sulthiame
SWTD	Sleep-wake transition disorders
SHY	Sleep hyperhidrosis
VPA	Valproic acid

Søvnforstyrrelser, epilepsi, EEG-funn og klinisk funksjon hos norske barn med føtalt alkohol spektrumforstyrrelse (FASD)

FASD beskriver et spekter av kliniske, utviklingsmessige, kognitive, motoriske og atferdsmessige vansker hos barn etter prenatal alkoholeksponering. FASD kan deles inn i undergruppene fullt og partielt føtalt alkoholsyndrom (ICD-10: Q86.0 FAS), statisk encefalopati og nevroutviklingsforstyrrelse basert på det amerikanske diagnosesystemet 4-Digit-Diagnostic-Code, som inkluderer gradering av fire nøkkelkriterier: 1. Vekstavvik, 2. Karakteristiske ansiktstrekk, 3. Skade/dysfunksjon i sentralnervesystemet og 4. Nivå av prenatal alkoholeksponering. Høyere skåre for hvert kriterium indikerer en diagnose mot full FAS. FASD er blant verdens ledende årsaker til mild intellektuell funksjonshemming og kan potensielt forebygges gjennom å unngå alkoholeksponering under svangerskapet. Det finnes få studier angående prevalensen av FASD, men den estimerte prevalensen av FAS i Norge er beregnet til 0,5–1 per 1000 og FASD til 0,5.1 per 100. I den første studien i denne doktorgraden undersøkte vi en kohort barn (n=53) diagnostisert med FASD ved Regional Kompetansetjeneste – Medfødte Russkader (RK-MR) ved Sørlandet Sykehus HF i forhold til søvnforstyrrelser. Dette inkluderte barn med og uten ADHD (Attention-Deficit Hyperactivity Disorder) eller epilepsi som komorbiditet. Søvn ble kartlagt ved at foreldrene fylte ut en norsk versjon av skjemaet Sleep Disturbance Scale for Children, og resultatene ble korrelert med kognitive og adaptive funksjoner. Forstyrret søvn ble funnet hos 79% av barna med lik prevalens i alle FASD-undergrupper. Barn med ADHD som komorbiditet, hadde økt forekomst av søvnforstyrrelser sammenlignet med de uten ADHD, og barna med forstyrret søvn hadde dårligere skåre for eksekutiv funksjon, en trend mot lavere arbeidsminneskåre og dårligere generell skåre for adaptiv funksjon. Studien understreker viktigheten av screening for søvnforstyrrelser hos alle barn med FASD siden søvnproblemer kan behandles. I den andre studien undersøkte vi hyppigheten av epilepsi, patologiske EEG-funn og mulige påvirkning på kognitive og adaptive funksjoner i en kohort av 148 barn diagnostisert med FASD ved RK-MR. Vi fant epilepsi hos 6% av barna sammenlignet med 0,7% i generell barnepopulasjon i Norge. Patologisk EEG ble funnet hos 17% av barna uten epilepsi, og ADHD som komorbiditet ble diagnostisert hos 64%. Barn med FASD og epilepsi og/eller patologiske EEG-funn hadde ikke lavere IQ eller adaptive skårer sammenlignet med de med normalt EEG, men de med frontal EEG-patologi (og uten epilepsi) hadde signifikant lavere skårer på IQ-indeksene Prosesseringshastighet og Arbeidsminne, uavhengig av om de hadde ADHD. Disse funnene kan indikere spesifikke eksekutive funksjonsvansker som kan påvirke læring og adaptiv funksjon.
Den tredje studien undersøkte såkalt «koherens mellom hjernhalvdelene» (ICoh) i en kvantitativ EEG (QEEG) analyse hos 81 barn med FASD, sammenlignet med 31 friske kontrollbarn. ICoh sier noe om hvordan de to hjernehalvdelene kommuniserer seg imellom. Lavere ICoh ble funnet i frontale og temporale avledninger i FASD-gruppen. Ved sammenligning av FASD-undergrupper hadde barn med FAS lavere ICoh oksipitalt. Redusert ICoh i det temporale alfa-båndet var korrelert med lavere utførings-IQ i FASD-gruppen. Funnene kan tyde på redusert sammenkopling mellom hemisfærene med innvirkning på kognisjon. Våre resultater kan indikere at QEEG kan være en mulig biomarkør for FASD.

Sleep Disturbances, Epilepsy, EEG findings and clinical function in Norwegian children with Fetal Alcohol Spectrum Disorder (FASD)

FASD describes a spectrum of clinical, developmental, cognitive, motor and behavioral difficulties in children following prenatal alcohol exposure. FASD can be divided into the subgroups full and partial Fetal Alcohol Syndrome (FAS) (ICD-10: Q86.0), Static encephalopathy and Neurobehavioral disorder based on the Diagnostic Guide for Fetal Alcohol Spectrum Disorders - The 4-Digit Diagnostic Code, which includes 1. Growth deficiency, 2. Characteristic facial features, 3. Damage/dysfunction of the central nervous system, and 4. Level of prenatal alcohol exposure. Higher score for each criteria indicates a diagnosis towards full FAS. FASD is one of the world's leading causes of mild intellectual disability and can potentially be prevented by avoiding alcohol drinking during pregnancy. There are few studies regarding the prevalence of FASD, and the prevalence of FAS in Norway is estimated at 0.5–1 per 1000 and FASD at 0.5-1 per 100. In the first study in this doctoral thesis, we examined a cohort of 53 children diagnosed with FASD at the Regional Competence Center for children with prenatal alcohol/drug exposure at Sørlandet Hospital HF with regard to sleep disorders. This group of children included those with and without ADHD (Attention-Deficit Hyperactivity Disorder) or epilepsy as co-morbidity. Sleep pattern was reported by the parents, using the form Sleep Disturbance Scale for Children. Results were correlated to cognitive and adaptive functions.

Disturbed sleep was very common (in 79%) with equal prevalence in all FASD subgroups. Children with ADHD as a comorbidity had more sleep disturbances compared to those without ADHD, and those with disturbed sleep had inferior scores for executive function, a trend towards lower working memory scores and reduced general scores for adaptive functioning. The study emphasizes the importance of screening for sleep disorders in all children with FASD, since sleep problems are treatable. In the second study, we investigated the frequency of epilepsy, pathological EEG findings and its possible implication on cognitive and adaptive functions in a cohort of 148 children diagnosed with FASD at the Regional Competence Center for children with prenatal alcohol/drug exposure. We found epilepsy in 6% of the children with FASD compared to 0.7% in the general child population in Norway. Pathological EEG was found in 17% of children without epilepsy and ADHD as a comorbidity was diagnosed in 64%. FASD children with epilepsy and/or pathological EEG findings did not have lower IQ or adaptive scores compared to those with normal EEG. However, those with frontal EEG pathology (and without epilepsy) had significantly lower scores on the IQ indices Processing speed and Working memory, regardless of any ADHD comorbidity. These findings may indicate specific executive function deficits that may affect learning and adaptive functioning. The third study examined inter-hemispheric coherence (ICoh) in a quantitative EEG (QEEG) analysis in 81 children with FASD, compared to 31 healthy controls. Lower ICoh was found in frontal and temporal derivations in the FASD group. When comparing FASD subgroups, children with FAS had lower ICoh occipitally. Reduced ICoh in the temporal alpha band was correlated with lower performance IQ in the FASD group. The findings suggest reduced connectivity between the hemispheres, which may have an impact on cognition in children with FASD. Our results may indicate that QEEG can be used as a biomarker for FASD.

1. Introduction

1.1. Background

Fetal alcohol spectrum disorder (FASD) is among the world's leading causes of mild mental retardation and the only cause that can be prevented 100% if the woman abstains from drinking alcohol already when planning to get pregnant [1]. Alcohol is a teratogen, and its direct adverse effect on fetal development is greater than of any other known psychoactive substance. A report from the National Academies of Science's Institute of Medicine stated, "Of all the substances of abuse (including cocaine, heroin, and marijuana), alcohol produces by far the most serious neurobehavioral effects in the fetus" [2]. Prenatal exposure to alcohol is quoted to be a key public health issue with a potential negative, lifelong impact on child and adolescent health [3]. In addition, alcohol is different compared to other teratogens since it is frequently and widely used by women in fertile age in most western countries. Any amount of alcohol during pregnancy can cause fetal harm with no known safe lower limit [1, 4]. Functional impairments due to disturbed early brain development are the most severe clinical consequences of prenatal alcohol exposure. The acronym PAE (prenatal alcohol exposure) defines alcohol consumed by the mother after the child is conceived. Even small amount of alcohol may be harmful to normal fetal development and the teratogenic effect can happen at any point during pregnancy since the central nervous system continues to develop and grow during fetal life. Prenatal alcohol exposure is based on the definition of a standard drink, but a standard drink (units) alcohol is defined differently. In a literature review by Drummond et al. (2020) where 21 European guidelines for the management of alcohol-related disorders were studied, the definition of standard drink varied from 8 grams to 20 grams of ethanol per drink [5]. In Norway, 12-15 grams of pure alcohol per unit is often considered as one standard drink. Despite of this definition, it`s important to specify that due to the challenges in quantifying prenatal alcohol exposure and the frequency in which children with FASD may be in the care of individuals other than their biological parents, additional criteria for PAE are used. This includes documentation of alcohol-related social or legal problems in proximity to the pregnancy or positive testing [6].

1.1.1. The consequences of prenatal alcohol exposure – diagnosis of FAS/FASD: Given the high rate of alcoholism throughout history, its effects on the fetus must have existed for millennia.

However, the claim that both Greeks and Romans were aware of fetal alcohol syndrome rests on incorrect citations. First in the 18th century, maternal alcohol consumption was suspected to be responsible for retarded fetal growth and neurological anomalies, but without any consequences [7]. In 1899, Nicloux [8] found that alcohol passed readily through the human placenta yielding a fetal blood concentration almost equal to that in maternal blood. In 1915, Ballantyne [9], founder of antenatal medicine and the journal *Teratologia*, clearly distinguished the genetic influence via germ cells from a toxin's influence on the embryo. Nevertheless, political developments did not look favorably on teratology and basic research on this issue was non-existent for decades. By 1967, alcohol teratogenicity was forgotten or ignored to such an extent that intravenous ethanol was introduced to suppress premature labor [10] - a treatment that persisted in the USA until 1978. Fetal alcohol syndrome (FAS) was characterized by Rouquette in 1957 [11] and by Lemoine in 1968 as consisting of 4 features: (1) facial anomalies, (narrow forehead, retracted upper lip, and cupped ears), (2) severe growth retardation (prenatal and postnatal), (3) malformations (limbs, cardiac, and visceral), and (4) central nervous system anomalies (hyperexcitability and mental retardation) [12]. Unfortunately, their studies, written in French, remained disregarded. Ulleland and co-workers were the first to report about the relationship between prenatal alcohol exposure and adverse neurologic outcome of the child in English in 1972 [13]. In 1973, Jones et al. [14] reported "the first association between maternal alcoholism and aberrant morphogenesis in the offspring." Since then, fetal alcohol syndrome (FAS) has achieved a separate diagnostic code (ICD-10: Q86.0) together with other congenital malformations. While FASD is an umbrella term describing a spectrum of medical, developmental, cognitive, motor, and behavioural disabilities in children with prenatal alcohol exposure [14].

1.1.2. The 4-Digit Diagnostic Code: However, the diagnostic assessment process for children exposed to intrauterine alcohol is still debated. There do currently exist nine relatively widely used national and international guidelines for the diagnosis of FASD, which to varying degrees build on each other. Internationally, there is consequently considerable professional disagreement on how FASD should be diagnosed. The different guidelines have different emphasis on physical, psychological and functional difficulties. The three most used guidelines are the two from the US and one from Canada: the 4-Digit Code [15] and the Institute of Medicine (IOM) guideline [16], as well as the Canadian guideline [17]. In addition, there are guidelines from: Australia [18], Denmark [19], Poland [20], Scotland/England [21] and from Germany [22]. There is, without doubt, a need to standardize the diagnosis of FASD and to agree on a common diagnostic tool that can replace the various guidelines [23]. Among other things, research and prevalence in different countries would then be more comparable. In research, there is no evidence for determining which of the existing guidelines should be "gold standard" for diagnostics [23]. In 2013, the 4-Digit Code was validated [24] and it is the preferred diagnostics system used in our center by an interdisciplinary team to diagnose fetal alcohol spectrum disorders. The University of Washington (Seattle) offers training and certification in the clinical use of the 4-Digit Code system and we emphasize education and training in the use of one of the guidelines to achieve the best possible diagnostic quality assessment in everyday clinical practice as well as in research.

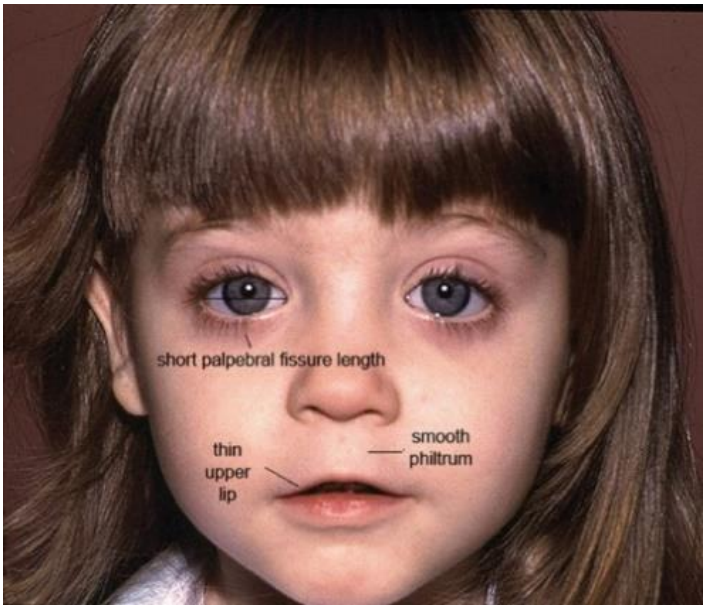

Figure 1. Child presenting with the three diagnostic facial features of FAS: 1) short palpebral fissure lengths (distance from A to B); 2) smooth philtrum; and 3) thin upper lip. Copyright 2024, Susan Astley Hemingway PhD, University of Washington.

Briefly, the 4 digits of the 4-Digit Code reflect the magnitude of expression of the 4 key diagnostic features of FASD, in the following order [25]:

1) Growth deficiency

2) FAS facial phenotype (see figure 1)

3) CNS structural/functional abnormalities

4) Prenatal alcohol exposure

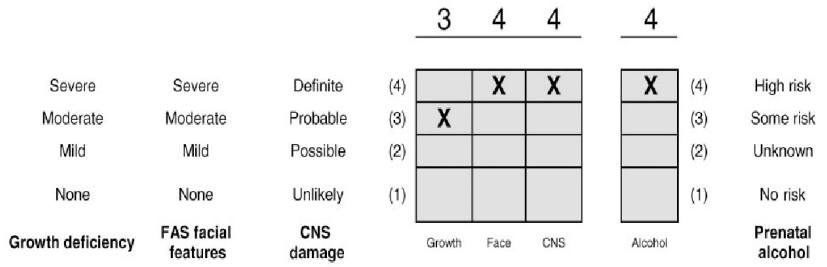

FIGURE 1
Four-Digit Diagnostic Code grid. The 4-Digit Code (3444) that is inserted in the grid is 1 of 12 codes that meet the diagnostic criteria for FAS.[5]

Figure 2. Copyright 2022, Susan Astley Hemingway PhD, University of Washington.

The extend of expression of each feature is ranked independently on a 4-point scale, with 1 reflecting complete absence of the feature and 4 reflecting a strong "classic" presence (see figure 2). Each Likert scaling is specifically case defined. This gives a total of 256 combinations or 4-Digit-Codes where 102 codes fall broadly under the umbrella of FASD. These codes are divided into four clinical FASD subgroups [15]:

1. fetal alcohol syndrome (FAS)
2. Partial FAS (PFAS)
3. Static Encephalopathy/Alcohol-Exposed (SE/AE)
4. Neurobehavioral Disorder/Alcohol-Exposed (ND/AE)

To extend the diagnosis of fetal alcohol syndrome with the umbrella term fetal alcohol spectrum disorder is justified by extensive evidence, which supports the inclusion of SE/AE and ND/AE. Even if not all individuals meeting the criteria for SE/AE and ND/AE have FASD. By definition, all children with FASD have a disorder caused (at least partly) by prenatal alcohol exposure. However, only the subset of individuals whose neurobehavioral disorder or static encephalopathy was (partly) caused by the prenatal alcohol exposure, have FASD. This, of course,

is an obvious weakness of the umbrella term, but in the absence of a specific biomarker that can causally connect prenatal alcohol exposure to neurodevelopmental outcome, there is no evidentiary way to identify which children would have FASD or not. Specific for SE/AE, only those whose CNS abnormalities were (partly) caused by prenatal alcohol exposure have FASD. Until a specific biomarker is identified, if such a biomarker exists, the 4-Digit Code does not claim causality of PAE in all children with SE/AE and ND/AE [24]. However, there is evidence-based knowledge showing that early diagnosis of FASD in children is important for some significant reasons. The diagnosis could help explain the child's difficulties based on disturbed early brain development of fetal origin. This may be important for the caregivers. The broad cognitive/neuropsychological assessment done in the course of the diagnostic process will be able to identify the child's strengths and weaknesses. Early diagnosis can lead to early, correct, and targeted support. Help for the mother if there is a drug problem can prevent prenatal alcohol exposure and children with FASD in subsequent pregnancies [26]. It has also been shown that early help can reduce the incidence of early death, mental health problems and substance abuse in young people and adults with FASD [27].

1.2. Pathophysiology

Ethanol can induce cell damage, leading to structural anomalies of grey and white matter in the brain. Studies involving animal models have shown that prenatal alcohol exposure affects all stages of brain development from neurogenesis, migration of neurons to myelination of the nerve fibers, through a variety of mechanisms, including disrupted cell-to-cell interaction, altered gene expression, oxidative stress, and growth factor signaling disruptions, which can lead to reduction in the size of different brain structures and the overall brain volume. This can cause microcephaly, agenesis or malformation of the corpus callosum, ventriculomegaly, small cerebellum, hippocampal pathology and a variety of other brain abnormalities due to neuronal and glial migration errors. It has been shown that maternal ethanol exposure is associated with deviations in cortical thickness in a number of brain areas in individuals with FASD [28-32]. Alcohol equilibrates rapidly between the maternal and fetal organism and is eliminated mostly through maternal metabolism. The exact mechanism by which alcohol causes its teratogenic effects is not exactly known. Most of collected data comes from animal models with prenatal alcohol exposure. Alcohol is a teratogen and causes irreversible damage to the developing central nervous system, the damage is widespread, causing not only a decrease in total brain volume but

also damage to different brain structures. It is known from animal models, that prenatal alcohol exposure affects all stages of brain development through a variety of mechanisms, that may result in cognitive, motor, and behavioral dysfunction [33]. Prenatal alcohol exposure, especially in the first trimester of pregnancy, can disrupt neuronal proliferation, migration, and synapsis formation, physiologically made possible by cell-adhesion molecule [34]. Several developmentally important molecular targets of alcohol, including the L1 neural cell adhesion molecule and $GABA_A$ receptors, are disrupted at blood alcohol concentrations attained after one or two standard drinks in humans (14 grams of pure alcohol). Brain lesions of FASD resemble those of L1 syndrome, a disorder caused by mutations in the gene for the developmentally critical L1 neural cell adhesion molecule. This phenotypic similarity may be a consequence of the ability of ethanol to inhibit L1 adhesion at concentrations attained after just one drink [35]. The GABAergic system is another key target of ethanol action in the brain, influencing GABAergic transmission presynaptically by increasing the release of GABA and postsynaptically by enhancing $GABA_A$ receptor function. Chronic ethanol exposure can alter expression of certain $GABA_A$ receptor subunits at synaptic and extrasynaptic sites [36]. Indeed, the GABAergic system plays an important role from the earliest stages of corticogenesis, influencing key developmental processes such as proliferation of neurons, neuronal differentiation, and migration [37]. Prenatal alcohol exposure in humans is also known to be linked to epigenetic changes in DNA methylation leading to alterations in gene expression in the child [38]. Increased brain volume was attributed to impairment of synaptic pruning in the preadolescent brain in animal studies, consistent with research in humans demonstrating the effect of prenatal alcohol on trajectories of later brain development [39]. There was no inflexion point in the dose–response curves to suggest a cut-off for prenatal alcohol effects, and significant effects were observed with as little as one US standard drink per week throughout pregnancy [35]. A recent prospective follow-up study of 670 women and their children suggested that even low-to-moderate levels of prenatal exposure to alcohol or an isolated binge drinking incident may place some fetuses at risk for FAS/PFAS [40].

1.3. Epidemiology and burden to society

The global prevalence of FASD among children and youth in the general population was estimated to be 7.7 per 1000 population [41]. Furthermore, 76 countries have a prevalence of FASD of >1% [1], which exceeds the prevalence of neurodevelopmental conditions, including

Down syndrome (trisomy 21), Edwards syndrome (trisomy 18), and spina bifida in the USA, and it is quite similar to the prevalence of autism spectrum disorders [42]. There are few studies from Europe regarding the prevalence of FASD; an Italian study reported a prevalence of 3.7–7.4 per 1000 live births for FAS and 2.3%–4.1% for FASD [43]. The Norwegian government has estimated the incidence of FAS at between *60 and 120 children* per year, and if children with the full range FASD were included, at *600-1200 children* per year [44]. The number of children with neuroimpairments due to prenatal exposure to other substances and illegal drugs is largely unknown. Another important fact is the number of women in fertile age who is drinking alcohol. A study from 2006 reported that 25% of women consume alcohol during pregnancy in Norway [45]. A study that analyzed 2015–2018 year data from the US National Survey on Drug Use and Health found that about 1 in 10 of pregnant women reported *current alcohol use*, 4.5% pregnant women reported *binge drinking* and alcohol use was highest among women who were in the *first trimester of pregnancy*, with about 20% reporting current alcohol use.

However, children who are adopted from countries with a higher prevalence of pregnant women drinking alcohol have dramatically increased risk of alcohol related fetal impairments. For instance, the prevalence of FASD is 62% among children with intellectual disabilities in care in Chile [46], and more than 50% in a cohort study of 71 children adopted from eastern Europe and assessed 5 years after adoption in Sweden [47]. Risk factors for alcohol use during pregnancy vary, but for instance first-trimester alcohol use was associated with unplanned pregnancy, age <18 years, frequent and binge drinking in adolescence, and a tolerant attitude to alcohol use in pregnancy [1]. In contrast, women who continued drinking alcohol throughout pregnancy were more likely to be older, had higher socioeconomic status, salary and educational levels, smoke, had a partner who consumed alcohol, and were less likely to agree with guidelines that recommended avoiding alcohol use in pregnancy [48, 49]. The highest prevalence estimates for FAS (46–68%) are in children with neurodevelopmental disorders in Russian orphanages [50]. FASD confers lifelong disability, and an estimated >11 million individuals aged 0–18 years and 25 million aged 0–40 years have FASD globally, see figure 3 [51].

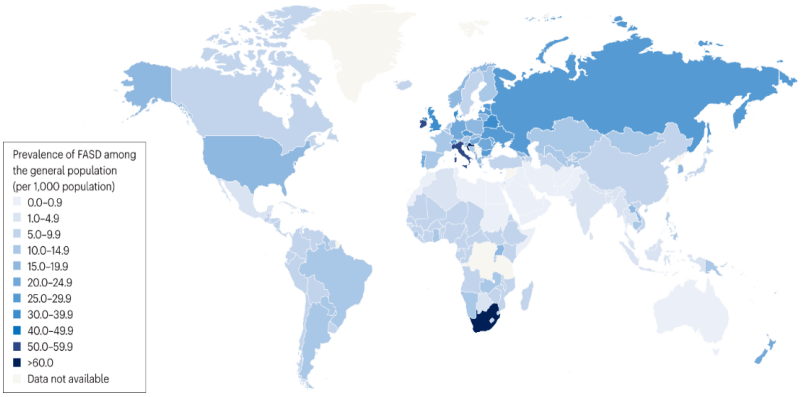

Figure 3 Copyright by Prof. Svetlana Popova, University of Toronto.

Prevalence of FASD worldwide, the highest prevalence (per 1,000) of FASD was in Russia and the WHO European Region, followed by the America and African Region. The lowest prevalence was (not very surprising) estimated in the Eastern Mediterranean Region. The pooled global prevalence of FASD was estimated to be around 8 per 1,000 in the general population [1].

Unfortunately, in most cases, the neuroimpairments seen in children with FASD will persist into adulthood. Secondary conditions, appearing in late childhood and adolescence, include high incidence of mental disorders (up to 94%), interrupted schooling (43%), conflict with law (42%), institutional placement (such as prison, psychiatric hospitalization), the inability to live independently (80%), and trouble getting work (80%) [52]. Numbers from Europe (Sweden) published by Ragmar et al. in 2015 showed comparable results in adults with FAS. The need for special education was 12 times higher and the chance to be unemployed was 3.5 times higher. The FAS group also had higher prevalence of psychiatric disorders (33% vs 5%) [53]. These conditions were thought to be largely preventable or less severe if FASD was diagnosed in early childhood with regular follow-up [54]. Costs for society could therefore be reduced dramatically if better health services for this group are established at an early age. Children with FASD generate huge costs for the public health system and society (16). Although no Norwegian cost studies exist, Canadian studies are likely relevant, given the similarities with Norway regarding public healthcare and educational systems. A recent Canadian study estimated an annual societal cost per FASD child of 21.642 Canadian dollars (1 Canadian dollar equals 0,74 US dollar), while the annual costs for all persons born with FASD (0–53 years of age) were estimated to be about 5.3 billion Canadian dollars based on a conservative FASD prevalence of 0.3% (17). In addition to the direct costs, FASD also results in indirect costs through the increased burden on the family

due to the child's primary and secondary disabilities. Equally hard to quantify in economic terms, is the child's burden of living with FASD in terms of markedly reduced health-related quality of life compared to both healthy controls and even to children born with extremely low birth weight (18). Children with FASD probably represent a patient group as large as children with autism spectrum disorders (1-1.5%), and far greater than the number of children with cerebral palsy (0.3%). It is paradoxical that huge resources are allocated in the specialist services in Norway to these other patient groups, but not to the early diagnosis, treatment, and follow-up of children with FASD, which would improve the prognosis and reduce later costs for society.

1.4. Clinical and neuropsychological characteristics of FAS/FASD

FASD encompasses a wide range of physical and neurodevelopmental signs with different clinical pictures. This includes the most severe condition fulfilling all criteria for the diagnosis of fetal alcohol syndrome (FAS), which refers to individuals who have a defined set of birth defects and neurodevelopmental disorders characteristic of the diagnosis [55], to milder symptoms associated with hyperkinetic behavioural disorders and more specific neuropsychological impairments [56]. In all diagnostic systems for FASD, three cardinal facial features are assessed, which include short palpebral fissures, a smooth underdeveloped philtrum, i.e. the midline groove in the upper lip that runs from the top of the lip to the nose, and a thin upper lip, see figure 4. Palpebral fissures can be assessed using a clear plastic ruler and measured from the inner canthi to the outer canthi. A measurement of ≤ 2sd from mean value according to age is considered short [15].

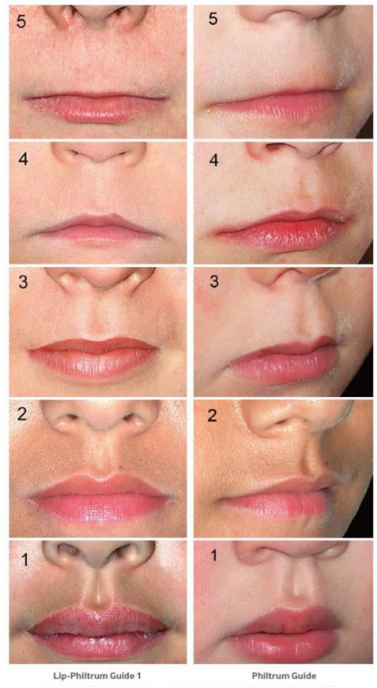

Figure 4: University of Washington Lip-Philtrum Guides are used to rank upper lip thinness and philtrum smoothness. The philtrum is the vertical groove between the nose and upper lip. The guides reflect the full range of lip thickness and philtrum depth. Copyright 2024, Susan Astley Hemingway PhD, University of Washington

The lip and philtrum are assessed separately using the lip-philtrum guide in the 4-Digit Code system, with five grades ranging from the most defined lip and philtrum (rank 1) through the least defined lip and philtrum (rank 5). The normal

range is represented by ranks 1–3, and an abnormal lip and philtrum are classified as a rank 4 or 5 [15]. Additional facial features can also include flat nasal bridge, epicanthal folds, midfacial hypoplasia, prognathism (underbite), and minor ear anomalies; however, these do not contribute to the overall diagnosis [6]. Additional clinical findings in children with FASD could be different types of hearing disorders such as delayed maturation of the auditory system, sensorineural hearing loss or central hearing loss [57]. The developing eye is also affected by prenatal alcohol exposure since the visual system continues to develop throughout fetal life. The external signs include short palpebral fissures, telecanthus (increased distance between the eyes), epicanthus fold, blepharoptosis (dropping of the upper eyelid), microphthalmos (small eyes) and strabismus (crossed eyes). Within the eyes, the signs and symptoms most commonly detected are optic nerve hypoplasia, increased tortuosity of the retinal vessels and impaired vision [58]. Several abnormalities within the heart, kidney, liver, gastrointestinal tract, and the endocrine systems are described as well, most often in children with full FAS [59]. Animal and human studies have consistently demonstrated intrauterine growth retardation among children with PAE, with reduced weight, length, and head circumference at birth [60]. Carter et al. showed that more than 50% of heavily alcohol exposed children were small for gestational age at birth and those born with growth retardation were exposed to higher levels of alcohol than children born with normal growth [60]. Assessment of the degree of growth deficiency is a key criterion that most, but not all diagnostic guides for FASD contain [16, 61]. Growth deficiency constitutes one of four key criteria in the 4-Digit Code [15]. The reason is that PAE can affect intrauterine growth causing reduced birth weight/length, as well as cause reduced postnatal growth.

Several publications have summarized the cognitive functioning of children with prenatal alcohol exposure in an attempt to define a specific neurocognitive profile of FASD [62]. However, due to methodological issues, the wide range of cognitive domains assessed and the miscellaneous neuropsychological tests used, no specific neurocognitive profile could be identified [63]. Common (and of huge importance) to children and adolescents with FASD, however, is that the impairments of the central nervous system are lasting and thus have impact in adulthood [64]. Children and adolescents may present symptoms such as severe behavioural problems, including hyperactivity, attention deficit, reduced impulse control and arrested social development even if their intelligence quotient is within normal range [65]. Behavioral and emotional disturbances are common and can be functionally disabling. However, adverse social outcomes are difficult to

attribute to FASD (only), because they can also reflect an individual's disruptive social circumstances, such as living in foster homes, experience of violence, physical and sexual abuse, and poverty [66]. In addition, sensory hypersensitivity is often described to sound, light and touch, and high or low pain threshold [67]. There is a great variety of possible functioning from mild to moderate mental retardation to normal cognitive functioning. Regardless of overall ability levels, different degrees of adaptive dysfunction are found in these patients. The clinical picture is further complicated by neuropsychological dysfunction, particularly attention/executive functioning, significant variability in performance from one day to another (on / off), difficulty learning from experience and emotional instability [63].

1.4.1. FASD and sleep

Recent research studies show that children with FASD often have sleep problems from infancy to adolescence, a problem that seems not very good understood and investigated by health care providers [68]. In healthy school-aged children, disturbed sleep is reported by about 20% of parents [69], while children with FASD are considered much more likely to experience such problems with a prevalence of 50-80% [70]. Reduced sleep duration and highly fragmented sleep (characterized by repetitive short interruptions of sleep) are the most commonly seen problems [71]. These problems with sleep can have immense impact on quality of life for both the child and the caregivers [68]. Polysomnography (PSG) is regarded as the gold standard for experimental sleep analyses [72], but the use of validated children`s sleep questionnaires is another possible approach which can lead to politely results [73]. Only a few studies have measured sleep by using both instrumental examination and caregivers' questionnaires and compared it to normative data [74]. Interestingly, they demonstrated that the results from sleep measurements by PSG and questionnaires are concordant to each other, which may implicate that the single use of sleep questionnaires could be sufficient [75].

1.4.2. FASD and ADHD

FASD and ADHD are associated with a range of neurocognitive problems with executive function deficits as distinctive characteristics of both disorders [76]. ADHD is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity that impairs functioning and development [77]. ADHD with related symptoms seems to be the most prevalent comorbid disorder reported with FASD [78, 79] and the prevalence is much higher compared to the general

(Norwegian) pediatric population (52% versus 3%) [79-81]. Yet, this numbers have to be interpreted with caution. A huge proportion of research on FASD typically relies on clinically-referred samples, which is problematic given that children and adolescents with obvious disruptive behaviors are much more likely to be referred to a specialized FASD diagnostic center [80]. Regardless, whether it is due to the referral bias or true co-morbidity, FASD children often receive many other diagnoses before appropriately diagnosed with FASD. ADHD is the most common referral diagnosis for children who later are diagnosed with FASD [82]. A systematic review by Weyrauch et al. concluded that FASD should be an important consideration in the evaluation of children with ADHD [79]. A recent animal study with rodents showed that moderate intrauterine exposure to alcohol led to augmented action impulsivity without causing major teratogenic effects. The researchers did not find any deficits in learning or motor function, meaning that the altered impulsivity could not be related to that, but should be seen as genuine attention problem [83].

There may be different pathways and explanations to the combination of ADHD and FASD, maybe different subsets of them also [84]. Some researchers promote the idea that ADHD in FASD is a particular clinical subtype of ADHD with both earlier debut, different clinical profile and varying response to specific drugs [85]. To highlight this from a pathophysiological point of view, we know that prenatal exposure to alcohol affects both the cholinergic system (hippocampus) [86], the glutamatergic system, mainly by the expression of glutamate receptors [87], and the dopaminergic system [88]. These effects have also been demonstrated in ADHD, suggesting that alterations of these neurotransmitter systems may be the cause of abnormal brain function and behavior in both ADHD and FASD [85]. Executive function is the main deficit in FASD and ADHD, and symptoms like lack of inhibition and attention problems may be related to this. A possible explanation could be that both groups may have structural and functional deficits in frontal-subcortical networks, connecting brain areas of executive functions [85]. However, the children with FASD usually perform worse than those with ADHD [89]. The information on genetic influence of ADHD is quite limited, but there is widespread agreement that genetic factors play an additional role [90]. Given the complexity of both ADHD and FASD, but also the apparent resemblance in pathophysiology and clinical picture, the coincidence of these diagnoses is not surprising.

1.4.3. Pathological EEG and/or epilepsy in children with FASD

The prevalence of seizures is up to 21% in children with FASD [91-96], while the prevalence of epilepsy in Norwegian children is estimated to be about 0.7% [97]. Among nonepileptic, seizure-free children, epileptic activity is found in about 2.5% on EEG registrations [98]. Much higher incidence of abnormal EEG findings is seen in children with developmental disorders, autism or neuropsychiatric conditions [99]. Only a few studies have systematically examined EEG records of adolescents and children with FAS/FASD, and EEG features in this patient group are poorly described [91, 95]. Bell examined 425 patients (age 2-49 years) diagnosed with FASD and found that 25 (6%) had verified epilepsy while 50 (12%) had experienced one or more seizures. A prospective study of 61 adoptive children (most from Eastern Europe) with learning difficulties and different severity of FASD showed that three children (5%) had epilepsy; in one of these children, seizures were first discovered on an EEG registration, while one patient showed electrical status epilepticus during sleep [93]. Many of the children had unspecific brain abnormalities such as corpus callosum hypoplasia or underdeveloped cerebellum (vermis hypoplasia), but none of them showed structural correlation to focal EEG findings. In the study by Boronat et al., as many as 14 children (23%) with FASD showed abnormalities in the EEG such as slow background activity and inter-ictal epileptiform activity [93]. An important question is whether this increased incidence of abnormal EEG is correlated with abnormal clinical functioning, such as regulatory disorders, attention deficit and cognitive difficulties as reported for children with epilepsy [100]. Even if this has not been investigated in children with FASD, EEG could be an important supplementary examination in the investigation of neurological and neuropsychological impairments and give valuable and accurate information about cerebral function. There are several studies showing that abnormal EEG activity may have adverse effects on cognitive functions, concentration and attention and possibly also on emotional functioning in patients with (congenital) brain impairments [101, 102].

1.4.4. Quantitative EEG (QEEG)/Coherence analysis

Quantitative electroencephalography (QEEG) is a different type of electrophysiological analysis that uses mathematical algorithms and has extended the evaluation of the EEG signal. With further developments of modern computers, QEEG frequency analysis based on Fast Fourier Transformation has become part of the scientific and clinical examination in medical fields such

as psychiatry and neurology [103]. QEEG increases diagnostic options and enlarges the interpretation of neurophysiological analysis because it can show more subtle dysfunctions. QEEG has established its role in neuro-psychiatry, for the further evaluation of comorbid neuropsychological deficits in epilepsy, stroke, dementia, depression, encephalopathy, learning and attention disorders [104]. 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 children with FASD 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 in an intra-hemispheric analysis. The same result is described as a typical finding in ADHD patients [105]. A different QEEG approach is the coherence analysis. The inter-hemispheric 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 [106]. By analyzing the synchrony between two EEG channels, ICoh can be used as an index of 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 as expression of strong structural or functional connection while low coherence represents rather weak connectivity [107]. 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 [108]. Deviations in coherence values have been reported in children with ADHD and epilepsy [109, 110]. Clarke et al. [109] found that ADHD children had reduced coherences in most regions compared to controls, while Varotto et al. showed widely reduced local connectivity in children with epilepsy [110]. Looking at inter-hemispheric coherence is especially interesting in the FASD group since structural and functional deviations in corpus callosum – the largest connection between the two hemispheres - have been reported extensively both in animal and human studies [28, 29, 111].

1.5. What this thesis adds

This study is one of very few prospective cross-sectional studies of children and adolescences with confirmed FASD in contrast to many studies using children with PAE only, or combinations of PAE and FAS/FASD. Additionally, we were able to take a deeper look at the different FASD subgroups with regard to comorbidities, EEG pathology and clinical differences. To our

knowledge, it is also one of the first studies that is able to compare electrophysiological pathology and cognitive findings in this clinical group. In addition, we used quantitative EEG and coherence analysis as a clinical diagnostic instrument to be able to detect deviations not visible on standard EEG. In contrast to the many studies on QEEG coherence in children and adults with different psychiatric and neurological diseases, to our knowledge, this is the first study on individuals with FASD. Hopefully, our findings may provide a small piece in the challenging process of diagnosing in children with FASD.

2. Aims of this thesis

The overall aim was to investigate clinical functioning including sleep of children and adolescents with FASD and to look at any relationships between the different FASD subgroups, electrophysiological activity and neuropsychological findings. Additionally, we were interested in the prevalence and severity of EEG pathology and epilepsies. Specific aims of the different papers:

Paper 1:

1) To examine the prevalence of sleep disturbances in a sample of 53 children with confirmed FASD
2) To examine the prevalence and possible differences of sleep disturbances related to FASD subgroups
3) To assess the relationship between sleep disturbances and co-morbidities
4) To investigate the possible impact of sleep disturbances on cognitive, executive and adaptive functioning in children with FASD.

Paper 2:

1) To investigate the frequency of epilepsy and pathological EEG findings in a sample of 148 children with confirmed diagnoses of FASD
2) To examine the relationship between epilepsy /pathological EEG findings and FASD subgroups
3) To investigate the relationship between epilepsy/pathological EEG findings and cognitive test results and adaptive functioning

4) To examine the relationship between focal EEG pathology and IQ indices adjusted for ADHD as comorbidity

Paper 3:

1) To investigate inter-hemispheric coherence differences between children with FASD with and without co-morbidities like ADHD and epilepsy, and healthy controls
2) To examine inter-hemispheric coherence differences between FASD subgroups
3) To reveal any correlation between reduced inter-hemispheric coherence and cognitive scores in the FASD group

3. Hypotheses

Based on previous research, we expected to find:

Paper 1:

1) An increased prevalence of sleep disturbances in children with FASD
2) Negative impact on sleep pattern and quality by severity of FASD subgroup and presence of co-morbidities (ADHD/epilepsy)
3) Reduced clinical functioning in children with sleep disturbances compared with those with normal sleep pattern

Paper 2:

1) An increased frequency of epilepsy and pathological EEG findings in children with FASD, and that such finding would have impact on neurocognitive and adaptive functioning regardless of ADHD comorbidity
2) An association between localization of EEG pathology and neuropsychological findings

Paper 3:

1) Quantitative EEG deviations indicating reduced inter-hemispheric coherence values in children with FASD compared with controls, even in absence of pathological findings on standard EEG
2) A relationship between quantitative EEG pathology and inferior cognitive scores in the FASD group.

4. Material and Methods

4.1. Study design and study population

All children and adolescents referred to the Regional Competence Centre for children with prenatal alcohol/drug exposure were invited to participate in the current research project. *Inclusion criteria*: Children and adolescents diagnosed with FASD after validated information about alcohol exposure in fetal life. Children who had been adopted and with missing information about exposure, but with dysmorphic features consistent with full Fetal Alcohol Syndrome were also included. Age should be between 3-17 years.

Exclusion criteria: Known genetic syndromes. Progressive brain and neuromuscular diseases. Major sensory defects (blindness and deafness).

Paper 1 and 2

In this prospective cross-sectional study, we included children and adolescents referred to the Regional Competence Center for children with prenatal alcohol/drug exposure (RK-MR) at Sørlandet Hospital in Arendal, Norway in 2020-2021 (paper 1) and in 2018–2022 (paper 2). All of them fulfilled FASD criteria after clinical assessment based on the 4-Digit Code.

The study sample in *paper 1* consisted of 53 children and adolescents with FASD (mean age = 10 years, SD = 3.8, age range 3-17 years; 63% males). In the inclusion period, 75 children were multidisciplinary assessed, 55 filled the diagnostic criteria for FASD and 53 of those consented to participate. The study sample in *paper 2* consisted of 148 children and adolescents with FASD (mean age = 10.2 years, SD = 3.9 years, age range 3-17 years; 60% males). In the inclusion period, 201 children were multidisciplinary assessed, 155 filled the diagnostic criteria for FASD and 148 of those consented to participate.

Paper 3

Children and adolescents referred to the Regional Competence Center for children with prenatal alcohol/drug exposure at Sørlandet Hospital in Arendal, Norway in 2018-22 and fulfilling a FASD diagnosis after clinical assessment based on the 4-Digit Code, were included in this cross-sectional case-control study.

Cases: 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 (mean age = 9.8 years, SD = 2.3 years, age range 6-14 years; 59% males). *Controls:* The control group consisted of 31 age-matched children, recruited from different schools in the city of Arendal (mean age = 10.5 years, SD = 2 years, age range 6-14 years; 45% males). 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.

4.2. Medical evaluation

All participants underwent a comprehensive standardized cognitive and neuropsychological assessment by a trained neuropsychologist and a clinical examination by a neuropaediatrician with long experiences within FASD. All examinations were done at the Sørlandet Hospital during a planned 2-day stay at the Department of Pediatrics. Somatic examination included an anthropometric, motor and neurological assessment. FASD was diagnosed based on the 4-Digit Code [15].

4.3. Demographics

Demographic information, co-morbidities such as epilepsy and ADHD, and available data on prenatal alcohol exposure were mainly collected prior to admission to the RK-MR. However, when ADHD was highly suspected in some children after the clinical assessment at our center, the children were referred back to the local child psychiatric department for evaluation of a diagnosis of ADHD. The local child psychiatric department then informed us about the result of their assessment. We also collected information about any use of sleep medication, behavior-regulating drugs and anti-seizure medication.

4.4. Socioeconomic status (SES)

Hollingshead's two factor index of social position based on education and occupation of one parent or the mean index of both parents was used to calculate socioeconomic status (SES) [112].

4.5. Cognitive Assessment (Paper 1, 2 and 3, see table 1)

The children were assessed cognitively with a complete version of the Wechsler Intelligence Scale (version depending on age and time point due to revised test versions). All testing was done by two very experienced neuropsychologists during the FASD assessment at our hospital. The children were tested 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 IV or V), Wechsler Adult Intelligence Scale - Fourth edition or Wechsler Nonverbal Scale of Ability (WNV). Most of the children were tested with WISC-IV or WISC-V (about 75%). To assess the child's daily functioning, we used the parent-reported Vineland Adaptive Behaviour Scales (VABS)-II. The Adaptive Behaviour Composite Score, based on communication, daily living skills and socialization, was recorded. Lower scores indicate poorer performance (Sparrow, 1989). Executive function behaviour in the home environment was evaluated by the parental reported Behavioural Rating Inventory of Executive Function (BRIEF). BRIEF assesses impairment of executive functions in daily life. Higher scores indicate poorer performance [113]. The cognitive assessment did not include specific diagnostics for ADHD but together with high BRIEF scores it could lead to a recommendation to asses for ADHD at the local child psychiatric department.

4.6. Sleep Assessment (Paper 1)

We used the Norwegian version of the Sleep Disturbance Scale for Children (SDSC) [114]. Caregivers were asked to fill out the questionnaire. A total score of sleep disturbance and scores on its six subdomains were calculated. The six subscales include DIMS = Disorders of initiating and maintaining sleep, DOES = Disorders of excessive somnolence, SBD = Disorders of sleep-related breathing, DA = Disorders of arousal, SHY = Sleep hyperhidrosis, and SWTD = Sleep-wake transition disorders. Summing up the six subdomains (with each item scored from 1 to 5) gives a total score from 26 to 130; where higher scores indicate greater difficulties with sleeping. We dichotomized the total score for analyses at the 75^{th} percentile (1 = sleep disturbance ≥ 75^{th} percentile, 0 = others) as cut-off, corresponding to the scaled TS-total score with a cut-off level for "Has sleep disorders" at 70 points, since 70 points are equivalent with the 75^{th} percentile. The variable "Has sleep disorders" (Yes/No) was therefore included in the analyses. The children were

divided into two age groups, one from 3-6 years, and the other from 7-17 years, due to the fact the normal sleep pattern significantly changes after the age of five.

Table 1. Neurocognitive standardized test assessed for FASD [114-117]

Cognitive domain	***Standardized test***	***Age (years)***
General cognitive functions	Wechsler Nonverbal Scale of Ability (WNV)	4-21
	Wechsler Preschool and Primary Scale of Intelligence (WPPSI-IV)	2-7
	Wechsler Intelligence Scale for Children (WISC-IV)	6-16
	Wechsler Intelligence Scale for Children (WISC-V)	6-16
	Wechsler Adult Intelligence Scale (WAIS-IV)	16-18
Attention / executive functions	Behavior Rating Inventory of Executive Function (BRIEF)	5-18
Daily functioning	Vineland Adaptive Behaviour Scales-II (VABS-II)	3-26
Sleep assessment	Sleep Disturbance Scale for Children (SDSC)	3-17

The broad neurocognitive testing is part of our center's assessment for FASD and the results are used both to generate best possible help for the children, but also as diagnostic criteria for CNS dysfunction, which is considered if results on the standardized cognitive/neuropsychological tests are -2sd or more from the average. The test-setup depends on age and cognitive function.

4.7. EEG (Paper 1-3)

We used the technical equipment and infrastructure available at the Department of Paediatrics, Sørlandet Hospital Arendal. The department is equipped with a video EEG monitoring unit, NicoletOne ™ Neurodiagnostic system (Scan-Med AS Norway - Drammen) providing EEG recording for a prolonged period with simultaneous video recording. The study participants underwent a long-term EEG recording using a standardized EEG protocol. EEG was recorded from 19 Ag/AgCl electrodes fixed with electrode fixation and contact cream accordingly to the 10-20 international system, referenced to CPz, with the grounds 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. The children sat in a comfortable armchair, with their arm and legs at rest. This EEG protocol includes a 2-hour, 20-channel EEG registration (international 10–20 system). Part of this registration was a defined period with closed eyes, hyperventilation, and photo-stimulation. The

EEG protocol was made in collaboration with the Department of Electrophysiology at the National Centre for Epilepsy (Statens Senter for Epilepsi-SSE).

A neuropediatrician was responsible for reading and interpreting the EEG and an electrophysiologist from SSE provided a second opinion on controversial findings. The EEG, as a non-invasive test, is included as part of the neurological assessment of the children referred to our centre. The children were registered with 19 channels (Nicolet One EEG- bandpass filter 0.53 sec, highpass to 70 Hz and 50 Hz notch, sampling frequency 256 Hz).

4.8. QEEG (Paper 3)

EEG was recorded using a NicoletOne-system (www.natus.com). *Processing of EEG data:* Two minutes of EEG data without artefacts, epileptic activity or signs of sleep or drowsiness were visually selected and filtered. EEG data was subsequently processed using the NicoletOne™. For the quantitative analysis (QEEG), we chose a segment with minimal presence of artifact and a length of at least 150 sec from which 10 sec 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. For QEEG analysis, a control group of 31 healthy age-matched children without epilepsy or any other neurologic disease were recruited for comparison.

Coherence analysis: Coherence analysis was carried out 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 allowed us to compare our data to existing coherence studies, which had 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 inter-hemispheric electrode pairs (FP1-FP2, F3-F4, F7-F8, C3-C4, T3-T4, T5-T6, O1-O2).

4.9. Statistical Analysis

Data was processed and analyzed using Statistical Package for the Social Sciences, version 25.0 (SPSS, IBM, Chicago, IL, U.S.A.). Are Hugo Pripp, MD, PhD, Researcher at Epidemiology and

Biostatistics, Oslo University Hospital-Rikshospitalet and statistician at Sørlandet Hospital assisted with the choice of methods and interpretation of the results (Paper 1-3).

Paper 1: To test for sample distribution, we used a histogram analysis and Shapiro–Wilk test. As most of data were not distributed normally, we used nonparametric tests to determine statistically significant differences, with a significance level set to .05. The Mann–Whitney U test was used for comparisons between groups of continuous variables. We used linear regression analysis to investigate whether sleep disturbances (SDSC scores) were associated with FASD subgroups and comorbidities. To deal with a very small amount of missing (anamnestic) data, we used imputation of data as reasonable guesses for missing data. The odds ratios (OR) with 95% confidence intervals (CI) were calculated and used as an estimate of the increased risk for children with FASD and ADHD to have sleep disturbances compared with those without ADHD as comorbidity.

Paper 2: 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 were implemented. *P* values ≤ .05 were considered statistically significant. Due to low percentage of missing data, we used imputation method for developing of reasonable guesses for missing data.

Paper 3: As 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. A one-way ANOVA was performed where inter-hemispheric coherence 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) were 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 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 Inter-hemispheric Coherence values according to frequency band and location (electrode pairs) resulting in a significant p-value of 0.002 for ICoh.

4.10. 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 [118].

5. Results

5.1. Main results from Paper 1

Among the 53 children with FASD, disturbed sleep was very common affecting 79% of the children. Difficulty falling asleep and maintaining sleep (DIMS) was the most common sleep problems encountered (74%), followed by disturbed sleep-wake transition (SWTD) (70%). SDSC total score was lowest for the FAS/pFAS subgroup and highest for the Neurobehavioral disorder subgroup, but without any significant differences between the groups. We found an ADHD prevalence of 47%, a prevalence for epilepsy as high as 9.4%, and abnormal EEG was found in 24.5% of the children. All children with confirmed epilepsy were treated with Lamotrigine and were seizure-free. Pathological EEG findings were equally distributed throughout the FASD subgroups and not overrepresented in those with ADHD comorbidity. When comparing the sleep score to relevant comorbidities, we found increased risk for disturbed sleep in children with FASD and ADHD compared to children with FASD without ADHD, see table 2 (odds ratio 1.36, 95% CI 1.03 – 1.79). No relationship with pathological sleep were found for other comorbidities or clinical factors such as epilepsy, SES, prenatal exposure to alcohol alone or the combination of alcohol and illicit drugs, or living condition, i.e. if the child lived with his/her biological parents or was in foster care. Additionally to the higher prevalence of sleep disturbance, we could also show that the IQ index *Working memory* score and the BRIEF *Behavior regulation index* (measure of one's ability to problem-solve or cognitively shift freely from one situation to another, regulate his or her emotions, and behavior) were compromised in children with sleep disturbance, independent of an ADHD comorbidity.

Table 2. Mean SDSC T-score with standard deviation according to age group, the use of sleep medicine, and comorbidities in the study group (n=53)

	n	Mean (std dev.)	p value
Age group			
Age 3-6 years	11	65.4 (15.2)	.60
Age 7-18 years	42	63.0 (14.4)	
Use of sleep medicine			
Yes	11	70.2 (13)	.19

No	42	61.7 (13.4)	
ADHD			
Yes	**25**	**66.8 (14)**	**.003**
No	**28**	**60.5 (14.4)**	
ADHD with treatment			
Yes	6	73.2 (10.8)	.42
No	19	64.8 (14.6)	
Epilepsy			
Yes	5	66.0 (20.4)	.27
No	48	63.2 (14)	

Abbreviations: FASD = fetal alcohol spectrum disorder, ADHD = attention-deficit hyperactivity disorder, EEG = electroencephalogram, std dev. = standard deviation.
Mann-Whitney U-test. The significance level is p< .05.

5.2. Main results from Paper 2

In our sample of 148 children, diagnosed with FASD, 94 (64%) had an ADHD diagnosis and nine children (6.1%) had epilepsy, see table 3. 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 (see examples of epileptic activity on EEG in figure 5 and 6). Six (67%) of the children with epilepsy were treated with lamotrigine (LTG), two received valproate (VPA) and one sulthiame (SUL). All were considered seizure-free on the current medication, which in all cases was the first anti-seizure medication offered. Abnormal EEG was found in 33 children (22%) including those with epilepsy, resulting in 24 (17%) children without epilepsy but with abnormal EEG. Pathological findings were seen as inter-ictal epileptic discharges, generalized slowing of background or focal slowing frontally or posteriorly. Cognitive and adaptive scores did not show any significant differences between those with or without epilepsy or abnormal EEG. However, the 10 children without epilepsy but with frontal pathology on EEG (focal slowing or focal spikes), had significantly reduced 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 versus pFAS/FAS) still showed significantly reduced results for these IQ indices in those with frontal EEG pathology.

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

pat	Sex	Age	sub-group	Classi-fication	EEG findings	age of debut	Developmental delay (severity)	Seizure evolution at follow-up	ASM
1	Male	8 y	SE	focal	focal IEDs (right temporal)	11 y	mild	Seizure free	LTG
2	Male	5 y	SE	focal	focal IEDs (left parietal)	4 y	no	Seizure free	LTG
3	Male	12 y	SE	focal	focal IEDs (left temporo-posterior)	11 y	no	Seizure free	LTG
4	Male	6 y	pFAS	focal	focal IEDs (right fronto-temporal)	6 y	no	Seizure free	SUL
5	Male	14 y	SE	genera-lized	Generalized nonspecific paroxysms	10 y	no	Seizure free	VPA
6	Male	14 y	SE	genera-lized	Generalized nonspecific paroxysms	12 y	no	Seizure free	LTG
7	Male	5 y	SE	focal	focal IEDs (right parietal)	3 y	no	Seizure free	LTG
8	Female	11 y	SE	Focal	focal IEDs (right posterior	9 y	no	Seizure free	LTG
9	Male	10 y	SE	Focal	focal IEDs (right posterior)	9 y	no	Seizure free	VPA

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

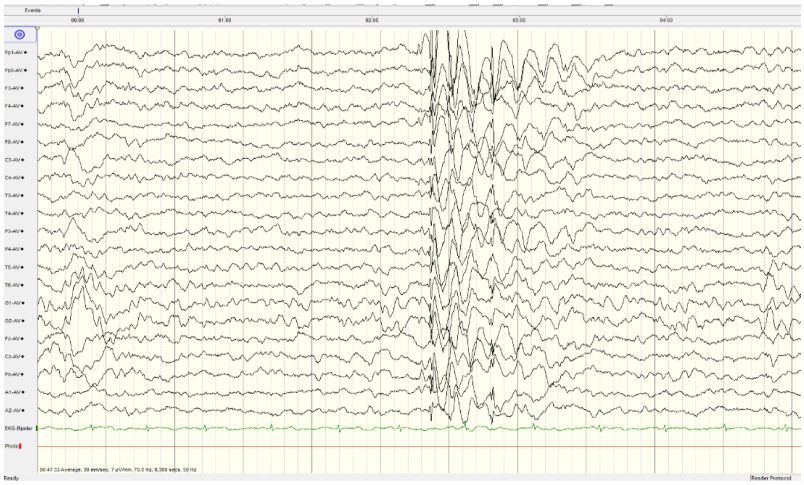

Figure 5. Generalized paroxysm of spikes and poly-spikes and wave complexes in patient 5 in Table 3. Timebase, Sensitivity 7µV/mm, 30mm/sec, High Cut 70 Hz, Low Cut 0.3 sec, Notch 50 HZ.

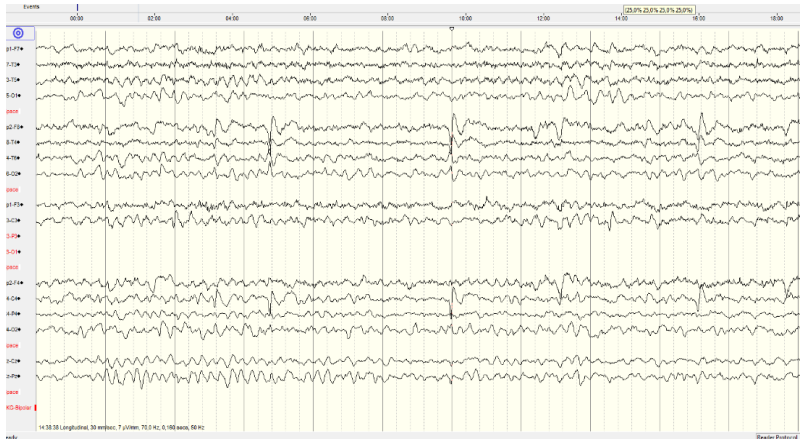

Figure 6. High-voltage spikes or spike and waves in the centrotemporal region in patient 4 in Table 3. Timebase 30mm/sec, Sensitivity 7µV/mm, High Cut 70 Hz, Low Cut 0.16 sec, Notch 50 HZ.

5.3. Main results from Paper 3

Of the 81 children in our sample, 44 (54%) had an ADHD diagnosis and six children had epilepsy (7.4%), four of them were treated with LTG, one with VPA and one with SUL. One of the children had generalized and five had focal epilepsy. Pathological EEG (epileptiform pattern, background slowing, and focal slowing) was found in 17 (21%) children including the six with epilepsy, resulting in 11 of 75 (15%) children without epilepsy but with abnormal EEG. When comparing the ICoh values for all children with FASD and the healthy controls, we found reduced values for the children with FASD in the frontal *delta* and *beta* bands (p<.001), and the temporal *alpha* (p<.01) and *theta* bands (p<.001), see table 4 and figure 7. 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* and *beta* band (p<.001), and the temporal *alpha* (p<.01), and *theta* band (p<.001). The comparison of ICoh values between thirty children with FASD without co-morbidities (epilepsy, pathological EEG and/or ADHD) and controls showed reduced values in the FASD group in the frontal *beta* band (p<.001) and the temporal *alpha* band (p<.001). When comparing the different FASD subgroups, a 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 and partial FAS.

To test for any correlations between the ICoh findings and cognition, the FASD group was dichotomized based on the mean value of ICoh in the control group (mean 0.38 μV^2, SD 0.07). An ICoh value of less than/equal to minus two standard deviations from the mean in controls was chosen as cut-off point (0.24 μV2). When testing for any significant effects on correlations between those groups and cognitive scores, we found significant correlations for the temporal (T3-T4) *alpha* band and Performance IQ (p=.04) and IQ index *Processing speed* (p=.02), respectively, meaning that those with reduced ICoh values had significantly lower cognitive scores, also after co-varying for co-morbidities.

Table 4. Significant differences with p<0.05 in inter-hemispheric coherence values between different FASD groups and healthy controls

	All FASD children	FASD without epilepsy/pathologic EEG	FASD without epilepsy/pathologic EEG and ADHD
Delta F3_F4	⇓	⇓	
Beta F3_F4	⇓	⇓	⇓
Alpha T3_T4	⇓	⇓	⇓
Beta F7_F8		⇓	⇓
Theta T5_T6	⇓	⇓	

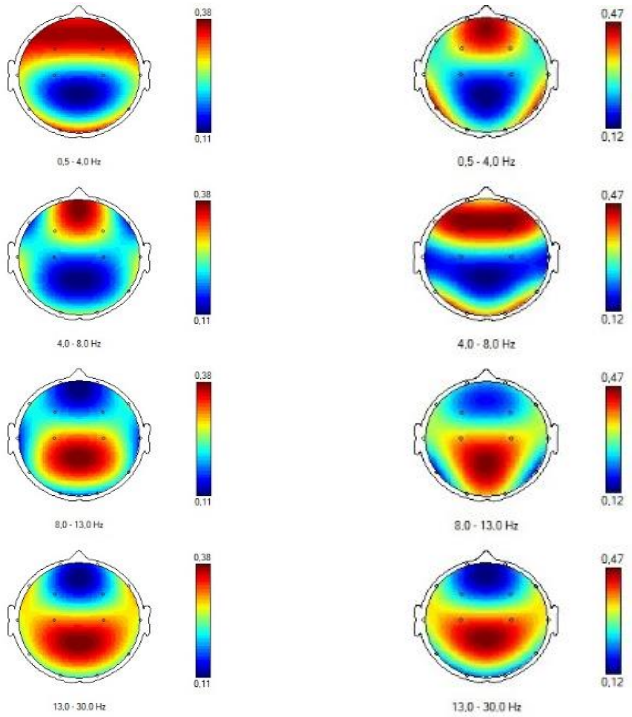

Figure 7. Cumulative spectral analysis with mapping for FASD children versus control group shown for the four frequency bands (*delta, theta, alpha, beta*). The picture shows both the ICoh value (0-1) and the distribution from frontal to occipital.

6. Discussion

6.1. Summary of main findings

The studies in this PhD thesis identified a high prevalence of disturbed sleep patterns aggravated by an ADHD as comorbidity in children and adolescences with FASD. The children with signs of sleep disturbances had inferior working memory, executive function and adaptive functioning, irrespective of the FASD subtype. Furthermore, we found an increased frequency of epilepsies in a sample of 148 children with FASD assessed at our center between 2018 and 2022. Epilepsy was found in 6.1% of the children, an 8.7 fold higher prevalence compared to Norwegian children in general where the prevalence is about 0.7%. An increased frequency of EEG pathology was also found in children without epilepsy, across all FASD subgroups. Children with FASD and frontal EEG pathology had normal total IQ, but significantly reduced IQ indices *Processing speed* and *Working memory*, which may indicate specific executive function deficits. When enhancing the EEG analysis with a quantitative EEG and comparing the results to an age-matched healthy sample, the findings of lower ICoh-values could imply hypo-connectivity between the hemispheres with impact on cognition in the FASD group. We could show a relationship between lower coherence values for the temporal *alpha* band and lower scores on Performance IQ and the *Processing speed* index.

6.2. How this thesis builds upon previous research

The prevalence of epilepsy is 0.7% and of ADHD 2% in Norwegian children [81]. The prevalence for sleep disturbances in healthy children is estimated at around 20% [69]. Previous research showed that both of these clinical conditions or co-morbidities are over-represented in children with FASD [78], but only a few studies have reported detailed data on epilepsy among persons with FASD, with relatively small study samples and most of them only including children and adults with full FAS. These studies reported epilepsy as co-morbidity in 3–21% of patients with FAS [91, 93-95]. Our research was based on a large sample of children and adolescences, including all FASD subgroups, with a confirmed FASD diagnosis after multidisciplinary clinical assessments. We had access to valid anamnestic data on comorbidities and an EEG registering allowing specifying the findings.

Paper 1 focused on sleep disturbances in children and adolescents with FASD. These are known as a massive problem and described to have immense impact on quality of life for both the child and the caregivers [68, 70-72, 74, 119, 120]. Different researchers showed very high prevalence, from 50% to 80% [121]. Our research was able to connect common comorbidities in FASD to sleep problems and its clinical impact on cognition.

Paper 2 gave a more detailed picture of the children with epilepsy in our sample, adding data to research done by Nicita et al. who reported detailed information on 11 children with FASD and epilepsy [95]. Additionally, we were able to correlate pathological EEG findings to significantly reduced scores on the IQ indices *Processing speed* and *Working memory*.

Paper 3 was one of the first studies on children with FASD using coherence analysis (QEEG) as a diagnostic instrument in FASD, to explore whether reduced inter-hemispheric coherence (indicating poor connectivity between the hemispheres) would have clinical correlates on cognition. In a current study by Bauer et al. from 2023, QEEG was used in an intra-hemispheric power analysis in children with FASD without epilepsy. They 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 ADHD patients [105]. We also reported a high prevalence of ADHD as comorbidity in the children assessed in our center. It is well known that children with FASD could have functional hypo-connectivity between the two hemispheres, due to structural alterations in the corpus callosum. We therefore chose to investigate inter-hemispheric measurements in favor of intra-hemispheric power analysis.

6.3. Validity of the study

Several issues should be addressed when considering the validity of our studies. In the following, I will address the internal validity in terms of methodological considerations, chance, bias and confounding, and the external validity in terms of generalizability.

6.3.1. Methodological considerations

6.3.1.1. *FASD 4-Digit Diagnostic Code*

The 4-Digit Diagnostic Code [15] and the IOM criteria [16] generate a spectrum of diagnoses under the umbrella of FASD and both systems maintain the three original core diagnostic

criteria (growth deficiency, facial anomalies, and CNS abnormalities). All children referred to our competence center at Sørlandet Hospital underwent a multidisciplinary assessment done by one team of very experienced professionals well trained in FASD diagnostics. In all children, we used the 4-Digit Code, the standard and preferred diagnostic system used in Norway. The 4-Digit Code is based on measuring the facial features from 2D digital photos using the FAS Facial Photographic Analysis Software [61], which was performed in all children in our study. However, several diagnostic systems exist and there is no evidence that one system is better or more valid for diagnosing FASD than the others [24, 122]. In a study by Peadon et al. [123], they received information about diagnostic system in use at 34 centers diagnosing FASD, 24 in USA, five in Canada and five in other countries (UK, Italy, Chile, South Africa). Twenty-three centers 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.

6.3.1.2. Sleep assessment

Polysomnography (PSG) is regarded as gold standard for experimental sleep analysis [72]. However, PSG is both cost and time consuming and is consider much more invasive compared to a questionnaire. The use of validated children`s sleep questionnaires [73] is another possible approach. A few studies have measured sleep by using both instrumental examination and caregivers' questionnaires. They compared it to normative data [74], demonstrating that the results from sleep measurements by PSG and questionnaires are concordant to each other, which may implicate that the single use of sleep questionnaires could be sufficient to get reliable answers [75]. The Sleep Disturbance Scale for Children (SDSC) is a 26-item sleep-related questionnaire that has demonstrated through validation an adequate level of internal consistency, test–retest reliability, and availability of normative data [114]. The SDSC is a scale developed to assess the presence of sleep difficulties in children within the previous six months. These psychometric properties of the SDSC were most frequently assessed in typically developing samples, while the children in our sample had a FASD diagnosis and many with co-morbidities. This may be a limiting factor in our study; however, there is evidence that the SDSC is reliable also in clinical populations [124]. As initially developed and validated for Italian children, the SDSC was afterwards validated for many other countries [125]. Even in absence of normative data for Norwegian children, the SDSC is widely used in Norway. It is, for instance, recommended as measuring tool for autistic

children and children with developmental disorders [126]. SDSC was answered by the caregivers and may be biased by their experiences with the child's sleep problems; on the other hand, a self-answered questionnaire reduces interviewer bias. The SDSC score was therefore compared to the caregivers' anamnestic description of disturbed sleep to the paediatrician to examine the reliability of the SDCS results. In those with high score, the problem with sleep was also reported to the paediatrician during the consultation. A possible weakness could be that foster care parents were less familiar with the child's usual sleeping patterns and that children in foster care in general might have difficultly establishing routine sleeping patterns. However, we did not find any statistical differences in sleep problems between children in foster care and the others. In addition, the foster care children in our study had been living with their foster family for several years when attending this study (mean duration >6 years).

6.3.1.3. Neuropsychological testing

All study children with FASD underwent a comprehensive standardized cognitive and neuropsychological assessment by a trained neuropsychologist. Two trained and experienced neuropsychologists tested all the children, reducing inter-rater bias. None of the assessments was blinded, as testing was part of the standard assessment for all children referred to our center for FASD diagnosing. It was not possible to use one single IQ assessment tool for all participants due to age differences and new versions of the tests with time. However, the correlation between Full IQ assessed by different versions of the Wechsler tests are high, and the agreement is best when Norwegian norming data is used [127]. 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-V), Wechsler Adult Intelligence Scale - Fourth edition (WAIS-IV), or Wechsler Nonverbal Scale of Ability (WNV) depending on age and function. In addition to Full, Verbal and Performance IQ, we explored the IQ indices *Processing speed* and *Working memory* as an expression of executive functions, since both of these indices representing different aspects of executive functioning [63].

The different IQ indices do not have the complete same structure in the different Wechsler tests and have slightly changed from one edition to the next. The comparison of IQ results from different editions and various ages could be seen as a source of biasing, but as mentioned above, the correlation between miscellaneous versions of the Wechsler Intelligence Scales is

good [127]. Due to the different versions of especially the WISC tests, the term Performance IQ is built on slightly different subtests. In WISC-IV, Performance IQ is defined by Processing Speed and Perceptual Organization, while WISC-V do not use this model anymore. Here, we chose to use the Fluid reasoning index (FRI) to define Performance IQ. The FRI is derived from two subtests: Matrix Reasoning and Figure Weights. In this way, we were able to compare the results from different cognitive assessments. To assess the child's daily functioning, we used the parent-reported Vineland Adaptive Behaviour Scales – second edition (VABS-II) (Sparrow, 1989), resulting in an Adaptive Behaviour Composite Score, based on communication, daily living and social skills. VABS scores have been validated in Scandinavian children [128]. It is well known that children with FASD have lower VABS scores than expected compared with the IQ scores [25, 129]. This is a known mismatch between cognition and adaptive functioning in these children and the combination of both IQ testing and VABS increases validation of our data.

6.3.1.4. EEG registration / QEEG analysis

Analyzing of EEG registration has some technical pitfalls since nearly 100% of such analyses are done manually and not computerized. Especially in (younger) children, the technical quality of an EEG could be disturbed by artifacts (movements, talking, chewing etc.). To avoid or minimize this, all EEG examinations were performed in a quiet environment and by very experienced technicians, who were used to work with children. Additionally, we used a standard protocol with a 2-hour registration. This increased the possibility to receive good technical quality. A very experienced neuropaediatrician and neurophysiologist evaluated EEG and controversial results were re-analyzed independently. All EEG analyses were done according to the terminology used in the last revised glossary by the International Federation of Clinical Neurophysiology (epileptiform pattern, background slowing, focal slowing) [130]. With regard to EEG data analysis, the amount of artifacts in the EEG record can vary widely by condition and/or by individual participant. Thus, it was important to examine the amount of EEG data available for analyses after the EEG power and coherence values had been computed by the Fourier analysis software. In line with other research in this field, we determined the amount of data considered appropriate for our analyses by 10 seconds [131]. This was done to avoid including children with very different amounts of data, which could result in questionable data analyses and conclusions. We also verified that the amount of EEG data between our clinical sample and the controls was similar, as it was critical to examine the EEG

coherence values for outliers to avoid misleading statistical results. When QEEG data was analyzed in the FASD children and controls, the investigator was blinded to group adherence to reduce research bias (observer bias) and to ensure internal validity.

6.3.1.5. Promises and challenges of cross sectional studies

Longitudinal, cross-sectional studies are observational studies that analyze data from a population at a single point in time. Usually, they are used to measure the prevalence, understand determinants, and/or describe features of a population. They are most often rather easy to conduct and can be useful for establishing preliminary evidence, for instance in planning a future study [132]. An important step in the design of a cross-sectional study is an accurate sample size determination, which in our study was about 50 participants. Planning a good sampling strategy is another essential component. In this thesis, all patients were referred to our center, resulting in a nonprobability or purposive sampling [133]. This fact is essential when interpreting our results and leads directly to limitations and generalization.

6.3.2. Limitations and generalization

A number of specific limitations of this PhD thesis have already been described, including methodological weaknesses and, quite important, the selection bias because we could not use any probability sampling technique. This leads to a rather low external validity [134]. Internal validity describes the degree to which the results are representative for the population studied [134]. The different studies in this thesis describe rather complete or fairly representative FASD samples assessed at our center. Thanks to the very high participation rate, the sources of bias have been reduced, and we believe that the internal validity was acceptable. Several issues regarding limitations to the generalizability of these studies will be discussed here. Additionally, and this is a disadvantage of any cross-sectional study, we were not able to make any statement about whether the increased frequency of epilepsy seen in our sample is causally related to the prenatal alcohol exposure or to other causes. However, this uncertainty applies to all comparable studies. Quite important to mention, is the fact that the FASD children included in our studies were not randomly selected, which may cause selection bias. Our findings on prevalence cannot and were not intended to be used as general prevalence data for children with FASD in Norway. We have therefore tried to replace the word “prevalence” with “frequency”. Nevertheless, frequencies of epilepsy, ADHD and pathological EEG findings in our study population have been compared to known prevalence in the general (Norwegian) child population, in order to be able to use a measure for comparison. Due to the

study design, it is not possible to say whether there are specific types of EEG pathologies or seizure disorders that are linked to prenatal alcohol exposure. To answer that, it requires larger clinical studies, not least, to determine any true cause–effect relationship between alcohol exposure and the increased risk of seizures. A standardized MRI examination was not part of this study, nor is MRI required in the assessment for FASD. In some of the study participants, we had access to MRI results from other hospitals, but due to the lack of standardization, we did not include them in our studies. Especially in the children with epilepsy, MRI would have helped to distinguish between structural and non-structural forms of (focal) epilepsies. Therefore, any true cause–effect relationship between FASD and epilepsy must remain speculative.

6.3.2.1. Sample size and study population

The different studies in this thesis included different sample sizes from 53 children in paper 1, to 148 children in paper 2 and 81 children in paper 3 (and 31 healthy controls). We did a power analysis for sample size determination, which in study one resulted in 23 participants, 46 in study two and 61 in study three, meaning that we had a sufficient number of children.

The participants in our different studies consisted of children and adolescents referred to our competence center between 2018 and 2022 for a clinical assessment of FASD. All children with confirmed FASD and their caretakers were asked to participate in the research study. Those, who did not fulfill the criteria for FASD, were not included in the study sample. Of all referred children between 2018 and 2022, 73% were diagnosed with FASD, and among eligible participants, about 90% gave there written consent to be part of the study. Another strength of this study was that we included children from the whole spectrum of FASD based on the 4-Digit Code, which made it possible to analyze not only the whole sample, but also the different FASD subgroups (FAS, pFAS, ND, SE).

A major concern with a clinical study sample is *selection bias*. As in many other studies on children with FASD, using a clinically referred sample and not randomly selected patients leads to some disadvantages. One is that children referred to a specialized third line competence center like ours, 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. On the other hand, our sample was quite similar to those referred in other studies regarding distribution of children in the different FASD subgroups [135], and frequency

of ADHD and epilepsy [93]. The same applied to the results of the IQ testing and Vineland scores [56]. This strengthens a possible generalization of our results.

6.3.2.2. Control group

In paper 3, the results of the ICoh of the children with FASD were compared with those of a reference group. The reason for the case-control design was the lack of normative data on coherence in Norwegian children. Reference or control samples are usually matched regarding age and sex, but in addition, and most importantly in this study, without any history of prenatal alcohol exposure. To confirm that, the mothers of all children in the control group were asked about the use of alcohol/illicit drugs in pregnancy. A weakness of study arises from the fact that one has to rely on the anamnestic data. We decided to use an age-matched sample of children from several schools in Arendal. The only other study on QEEG in children with FASD included an age-matched sample of children who were hospitalized with functional abdominal pain [105].

6.3.2.3. The reliability of anamnestic data on prenatal alcohol exposure

Using the 4-Digit Code, the criterion of prenatal alcohol exposure generates four clinically meaningful categories. Rank 4: confirmed exposure to high levels of alcohol; Rank 3: confirmed exposure, but the level is less than Rank 4 or not specified; Rank 2: unknown exposure (neither confirmed absent nor confirmed present); and Rank 1: confirmed absence of exposure from conception to birth. In the absence of a clear consensus on the amount of alcohol that can actually be toxic to the fetus, any exposure should be reported [15]. Pregnancy anamnesis is an important part in FASD diagnostics. Exposure-specific biomarkers for verifying prenatal substance use are still subjects of research and not available for clinical usage except in the neonatal period (meconium sample). Such biomarkers are not available during later child assessments [136]. However, it is quite challenging to obtain reliable data related to prenatal alcohol exposure, simply because it may be difficult to remember many years back exactly what someone consumed, for example, before a confirmed pregnancy.

Another known problem would be under-reporting. Additionally, our clinical sample consisted of children whereof only 13-17% of them were living with their biological mothers. Anamnestic data on alcohol or substance use is reliable, but often limited on reports from social welfare services or clinics treating pregnant women with addiction disorder. Even if the use of prenatal

alcohol exposure was confirmed in our study, we did not try to collect data on the exact amount and period of alcohol use in pregnancy since it does not affect the diagnosis of FASD in the 4-Digit Code. If it is not possible to get any information on prenatal alcohol use (Rank 2), Fetal Alcohol Syndrome - FAS is the only FASD subgroup that can be diagnosed with unknown PAE. An advantage of the 4-Digit-Code is that the grading of PAE as Rank 3 or 4 has no effect on the outcome of the diagnostic assessment (the exact amount of alcohol is not particularly important). An example of PAE Rank 2: Unknown is, for example, when the child is adopted or the biological mother is dead, and there is no health information or legal documents on verified PAE. No risk corresponds to PAE Rank 1 and is used if the biological mother informs about total abstinence from alcohol during pregnancy from the time of conception.

In our study, the biological mother or the referring instance was our primary source of information about PAE. Secondarily, we used written documentation (hospital documents, blood test findings, court documents) that could confirm PAE. Information from partners, relatives, and health and child protection workers etc. was not relied on since we did not consider it to have good enough validity.

6.3.3. Chance

The role of chance may occur at any time when a sample of population is examined. The p-value is defined as the probability that the effect observed could have occurred by chance alone, reflecting both the magnitude of the difference between the groups, and the sample size [137]. A large effect may therefore not achieve significance if the sample size is insufficient (Type II error – false negative). Our main findings are not likely to be due to chance because of p-values < 0.05 and consistent findings. Nevertheless, some of the subgroup analysis resulted in small sample sizes, and this should be taken into account when interpreting the results. Another concerning fact is testing for multiple hypothesis as done especially in paper 3. If multiple hypotheses are tested, the probability of observing a rare event increases, and therefore, the likelihood of incorrectly rejecting a null hypothesis increases (type I error – false positive) [138]. There is no consensus regarding when, and if so, how to adjust for multiple hypotheses. The simplest method is the Bonferroni correction, which means dividing the unadjusted significant p-value (0.05) by the number of hypotheses, to create an adjusted

significance level [139]. In our study, coherence estimates were derived for four different frequency bands on seven inter-hemispheric electrode pairs. This will give a Bonferroni corrected significance value of p = 0.05 / 28 = 0.002. However, the Bonferroni correction is very conservative and controversial. In an article by Perneger, the author concludes that adjusting statistical significance for the number of tests that have been performed (Bonferroni), creates more problems than it solves. The main weakness is that the interpretation of a finding depends on the number of other tests performed, and when the likelihood of type II errors is increased [140].

6.4. Discussion on the main findings

6.4.1. FASD and Sleep

6.4.1.1. *Sleep Disturbance*

A possible mechanism of sleep disturbances in children with prenatal exposure to alcohol has been shown in animal studies. Prenatal alcohol exposure was associated with thalamic, hypothalamic, and endocrinal changes and long-term disruption in sleep-awake rhythmicity [141]. An appropriate development of the thalamus and hypothalamus is vital for the control of state regulation [142, 143]. Neuronal systems, that usually maintain sleep through sensory inhibition, behavioral inhibition and neuroendocrine regulation, may be compromised by prenatal exposure to alcohol [144]. MRI studies have demonstrated volume loss in these brain structures in children with FASD [145], structures responsible for various kinds of state regulation. Children with FASD frequently show such state regulating problems; disrupted sleep being one of them [71], that may affect sleep onset, sleep-wake cycling, and sleep hygiene (Chen et al., 2012, Goril et al., 2016). As shown in previous research and described as typical pediatric insomnia (Owens and Mindell, 2011), difficulty falling asleep/maintaining sleep and sleep-wake transition were the main affected domains in our study. Increased scores in these two domains (DIMS and SWTD), mainly explained the high SDSC Total Score for the children in our study. Our findings confirm data from previous research, and the overall frequency of sleep disturbances was very high among our sample with FASD children. Similar results are shown for children with other neurological diseases such as epilepsy [146, 147], but the prevalence of sleep disorders seems to be even higher in FASD [70]. About 79% of the children in our study scored above the SDSC cutoff for clinically significant sleep disturbances.

Considering the fact that among the different FASD subgroups, the grade of severity is increasing from Neurobehavioral Disorder to full FAS, it was a bit surprising that we did not find any significant differences in the frequency of sleep disturbances between FASD subgroups.

Children with FAS/pFAS - the most severe forms of FASD - did not have poorer sleep than children within the other FASD subgroups. Olateju et al. described a relationship between PAE and alterations of the brain neuropeptide hypocretin and cholinergic neurons, both responsible for the regulation of circadian sleep-wake cycle [148]. This is described as a common pattern after PAE and not related to a specific type of FASD, which may explain the lack of differences among our FASD subgroups. Neither did our results indicate any significant relationship between sleep disturbances and age group, SES, whether the child had been exposed to alcohol only or alcohol and illicit drugs combined, or the child's living conditions (with biological parents, in foster home, adopted). It is a well-known fact, that sleep disturbances represent a multifactorial problem and that several environmental factors may have a huge impact on sleep [121]. Lewien et al. pointed out that lower SES and less stable caregiving was associated with increased sleep-related difficulties in healthy adolescents [149]. When interpreting our results with regard to sleep, it is important to take into account that our sample size was relatively small and inhomogeneous. Additionally, all of the children in our sample were referred to our center and not randomly chosen. This may result in biasing and the data allows limited generalization. Nevertheless, the results underline the significance of sleep disturbance in all children with FASD.

6.4.1.2. *Sleep disturbance and Comorbidities*

The children with FASD and ADHD comorbidity had more sleep problems than those without ADHD, while this was not the case for those with epilepsy or abnormal EEG. The prevalence of ADHD in FASD is considered to be much higher compared to the general pediatric population (47 – 94% versus 9%) [78]. In our study, 47% (paper 1), 64% (paper 2) and 54% (paper 3) of the children with FASD had ADHD, which is in accordance with the results from a recent meta-analysis by Lange et al., reporting ADHD to be the most common co-morbid disorder among children with FASD with a prevalence of 52.9% [42]. The children with ADHD in our study sample had more often sleep disturbances compared with those without ADHD resulting in an odds ratio of 1.36; 95% CI 1.03-1.79. Both ADHD and FASD are commonly

associated with sleep disturbances, possibly due to shared pathophysiology and sleep problems may themselves foster ADHD-like symptoms**.** The complex relationship between these conditions and the very high prevalence of sleep disorders makes it challenging to decide whether sleep problems are comorbidity or, conceivably, a fundamental feature of FASD and ADHD [150]. Children with FASD and sleep disturbances (whether with or without ADHD) had inferior executive function scores in our sample, which is in line with other research, where the majority of studies showed a correlation between sleep and measures of attention, executive functions and processing speed [151].

Our finding that children with confirmed FASD had increasing sleep problems throughout childhood, even after controlling for several potential confounding factors, supports the view that prenatal exposure to alcohol could have a direct teratogenic effect on parts of the nervous system involved in sleep regulation. The detection and treatment of such sleeping problems may lead to better functioning, behavior and learning. Sleep-based therapies, introduction of structured evening routines for the child, counselling to parents, sleep medication, and other hands-on activities could have a significant impact on a child's sleep disorder management [152]. These therapies can assist individuals in the development of appropriate behavioural responses required for effective daily functioning [142].

6.4.2. FASD and Epilepsy

We found an increased frequency of epilepsy among children with FASD ranging from 6.0 – 9.4% in our three study samples and a high number of children in all FASD subgroups with pathological EEG-findings (21%-24.5%) even in absence of epilepsy. In the study by Bell et al., epilepsy was diagnosed in 25 (5.9%) of 425 patients with FASD, which is well in agreement with our findings [91]. Several neurodevelopmental disorders such as cerebral palsy and autism lead to increased risk of epilepsy [153]. Only a couple of studies investigated epilepsy among persons with FASD, but with relatively small study samples and/or including only subjects with FAS. We found most of the children with epilepsy (89%) within the FASD subgroup Static encephalopathy (alcohol exposed) and none in the FAS subgroup. In the 4-Digit Code, epilepsy reflects a confirmed affection of the CNS (CNS Rank 4) and will therefore exclude the subgroup Neurobehavioral disorder (alcohol exposed), which has CNS Rank 2. When taking a closer look on the epilepsy patients in our sample, the findings differ from those reported by Nicita et al. and Boronat et al. [93, 95] where most of the children with epilepsy

had a diagnosis of FAS or pFAS, noting that they used different classifications and different study samples. Another difference was seizure control, which was easily obtained by using common anti-seizure drugs (ASDs) at standard dosages in all children with epilepsy in our sample, while other studies showed an increased percentage of children with FASD with difficult to treat epileptic syndromes [91, 93, 95].

A causality between prenatal alcohol exposure and epilepsy cannot be confirmed in our study. Especially in those two patients with generalized epilepsy and the one with the centro-temporal spikes, a genetic cause for the epilepsy would be suspected [154, 155]. However, in children with PAE, there is an overlap in neuropathological and functionally impaired brain structures with those that are known to be associated with the genesis of epileptiform activity [156]. MRI studies have shown permanent alteration in the physiology of the hippocampus and other cortical structures [29, 157], thus promoting epileptic activity and enhancing kindling. The frequency of children with pathological EEG findings without epilepsy in our study group was clearly increased compared to 2.45% in the general pediatric population [98], in line with previous studies in children with FASD [91, 94]. In contrast to former studies, we were able to give detailed information on the type of EEG abnormalities. 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 [158]. In the nine children with epilepsy in our sample, and this might be the case in all studies on epilepsy in FASD, it was not possible to make any statement about causality. The epileptic disorder may be related to the prenatal exposure to alcohol or of genetic origin, or the combination of those.

6.4.3. Cognitive and adaptive scores with or without epilepsy and/or pathological EEG

Diminished neuropsychological functioning in children with FASD is well documented by numerous researchers [159], and research on children with different types of epilepsies indicates specific cognitive weaknesses, as deficits in memory and executive functioning. This can be seen even in mild epilepsies with good seizure control [160]. Further was focal EEG

pathology associated with different neuropsychological problems, as cognitive impairment and behavioral problems even in absence of clinical epilepsy and this may lead to adverse effects on attention and emotional functioning in children [102, 161]. It is also assumed that absence seizures with generalized spike-waves of frontal onset influence working memory as part of frontal functions [162]. In our study sample of 148 children with FASD, mean full IQ score of 83 (SD 12) was similar in children with FASD with or without epilepsy, with not surprisingly highest score in the "mildest" FASD subgroup Neurobehavioral disorder (alcohol exposed) (IQ 87), with significantly lower score (IQ 78) in the pFAS and FAS subgroups (p=.002). We found corresponding results in study 1 (IQ 80) and study 3 (IQ 84) with smaller sample sizes. Vineland Adaptive Behavior Scales showed even lower scores (General Adaptive function (GAF) score 59-63) than expected based on the IQ scores, a known mismatch between cognition and adaptive functioning in children with FASD [24, 163]. Carr et al. argued that reduced adaptive functioning was found regardless of FASD subtype (Carr et al., 2010).

Our results indicated that neither an epilepsy as comorbidity nor pathological EEG findings in general led to any differences in neurocognitive functioning. However, the children with frontal EEG pathology, but without an epilepsy had reduced scores on *Processing speed* and *Working memory* indicating reduced executive functioning. These specific cognitive deficits could not be explained by other risk factors such as ADHD comorbidity or prematurity. Executive functions typically include inhibition, working memory, switching and updating [164]. Additionally, processing speed, which is how quickly an individual can perceive and process information and/or initiate a response [165], could also be seen as a component of executive functioning [166]. These associations could be shown irrespective of presence or absence of ADHD comorbidity and may indicate altered functioning in the frontal lobe. In addition to their involvement in motor function and language, the frontal lobes play important roles in a multitude of cognitive processes, such as executive function, attention and memory, additionally to processes underlying emotions, mood and personality [167]. Processing speed and working memory are fundamental supportive 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 [168]. A functionally impaired frontal lobe, with focal pathology on the EEG as seen in our study, could result in affected motor

activity and in disturbed attention. Similarly, Niedermeyer et al. described ADHD as a frontal neuronal dysfunction under more benign circumstances [162].

Disturbed frontal lobe functioning leads to impaired response inhibition and working memory deficits [169]. Alterations in the frontal lobe in children with FASD has been shown both structurally with reduced volume on MRI by Astley et al. and on frontal processing by neuropsychological testing by O`Hare et al. Working memory tasks were less efficient suggesting functional recruitment abnormalities [170]. Prenatal exposure to alcohol was associated with a malpositioning of GABAergic interneurons in the frontal cortical plate, and impaired GABAergic signaling is known to trigger various forms of epilepsy [171]. Additionally, PAE led to microscopic impaired neuronal and glial migration, including heterotopias [172]. Heterotopias could be associated with seizures or abnormal EEG [93].

6.4.4. Correlation of reduced ICoh and cognitive scores

We speculate that the decreased ICoh seen in the FASD group could be related to impaired transcallosal pathways, a hypo-connectivity between the right and left hemisphere partly due to reduction in corpus callosum. Our findings of concomitant reduced cognitive functioning may indicate that this hypo-connectivity had clinical consequences. Our findings with reduced ICoh in children with FASD point towards an altered inter-hemispheric communication. If this was the case, we wondered whether these results were reflected in reduced cognitive scores. Diminished temporal ICoh (T3-T4) *alpha* band correlated with lower scores on Performance IQ *(p=.04)* and the *Processing speed index (p=.02).* We did already find an association between EEG pathologies and reduced executive scores in our larger sample of 148 FASD children. Performance IQ provides a measure of an individual's overall non-verbal 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 [173]. Deficits in these areas contribute to executive function problems, including initiation, inhibition, mental flexibility, novel problem solving, planning and regulation of emotions [173]. Such deficits may be partly explained by diminished inter-hemispheric

transfer of complex sensory information and learning [174]. White matter abnormalities, seen as gliosis, myelin deviations, and fiber loss and reduced volume of corpus callosum (CC), are among the most well replicated MRI findings in FASD and contribute to impaired functional connectivity and deficits in executive function [175].

6.4.5. Inter-hemispheric Coherence differences between the FASD group and controls

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 [176]. Comparing the children with FASD to healthy controls, we found significantly lower coherence for *delta*, *beta* and *alpha* waves in frontal and temporal regions in the FASD group. To interpret our results, it might be helpful to look at coherence studies on other diseases, as for instance ADHD, CC dysgenesis and CP. Barry et al. found that children with ADHD had lower *alpha* ICoh compared to controls in frontal and temporal regions, suggesting reduced cortical differentiation and specialization in ADHD [177], particularly in cortico-cortical circuits [178]. Our results with decreased ICoh in the frontal and temporal areas in the FASD group could be interpreted in the same direction. Kulak et al. showed that children with hemiplegic CP had lower ICoh in the temporal, parietal and occipital derivations for the *alpha* band, suggesting hypo-connectivity between the right and left hemisphere, due to a unilateral brain lesion [176]. Decreased EEG coherence has also been reported in children with such anatomic disconnection as agenesis of the corpus callosum [179].

Structural changes in the corpus callosum is relatively often seen in children with FASD [111]. The corpus callosum is an important neurophysiological structure in learning and inter-hemispheric transfer of sensory-motor information, as well as contributing to language processing and cognitive functions [180]. Coben et al. [181] found low inter-hemispheric *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 under-connectivity. Another study on children with Asperger syndrome found reduced frontal inter-hemispheric coherence (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 [182]. We found signs of frontal lobe dysfunction also in paper 2 as abnormal frontal

EEG findings and reduced executive scores (*Processing speed* and *Working memory)*. Using ICoh analysis, the results in the children with FASD and the interpretation might be the same. Deficits in network connectivity occurred in children with FASD with functional MRI studies showing aberrant frontal-parietal connectivity [183]. Network abnormalities positively correlated 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 [66].

To look for ICoh differences within the FASD group, we divided the FASD children into those with FAS/pFAS, and those with *non-syndromic* forms (SE/AE and ND/AE) [23]. We found significantly lower *alpha* ICoh at the occipital pair, even after correction for co-morbidities with known impact on ICoh. Similar results were shown in preterm children with CP, suggesting that these findings could correspond to the neuroanatomical posterior thinning of the CC, often seen on MRI in preterm born children [184]. Children with FASD tended to have not only a smaller brain but also a disproportional reduction in specific brain structures, including CC on MRI [29]. Already in 1996; Riley et al. described a significant reduction in size of the anterior and the two posterior regions of the corpus callosum [111]. Corpus callosum, being the largest commissural white matter bundle in the human brain, is the main route for inter-hemispheric transfer of information, and it is involved in a large number of cognitive processes [185]. Recent MRI research on FASD children demonstrated bimodal damage mostly in the *posterior* CC, more frequently than the reduction in the whole section area [29]. The size reduction affected the posterior CC region most severely, and the degree of reduction correlated to the amount of prenatal alcohol consumption [28, 29, 111]. Independent of CC abnormalities altered ICoh in occipital lobe networks have been reported in children with ADHD [186]. Our results may be describing functional and anatomical hypo-connectivity between posterior brain regions in the more severely affected children with FASD.

7. Clinical Implications

7.1. Sleep and FASD

Sleep disturbances are significantly more common in children with ADHD [187] and even more common in children with FASD. Different authors describe the importance of well-regulated sleep [188] and the fact that sleep disturbance may affect several aspects such as memory, learning, cognitive flexibility, verbal functions and attention, which are cognitive domains that may already be affected in children with FASD [189]. In our study, the FASD children with sleep disturbances showed significantly inferior executive function scores and a trend towards lower working memory score (p=.08), compared with the FASD children without abnormal sleep. This may result in reduced functioning during daytime. Sleep disturbances in general still remain unrecognized and undertreated in children [188], and the same applies for children with FASD [68, 71, 74]. The fact that sleep problems can further exacerbate neurobehavioral and cognitive conditions makes screening and treatment of sleeping disturbance of huge importance [68]. Our findings underline the need of sleep evaluation of all children with FASD and should be a reminder to healthcare providers regarding the high prevalence and severity of sleeping problems in these children. Clinicians should include a standardized assessment of sleep, and we recommend the use of a sleep questionnaire to improve diagnosis and treatment. Larger samples and further research on this topic could help to establish guidelines about the most effective methods of examination and intervention of sleep disturbances in children not only with FASD but also with other neurodevelopmental disorders.

7.2. Pathological EEG findings in non-epileptic children with FASD

The correlation of subclinical EEG pathology to specific cognitive scores in children with FASD has not been reported before. Although EEG pathology did not seem to influence total IQ and global adaptive functioning, it was associated with neuropsychological deficits in *processing speed* and *working memory*, representing important aspects of executive functioning. Many studies have found a relationship between executive functions with specific learning disabilities [190] and we speculate that such deficits may increase the chance of learning disorders in children with FASD. Based on this concern, we suggest a rather low threshold for

considering EEG examination in children with FASD, even in the absence of clinical seizures. Children with FASD and focal frontal EEG pathology need special attention and one could speculate that antiepileptic drug treatment may lead to an improvement in frontal functioning, especially if cognitive tests show reduced scores on processing speed and working memory. However, any beneficial effects of medication on cognitive/executive functioning should be balanced against any side effects from medication in children without clinical epilepsy. The effect of anti-seizure medication on subclinical EEG pathology is well documented, but the effect on cognition is controversially discussed [191, 192].

7.3. QEEG in FASD

Our findings of significantly reduced ICoh values in children with FASD compared with controls could imply inferior connectivity between the two hemispheres through corpus callosum. Those with poorest ICoh in the FASD group had lower scores on Performance IQ and *processing speed index*, indicating possible clinical consequences on overall non-verbal and visuospatial intellectual abilities and the fluency with which the brain receives, understands and responds to information. Our study supports the idea that QEEG might be a useful biomarker in the diagnosis of FASD, but more research is needed. It remains to be seen whether these findings using QEEG in children with FASD will have clinical consequences in the future.

8. Suggestions for the Future

The recruitment of children with FASD to our research project was possible due to the close collaboration with the clinical work at the Regional Competence Center for children with prenatal alcohol and/or drug exposure (RK-MR). The center will assess about 50-60 children every year, and according to experience, about 70% will end up with a FASD diagnosis. The recruitment of children and adolescents to future research studies will be feasible. FASD is a clinical diagnosis and like most clinical diagnoses, it encompasses a certain degree of uncertainty. Our research seeks to add some new aspects to a well-established clinical pathway, as well as we try to enlarge the diagnostic portfolio with an assessment tool that has not yet been widely used, the QEEG. Our results represent just the beginning and subsequent, additional studies should be performed to confirm our initial findings. Incorporation of

structural brain MRI, or even better, multimodal quantitative MR, into such studies could lead to a better understanding of morphological, anatomical and functional impairments of the brain, particularly in the areas found to be altered in our EEG studies. Studies on FASD children with MRI are well established and the inclusion of different imaging modalities like diffusion tensor imaging (DTI) and tractography to our basic research on EEG and QEEG would greatly expand the amount of knowledge gain.

Additionally, comparison of findings on EEG and MRI/DTI might help to get a deeper insight into a possible cause–effect relationship between FASD and epilepsy, something that must remain speculative at the moment. The reduced ICoh found in our study could be compared with segmented corpus callosum volumes and corresponding diffusion metrics in a future study to look for structure-function relationships in the brains of children with FASD. There is currently no standard genetic test battery as part of our clinical assessment for FASD. At present, this is confined to children in whom a genetic syndrome is suspected as a differential diagnosis. In a future EEG study, genetics could be implemented.

Another area of interest where we still need some answers is the question of the clinical consequences of our findings. As shown in our results, there are brain areas with compromised function with consequences on scores for Performance IQ, processing speed and working memory, all potentially responsible for altered cognitive functioning. This may have direct consequences for the child's performance at school and in daily life functioning. It would therefore be of great interest to consider longitudinal observational follow-up studies and intervention studies using sleep medication or anti-epileptic medication to close present knowledge gaps.

9. Conclusion/key message

This PhD thesis sought to advance our understanding of possible relationships between sleep, epilepsy, EEG findings and cognitive function in children with FASD. We succeeded in emphasizing the importance of sleep disorders as a frequent comorbidity in children with FASD. Additionally, we were able to confirm the significantly increased frequency of epilepsies and to give detailed information on these children. The comparison of EEG findings and neuropsychological test results showed that frontal EEG pathology (even in non-epileptic children and regardless of any ADHD comorbidity) led to significantly lower scores on the IQ indices *Processing speed* and *Working memory* with possible impact on specific executive performance that may affect learning and adaptive functioning. Additionally, our results open up for a possible (drug) intervention that may improve the altered cognitive functioning.

As the first study on inter-hemispheric coherence in children with FASD, our findings suggested reduced connectivity between the brain hemispheres with an impact on cognition. Our results may indicate that QEEG should be considered as a possible biomarker for FASD, but more research is needed.

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Article 1

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ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH

RESEARCH ARTICLE

Sleep disturbances in Norwegian children with fetal alcohol spectrum disorders (FASD) with and without a diagnosis of attention-deficit hyperactivity disorder or epilepsy

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Abstract

Background: Fetal alcohol spectrum disorder (FASD) describes a combination of developmental, cognitive, and behavioral disabilities in children with prenatal exposure to alcohol. The literature suggests that there are higher rates of sleep disturbances in these children. Few studies have investigated sleep disturbances in relation to com- mon comorbidities of FASD. We examined the prevalence of disturbed sleep and the relationship between parent-reported sleep problems in different FASD subgroups and comorbidities like epilepsy or attention-deficit hyperactivity disorder (ADHD) and impact on clinical functioning.

Methods: In this prospective cross-sectional survey, caregivers of 53 children with FASD completed the Sleep Disturbance Scale for Children (SDSC). Information about comorbidities was collected, and EEG and assessment of IQ, daily-life executive and adaptive functioning were performed. Group comparisons and ANCOVA interaction models were used to test the associations between different sleep disturbances and clinical factors that could interfere with sleep.

Results: An abnormal sleep score on the SDSC was very common, affecting 79% of children (n = 42) with equal prevalence in all FASD subgroups. Difficulty falling asleep was the most common sleep problem, followed by difficulty staying asleep and wak- ing early. The incidence of epilepsy was 9.4%, with an abnormal EEG seen in 24.5%, and a diagnosis of ADHD in 47.2% of children. The distribution of these conditions was equal in all FASD subgroups. Children with signs of sleep disturbance had poorer working memory, executive function, and adaptive functioning. Children with ADHD had a greater prevalence of sleep disturbance than those without ADHD (OR 1.36; 95% CI 1.03 to 1.79). **Conclusion:** Problems with sleep are very common in FASD children and seem in- dependent of FASD subgroup and the presence of epilepsy or a pathological EEG finding, while those with ADHD had more sleep problems. The study underscores the importance of screening for sleep disturbances in all children with FASD as these problems may be treatable. K **E Y WO R D S** ADHD, BRIEF, epilepsy, fetal alcohol Spectrum disorder, IQ, sleep

INTRODUCTION

Fetal alcohol spectrum disorder (FASD) is a commonly used term describing a spectrum of somatic and neurocognitive/neuropsychiatric disorders in children with prenatal exposure to alcohol (Jones & Smith, 1973). FASD may be divided into the subgroups full and partial fetal alcohol syndrome (FAS /pFAS), static encephalopathy (alcohol exposed), and neurobehavioral disorder (alcohol exposed) based on the diagnostic system the 4-Digit Code by the degree of presence of four key criteria, which include (1) growth deficiency, (2) characteristic facial features, (3) central nervous system (CNS) damage/dysfunction, and (4) level of prenatal alcohol exposure. Higher scores for each criterion indicate a diagnosis toward full FAS (Astley, 2010).

FASD is the world's leading cause of mild intellectual disability and is potentially preventable through avoidance of alcohol exposure in pregnancy (Scholin et al., 2021). Ulleland and co-workers, in the late 1960s, were among the first researchers to identify a relationship between prenatal alcohol exposure and adverse neurologic outcome (Ulleland, 1972). Today, we know that the harmful effects of alcohol on the developing brain encompass a wide range of physical and neurodevelopmental signs from the most severe condition fulfilling all criteria for the diagnosis of full FAS to less severe forms within the spectrum. The term FAS refers to individuals who have a specific set of birth defects, facial dysmorphic signs and neurodevelopmental disorders characteristic of the diagnosis (Jones & Smith, 1973). From around the year 2000, the use of the term FASD appeared including children with the absence of facial features and growth retardation, but with severe behavioral problems, hyperactivity, attention-deficit, reduced impulse control and arrested social development, even with intelligence quotient within the normal range (Rasmussen et al., 2011). There is a great variety of functioning from intellectual disability to normal cognitive functioning. The clinical picture is further complicated by significant variability in performance, difficulty learning from experience and emotional instability (Kingdon et al., 2016), but common to children with FASD is that the impairments of the central nervous system are lasting (Rasmussen et al., 2011).

Data on prevalence, especially in Scandinavia, are limited, but studies rate the prevalence in Norway at 0.5 to 1 per 1000 for FAS and at 0.5 to 1 per 100 for FASD. Based on this prevalence, the Norwegian Health Authorities estimated the incidence of FASD at 600 to 1200 children per year (H-O, 2012).

Sleep in children with FASD

Clinical evidence from parents' reports shows that children with FASD often have sleep disturbances from infancy to adolescence, a problem that seems poorly understood and investigated by healthcare providers (Ipsiroglu et al., 2013). In healthy school-aged children, disturbed sleep was reported by about 20% of parents, while children with FASD are considered much more likely to experience sleep problems with a prevalence of 50% to 80% (Goril et al., 2016). Hanlon-Dearman and colleagues found an association between FASD and reduced sleep duration and higher fragmentation of sleep (characterized by repetitive short interruptions of sleep; Hanlon-Dearman et al., 2018). Most of these earlier studies were limited by a lack of control for biasing factors such as comorbidities or poor study design (Chandler-Mather et al., 2021). Nevertheless, problems with sleep in children in general can have immense impact on quality of life for both the child and the caregivers (Ipsiroglu et al., 2013).

Polysomnography (PSG) is regarded as the gold standard for experimental sleep analyses. The use of validated children's sleep questionnaires (Bonuck et al., 2017) is another possible approach. Only three studies have measured sleep by using both instrumental examination and caregivers' questionnaires and compared it with normative data (Chen et al., 2012). Interestingly, they demonstrated that the results from sleep measurements by PSG and questionnaires are concordant with each other, which may implicate that the single use of sleep questionnaires could be sufficient (Markovich et al., 2014).

Abnormal EEG and/or epilepsy in children with prenatal alcohol/drug exposure

Both the IOM (Institute of Medicine) guidelines and the 4-Digit Code add epilepsy or documentation of recurrent nonfebrile seizures to the potential assignment of children to the diagnostic categories of FAS or PFAS (Astley, 2013; Hoyme et al., 2016). The estimated prevalence of seizures is 3% to 21% in children with FASD (Bell et al., 2010), while the prevalence of epilepsy in Norwegian children is 0.7% (Suren et al., 2013). Among healthy children without epilepsy, abnormal EEG can be found in 1% to 2%. Significantly higher incidence of abnormal EEG findings is seen in children with developmental disorders or neuropsychiatric conditions (Petruzzelli et al., 2021). The term "abnormal" refers to changes in background activity as well as more specific findings such as spikes, polyspikes, and spike-and-wave activity (Britton et al., 2016). Only a few studies have systematically examined EEG records of children with FASD, and EEG features in this patient group are poorly described (Bell et al., 2010). There are several studies, showing that such abnormal EEG activity may give lead to adverse effects on cognitive functions, concentration and attention, and possibly emotional functioning in patients with early cognitive dysfunction (Riva et al., 2013). There is no data on relationship between sleep disturbances, abnormal EEG findings, and epileptic disorders in children with FASD, but it is a well-known fact that sleep and epilepsy interact in a complex bidirectional way (Zambrelli et al., 2020). Sleep deprivation can increase seizure frequency while a higher seizure frequency can disturb sleep, which suggests that there may be a vicious cycle (Lee et al., 2021).

FASD and ADHD

According to the literature, ADHD (attention-deficit hyperactivity disorder) is one of the most common comorbidities in FASD (Fryer et al., 2007). The prevalence of ADHD in individuals with FASD is

much higher than in the general pediatric population (49% to 94% vs. 9%; Kingdon et al., 2016). A recent animal study with rodents showed that intrauterine alcohol exposure led to augmented action impulsivity while no deficits in learning or motor function were detected (Wang et al., 2021). Both ADHD and FASD are commonly associated with sleep disturbances, possibly due to shared pathophysiology (Biancardi et al., 2021), but to our knowledge, there is no data available on the comorbidity and/or prevalence of the combination of FASD, ADHD, and sleep disorders.

Study aims

The objectives of the study were to (1) examine the prevalence of sleep disturbance in a sample of 53 children with confirmed diagnoses of FAS/FASD, (2) examine the prevalence and possible differences of sleep disturbance related to FASD subgroup, (3) assess the relationship between sleep disturbance and comorbidities, and finally (4) investigate the possible impact of sleep disturbance on cognitive, executive, and adaptive functioning in children with FASD. We hypothesized that there would be an increased prevalence of sleep disturbances in children with FASD and that FASD subgroup and presence of comorbidities (ADHD/epilepsy) would have impact on sleep and any sleep disturbances. We also hypothesized reduced clinical functioning in children with sleep disturbance compared with those with normal sleep pattern.

MATERIAL AND METHODS

Study design

In this prospective cross-sectional survey, we included children and adolescents referred to the Regional Competence Center for children with prenatal alcohol/drug exposure at Sørlandet Hospital in Arendal, Norway, in 2020 to 21. All of them fulfilled an FASD diagnosis based on the 4-Digit Code after clinical assessment.

Participants

The study sample consisted of 53 children and adolescents with FASD (mean age = 10 years, SD = 3.8, age range 3 to 17 years; 63% males). Seventy-five children were multidisciplinary assessed, 55 filled the diagnostic criteria for FASD and 53 of those consented to participate. According to FASD subgroup, 24% had FAS/pFAS and 35% had static encephalopathy (alcohol exposed). Neurobehavioral disorder (alcohol exposed) was diagnosed in 41% of patients.

Demographics

Demographic information, comorbidities such as epilepsy and ADHD, and available data on prenatal alcohol exposure were mainly collected prior to admission. However, when ADHD was highly suspected in some children after the clinical assessment at our center, the children were referred back to the local child psychiatric department with the question of a diagnosis of ADHD. The local child psychiatric department then informed us about the result of their assessment. We also collected information about the use of sleep and/or antiseizure medication.

Clinical assessment

The diagnosis of FASD and FASD subgroup was based on the 4-Digit Code. All participants underwent a comprehensive standardized cognitive and neuropsychological assessment by a trained neuropsychologist and a clinical examination by a neuropediatrician with long experiences within FASD. The clinical assessment did not include specific diagnostics for ADHD, but it could lead to a recommendation to asses for ADHD at the local child psychiatric department.

1. The children were assessed cognitively with a complete version of the Wechsler Intelligence Scale for Children (WISC--IV/V; Wechsler, 2008). WISC comprises four indices: Verbal Comprehension Index, Perceptual Reasoning Index, Working Memory Index and Processing Speed Index, and Full Scale IQ. In this paper, scores on Full Scale IQ and the Working Memory Index are reported. For those older than 16 years, the Wechsler Adult Intelligence Scale (WAIS IV) was used.
2. To assess the child's daily functioning, the children were examined using the parent-reported Vineland Adaptive Behavior Scales-II. The Adaptive Behavior Composite Score, based on communication, daily living skills, and socialization, was recorded. Lower scores indicate poorer performance.
3. Executive function behaviors in home environment were evaluated by the parental-reported Behavioural Rating Inventory of Executive Function (BRIEF). Higher scores indicate poorer performance (Gioia et al., 2002).

Sleep measurement

To collect information on sleep pattern, we used the Norwegian version of the Sleep Disturbance Scale for Children (SDSC). The SDSC is a sleep-related questionnaire that has demonstrated through validation an adequate level of internal consistency, test–retest reliability, and availability of normative data (Bruni et al., 1996). All caregivers filled out the standardized sleep questionnaire. A total score of sleep disturbance and scores on its six subscales were calculated. The six subscales include DIMS = Disorders of initiating and maintaining sleep, DOES = Disorders of excessive somnolence, SBD = Disorders of sleep-related breathing, DA = Disorders of arousal, SHY = Sleep hyperhidrosis, and SWTD = Sleep–wake transition disorders. Summing up the six subdomains (with each item scored from 1 to 5) gives a total score from 26 to 130; where higher scores indicate

greater difficulties with sleeping. The general population sample's SDSC scores became our normative data for the local pediatric population and were used to calculate T-scores. In accordance with Bruni et al. (1996), we dichotomized the total score for analyses at the 75th percentile (1 = sleep disturbance ≥75th percentile, 0 = others) as cut-off, corresponding to the scale TS-total score with a cutoff level for "Has sleep disorders" at 70 points. The variable "Has sleep disorders" (Yes/No) was therefore also included in the analyses. The children were divided in two age groups, one from 3 to 6 years, and the other from 7 to 17 years, due to the fact that normal sleep patterns significantly change after the age of five. The SDSC score was compared with the caregivers' anamnestic description of disturbed sleep to the pediatrician to examine the reliability of the SDCS results.

EEG measurement

All children underwent a standardized EEG examination at Sørlandet Hospital. The EEG protocol includes a 2-h, 20-channel EEG registration using a Nicolet One EEG system by Scan-Med Norway. The EEG was consequently performed at the same time at 1 PM trying to avoid the effect of disturbed night sleep. Epilepsy and seizures were classified according to the International League Against Epilepsy Classification. A neuropediatrician was responsible for interpreting of the EEG and an electrophysiologist from the National Centre for Epilepsy in Oslo was able to provide a second opinion on controversial findings. Abnormal EEG patterns were defined according to the terminology used in the last revised glossary by the International Federation of Clinical Neurophysiology (epileptiform pattern, background slowing, and focal slowing; Kane et al., 2017). Historically, EEG (as quantitative EEG analyses) played a diagnostic role in the assessment of children with ADHD, but more recent reviews have concluded that EEG currently cannot be used as a diagnostic tool (Lenartowicz & Loo, 2014) for that purpose.

Statistics

We transferred clinical and demographic data into an electronic database and processed data using the Statistical Package for the Social Sciences (SPSS, IBM, Chicago, IL, U.S.A.), version 25.0. To test for sample distribution, we used a histogram analysis and Shapiro–Wilk test. As most of data were not distributed normally, we used nonparametric tests to determine statistically significant differences, with a significance level set to 0.05. Quantitative variables were expressed using the median and minimum and maximum. The Mann–Whitney *U* test was used for comparisons between groups of continuous variables. We used linear regression analysis to investigate whether sleep disorders (SDSC scores) were associated with FASD subgroups and comorbidities. To deal with a very small amount of missing (anamnestic) data, we used imputation of data as a reasonable guess for missing data. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated and used as an estimate of the relative risk for children with FASD and ADHD to have sleep disturbances compared with those without ADHD as comorbidity.

TABLE 1 Clinical characteristics of the study participants ($n = 53$).

Male	33 (62.3%)
Female	20 (37.7%)
Age groups	
3 to 6 years	11 (20.7%)
7 to 17 years	42 (79.3%)
Alcohol only	34 (64.2%)
Alcohol and other illegal drugs	19 (35.8%)
Living conditions	
With biological parent(s)	9 (17%)
In foster care	32 (60.4%)
Adopted	12 (22.6)
SES (Hollingshead Four-Factor Index of Socioeconomic Status)	SES 1 to 2: 17—32.1% SES 3 to 4: 36—67.9%

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/parents agreed to participate in the study by signing the informed consent form.

RESULTS

Clinical characteristics

Clinical characteristics of the study population are shown in Table 1. The 53 participants included 33 boys (62%) and 20 girls (38%) whose ages ranged from three to 17 years (mean age 10.1 ± 3.8 years). The children were categorized according to FASD subgroups and divided into two age groups (3 to 6 years and 7 to 17 years). Prenatal exposure to alcohol alone was confirmed in about two-thirds of the cases (64%), while exposures to both alcohol and other drugs were confirmed in about one-third (36%) of cases. Based on the 4-Digit Code, full and partial FAS/pFAS was diagnosed in 13 children (24.5%), static encephalopathy with known exposure to alcohol in 18 children (34%) and neurobehavioral disorder (alcohol exposed) in 22 (41.5%) of the children. Most of the children (33% to 62%) were in foster care, 11 were adopted (21%), and 9 (17%) were living with their biological parents. The SES (Hollingshead Four-Factor Index of Socioeconomic Status) was dichotomized, 17 children (32.1%) lived with socioeconomic status 1 to 2 and 36 (67.9%) with status 3 to 4. Thirty-three children (62%) had one or more comorbidities other than ADHD and epilepsy. The most common were eating difficulties (39.6%) and learning disorders (30.2%). The most common mental health condition was reactive attachment disorder (ICD10-F94.1) in seven children (13.2%; Table 2).

Sleep disturbance in FASD children

Based on the SDSC, disturbed sleep was very common among children with FASD, affecting 42 (79%) of the children (Table 3), with increased prevalence in all the FASD subgroups. Difficulty falling asleep and maintaining sleep (DIMS) was the most common sleep problem encountered (74%), followed by disturbed sleep–wake transition (SWTD; 70%) and disorders of arousal (DA; 59%). Sleep-related hyperhidrosis (SHY) had the lowest score (30%). In the category sleep–wake transition disorder (SWTD), only one clinical group had an increased score, that is, the 11 children already using sleep medication prior to our assessment (an antihistamine medication in two children and melatonin in nine children). Table 4 shows that the mean SDSC total T-score for the entire sample ($n = 53$) was 63.49, with the lowest score for the FAS/pFAS subgroup (60.69) and highest score for the neurobehavioral disorder (alcohol exposed) subgroup, but without any significant differences between the groups. Neither did we find any significant FASD subgroup differences for each of the SDSC domain scores. To examine the reliability of the SDCS results, we compared the SDSC scores to the caregivers' anamnestic description of disturbed sleep. Those who informed about sleep disturbances in the interview with the pediatrician had significantly higher SDSC T-scores than those who did not inform about problems with sleep (*T*-score 79 vs. 56, $p > 0.001$).

FASD and comorbidities

Table 5 presents the prevalence of ADHD and epilepsy/abnormal EEG in the whole sample and the different FASD subgroups. Of the 53 children, 25 (47%) had a confirmed ADHD diagnosis whereof six (24%) were receiving *central* nervous system *stimulants*. The highest prevalence of ADHD was seen in the static encephalopathy subgroup (55.6%), showing a trend towards significance compared with the neurobehavioral disorder group where 37% of children had ADHD ($p = 0.08$). Five children had epilepsy (9.4%); all of them were treated with antiseizure medications (Lamotrigine), and none was in the FAS/pFAS subgroup. Pathological EEG was found in 13 (24.5%) children including the patients with epilepsy. These pathological findings were equally distributed throughout the FASD subgroups and not overrepresented in the ADHD group ($p = 0.09$ in a linear regression model). Table 6 provides further details on the specific EEG findings. Even if not intended, five of the children (9.4%) fell asleep during EEG registration with an average sleep duration of 6.4 min, but not leading to additional pathological findings. Two of the nine children with epileptiform activity on EEG had generalized epileptiform discharge on EEG, while seven had focal epileptiform activity. Two children had generalized and two focal slowing on EEG background activity.

The relationship between sleep disturbances and background variables and comorbidities

In Table 7, we present the relationship between mean SDSC T-scores in the presence or absence of comorbidities like ADHD and epilepsy. Additionally, we relate SDSC scores to relevant factors such as the socioeconomic status (SES), if prenatal exposure to alcohol or the combination of alcohol and illicit drugs, or living condition, that is, if the child lived with his/her biological parents or was in foster care. We did find a significant increased risk for disturbed sleep in children with FASD + ADHD compared with children without an ADHD diagnosis ($p = 0.003$). A higher proportion of children with ADHD, 23 (92%) had sleep disturbances, compared with 19 children (68%) without ADHD (OR 1.36; 95% CI 1.03 to 1.79). Data demonstrated no significant relationships between sleep disturbances and age groups ($p = 0.6$), the comorbidity epilepsy ($p = 0.23$), SES ($p = 0.13$) or whether intrauterine exposure to alcohol only or alcohol and illegal drugs in combination ($p = 0.26$).

Clinical functioning in children with and without sleep disturbances

Table 8 presents neuropsychological findings in all children with FASD and in those with and without sleep disturbances. Those with disturbed sleep had inferior executive function scores and a trend toward lower working memory score ($p = 0.08$) and inferior general adaptive

TABLE 2 Most common comorbidities (other than ADHD and epilepsy), including mental health conditions in the study population. Diagnostic categories with <4 cases are not listed.

ICD 10 diagnostic code	Name of diagnostic category	No of children	% of children
F80	Specific developmental disorder of speech and language	4	7.5
F81	Specific developmental disorder of scholastic skills	16	30.2
F82	Specific developmental disorders of motor function	7	13.2
F43	Reaction to severe stress and adjustment disorders (PTSD included)	4	7.5
F94.1	Reactive attachment disorder	7	13.2
F98	Other behavioral and emotional disorders with onset specific to childhood and adolescence	4	7.5
F40, F41, F42, F91, F93, F95	Other mental health condition	5	9.4
E44, E66.9, R62.8, R63.3	Eating difficulties	21	39.6

Abbreviation: ADHD, attention-deficit hyperactivity disorder.

TABLE 3 Results of the SDSC total and subscales in all children with FASD and in the different FASD subgroups. T-score cutoff >70 for those with disturbed sleep.

Sleep pattern		All FASD children ($n = 53$)	FAS/pFAS ($n = 13$)	Static encephalopathy (alcohol exposed) ($n = 18$)	Neurobehavioral disorder (alcohol exposed) ($n = 22$)
Total	Disturbed	42 (79%)	9 (69%)	15 (83%)	18 (82%)
	Normal	11 (21%)	4 (31%)	3 (17%)	4 (18%)
DIMS	Disturbed	39 (74%)	9 (69%)	13 (72%)	17 (77%)
	Normal	14 (26%)	4 (31%)	5 (28%)	5 (23%)
SBD	Disturbed	30 (57%)	7 (54%)	13 (72%)	12 (55%)
	Normal	23 (43%)	6 (46%)	5 (28%)	10(45%)
DA	Disturbed	31 (59%)	8 (62%)	9 (50%)	14 (64%)
	Normal s	22 (41%)	5 (39%)	9 (50%)	8 (36%)
SWTD	Disturbed	37 (70%)	7 (54%)	12 (67%)	18 (82%)
	Normal	16 (30%)	6 (47%)	6 (33%)	4 (18%)
DOES	Disturbed	30 (57%)	8 (62%)	9 (50%)	13 (59%)
	Normal	23 (43%)	5 (38%)	9 (50%)	9 (41%)
SHY	Disturbed	16 (30%)	3 (23%)	8 (44%)	5 (23%)
	Normal s	37 (70%)	10 (77%)	10 (56%)	17 (77%)

Note: FASD subgroups are based on the FASD 4-Digit Code.

Abbreviations: DA, Disorders of arousal; DIMS, Disorders of initiating and maintaining sleep; DOES, Disorders of excessive somnolence; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; pFAS, partial fetal alcohol syndrome; SBD, Disorders of sleep-related breathing; SDSC, Sleep Disturbance Scale for Children; SHY, Sleep hyperhidrosis; SWTD, Sleep–wake transition disorders.

function score ($p = 0.10$). Full-IQ was similar in the two groups. Those with ADHD did not differ from those without ADHD with regard to neuropsychological scores (data not shown).

DISCUSSION

The overall prevalence of sleep disturbances was very high among children with FASD, with 79% of children scoring above the SDSC cutoff for clinically significant sleep disturbances. We did not find any significant differences in the prevalence of sleep disturbances between the different FASD subgroups. Neither did our results indicate any significant relationship between sleep disturbances and age group, socioeconomic status or whether the child had been exposed to alcohol only or alcohol and illegal drugs combined. Children with sleep disturbances had inferior executive function scores. Those with diagnosed ADHD had more sleep problems than those without, while this was not the case for those with epilepsy or abnormal EEG.

Prevalence of sleep disturbances in FASD

Our study findings of 79% of FASD children scoring above the cutoff for clinically significant sleep disturbances confirm the high prevalence of sleep disorders in this group. Sleep problems did not differ according to age or FASD subgroup, underlining the need of formal sleep assessment as an integral part of the multidisciplinary diagnostic assessment for any child with FASD. Similar results are shown for children with other neurological diseases such as epilepsy (Wajszilber et al., 2018; Zambrelli et al., 2020), but the prevalence of sleep disorders seems to be even higher in FASD. Animal studies have demonstrated that intrauterine exposure to alcohol was associated with thalamic, hypothalamic, endocrinal changes, and long-term disruption in sleep–awake rhythmicity (Weinberg, 1994). Appropriate development of the thalamus and hypothalamus is vital for the control of sleep, and quantitative MR imaging studies have demonstrated volume loss of these brain structures in children with FASD (Treit et al., 2020). According to the current knowledge, children with FASD may have difficulties with different types of state regulation; sleep being one of them (Hanlon-Dearman et al., 2018). These impairments may affect sleep onset, sleep–wake cycling, and sleep hygiene. Neuronal systems that usually maintain sleep through sensory inhibition, behavioral inhibition, and neuroendocrine regulation may be compromised by prenatal exposure to alcohol (Lebel et al., 2008). The high SDSC total score for these children in our study was mainly driven by increased scores in the two domains related to difficulty falling asleep and maintaining sleep (DIMS) and sleep–wake transition (SWTD), typically described as pediatric insomnia (Owens & Mindell, 2011). This corresponds to previous research results within this patient group (Chen et al., 2012; Goril et al., 2016). If DIMS/SWTD is the main finding from a sleep medicine perspective, RLS (restless legs syndrome) as a comorbidity and/or differential diagnosis must be considered (Klingelhoefer et al., 2016). We did not perform a standardized examination regarding RLS, but asked caregiver about symptoms on "restlessness," such as "twitching/jerking/kicking off blankets." That was not the case in our patients.

TABLE 4 Mean SDSC T-scores and standard division for the whole sample and FASD subgroups.

	All children ($n = 53$)	pFAS/FAS	Static encephalopathy (alcohol exposed)	Neurobehavioral disorder (alcohol exposed)	p-Value
Total sleep disorders					
T-score (mean)	63.5	60.7	64.3	64.5	0.56
Standard division	14.4	15.4	14.1	14.6	
DIMS					
T-score (mean)	66.5	62.6	65.4	69.9	0.54
Standard division	19.3	16.3	15.5	19.3	
SBD					
T-score (mean)	51.7	51.5	54.6	49.6	0.18
Standard division	8.5	10.2	9.8	5.6	
DA					
T-score (mean)	60.2	60.5	59.8	60.2	0.87
Standard division	16.9	18.8	17.9	15.7	
SWTD					
T-score (mean)	60.6	58.7	59.7	62.4	0.58
Standard division	15.5	16.9	13.8	14.1	
DOES					
T-score (mean)	54.6	54.5	53.4	55.6	0.84
Standard division	11.3	12.2	11.1	11.4	
SHY					
T-score (mean)	49.8	49.1	52.9	47.7	0.36
Standard division	11.3	9.8	14.8	8.6	

Note: FASD subgroups from 4-Digit Code (Astley, 2004). Kruskal–Wallis test. The significance level is $p < 0.05$.

Abbreviations: DA, Disorders of arousal; DIMS, Disorders of initiating and maintaining sleep; DOES, Disorders of excessive somnolence; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; pFAS, partial fetal alcohol syndrome; SBD, Disorders of sleep-related breathing; SDSC, Sleep Disturbance Scale for Children; SHY, Sleep hyperhidrosis; SWTD, Sleep–wake transition disorders.

TABLE 5 Comorbidities and FASD subgroups (from 4-Digit Code).

	All FASD children ($n = 53$)	FAS/pFAS ($n = 13$)	Static encephalopathy (alcohol exposed) ($n = 18$)	Neurobehavioral disorder (alcohol exposed) ($n = 22$)
ADHD				
Yes	25 (47%)	7 (54%)	10 (56%)	8 (36%)
No	28 (64%)	6 (46%)	8 (44%)	14 (64%)
Epilepsy				
Yes	5 (9%)	0	3 (17%)	2 (9%)
No	48 (91%)	13 (100%)	15 (83%)	20 (91%)
Pathological EEG				
Yes	13 (25%)	3 (23%)	4 (22%)	6 (27%)
No	40 (75%)	10 (77%)	14 (78%)	16 (73%)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalogram; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; pFAS, partial fetal alcohol syndrome.

Prevalence of sleep disturbance related to FASD subgroup and exposure

Contrary to our hypothesis, no significant difference in the prevalence of sleep disturbances was found between the FASD subgroups, indicating that sleep disturbance in these children is a major problem in all FASD subgroups. Olateju et al. (2019) mentioned a relationship between prenatal alcohol exposure and the alterations of cerebral orexinergic (hypocretin) and cholinergic neurons responsible for the regulation of circadian rhythms. This, which is described as common pattern and not related to FASD subgroup, may explain the lack of differences in sleep disturbances among

TABLE 6 Specific EEG findings in the study group.

EEG findings	Number (*n*)	Percentage %	Type of epileptiform activity	*n*/%
Falling asleep during EEG registration	5/53	9.4%		
Pathological (awake)	13/53	24.5%		
Epileptiform activity	9/13	69.2%	Generalized epileptic discharges	2/9; 22%
Generalized slowing	2/13	15.5%		
Focal slowing	2/13	15.4%	Focal epileptiform activity	7/9; 78%

TABLE 7 Mean SDSC T-score and standard division related to comorbidities and relevant background variables in the study group ($n = 53$)

	n	Mean (SD)	*p*-Value
Age group			
Age 3 to 6 years	11	65.4 (15.2)	0.60
Age 7 to 18 years	42	63.0 (14.4)	
Use of sleep medicine			
Yes	11	70.2 (13)	0.19
No	42	61.7 (13.4)	
ADHD			
Yes	**25**	**66.8 (14)**	**0.003**
No	**28**	**60.5 (14.4)**	
ADHD with treatment			
Yes	6	73.2 (10.8)	0.42
No	19	64.8 (14.6)	
Epilepsy			
Yes	5	66.0 (20.4)	0.27
No	48	63.2 (14)	
Pathological EEG			
Yes	13	63.2 (15.5)	0.68
No	40	63.6 (14.3)	
SES			
SES 1 to 3	17	68.6 (15.4)	0.13
SES 3 or 4	36	61.1 (13.5)	
Exposure			
Alcohol only	34	62.5 (15.5)	0.26
Alcohol and other illegal drugs	19	65.3 (12.5)	
Living condition			
With biological parents	9	64.5 (15.2)	0.32
In foster care	32	60.4 (19.1)	

Note: Mann–Whitney *U*-test. The significance level is $p < 0.05$.
Abbreviations: ADHD, attention-deficit hyperactivity disorder; EEG, electroencephalogram; FASD, fetal alcohol spectrum disorder; SES, Hollingshead Index of Socioeconomic Status.

FASD subgroups. Children with FAS/pFAS—the most severe forms of FASD—did not have poorer sleep than children within other FASD subgroups. Neither did our results indicate any significant relationship between sleep pattern and age, socioeconomic status, or whether the child was exposed to alcohol only or combined alcohol and illegal drugs. This is in contrast to findings by Lewien et al. (2021), suggesting that lower SES and less stable caregiving was associated with increased sleep-related difficulties in healthy adolescences.

Sleep disturbance and comorbidities

The prevalence of epilepsy is 0.7% and of ADHD 2% in Norwegian children (Suren et al., 2013), while we found a prevalence by 9% and 47% in our sample of children with FASD. Additionally, we found EEG pathologies in almost 25% of the patients. Even if not intended or proceeded according to international recommendations for EEG after sleep deprivation, disturbed sleep may have influenced the EEG findings, especially in children with generalized discharges where sleep deprivation is a known trigger (Renzel et al., 2016). The prevalence of ADHD in FASD is also considered to be higher compared with the general pediatric population (47% to 94% versus 9%; Kingdon et al., 2016). In our study, 47% of the children with FASD had ADHD, which is in accordance with the results from a recent meta-analysis by Lange et al. (2018), reporting ADHD to be the most common comorbid disorder among children with FASD with a prevalence of 52.9%. The children with ADHD in our study had more sleep disturbances than those without ADHD. *Both* ADHD and FASD are commonly associated with sleep disturbances, possibly due to shared pathophysiology (Biancardi et al., 2021). Cortese et al. (2009) showed in a meta-analysis including 722 children with ADHD that these children had significantly higher scores on most of the examined sleep parameters.

Strength and weaknesses

Using a questionnaire filled out by the caregiver only to record sleep disturbances in children could be a weakness of our study. Only a few studies have evaluated sleep disturbances in FASD children using a standardized questionnaire (Chen et al., 2012), while one used polysomnography (PSG; Goril et al., 2016). Interestingly, these studies demonstrated that the results from sleep measurements by PSG and questionnaires are equivalent to each other, which may imply that the single use of questionnaires could be

TABLE 8 Clinical functioning in FASD children—all children and those with and without sleep disturbance.

	All children with FASD ($n = 53$)	FASD with disturbed sleep ($n = 42$, 79%)	FASD with normal sleep ($n = 11$, 21%)	p-Value
Full-IQ score (mean score/SD)	80.1 (12.2)	79.6 (13.2)	82.3 (8.3)	0.48
Working memory index (mean score/SD)	78.4 (10.5)	76.9 (13.3)	82.9 (4.7)	0.08
BRIEF behavior regulation index (mean/SD)	**74 (11.3)**	**76.2 (12.2)**	**67 (8.5)**	**0.008**
BRIEF metacognition index (mean/SD)	70.7 (8.6)	71.9 (8.9)	66.8 (9.7)	0.10
BRIEF general cognitive index (mean/SD)	74 (9.2)	75.8 (9.5)	68.3 (8.6)	0.02
VABS composite score (mean/SD)	59.7 (8.9)	58.5 (9.2)	63.8 (8.2)	0.10

Note: Mann–Whitney *U*-test. The significance level is $p < 0.05$.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; BRIEF, Behavior Rating Inventory of Executive Function; FASD, fetal alcohol spectrum disorder; SD, standard deviation; VABS, Vineland Adaptive Behavior Scales.

sufficient when it comes to find a proper way to screen for sleeping problems (Markovich et al., 2014), as in our study. Another issue for consideration could be the high number of children in foster care referred to our center (62%). A possible weakness could be that foster care parents are less familiar with the child's usual sleeping patterns and children in foster care in general might have difficulty establishing routine sleeping patterns. However, we did not find any statistical differences in sleep problems between children in foster care and the others. In addition, the foster care children in our study had been living in the family for several years when attending this study (mean 6.7 years SD 3.2). Our results are limited to a group of 53 Norwegian children diagnosed with FASD, and as for many other studies on children, our research relies on a clinically referred sample. This may be problematic with regard to generalization of the results to all children with FASD, given that children referred to a specialized competence center as ours, are more likely to be more severely impaired, are more often recruited from foster care (as shown in the results), and have crossed a threshold where caretakers are seeking help. However, the distribution of children in the different FASD subgroups in our study is quite comparable to a much larger sample, which also included mostly clinically referred children (Astley, 2010). Strength of study is that our patients underwent a clinical assessment done by professionals within the field of FASD, and all of the children had a confirmed diagnosis of FASD based on 4-Digit Code.

Clinical implications

Different authors describe the importance of well-regulated sleep and the fact that sleep disturbance may affect several aspects such as memory, learning, cognitive flexibility, verbal functions, and attention, which are cognitive domains that may already be affected in children with FASD (Jan et al., 2010). In our study, the children with sleep disturbances had similar IQ, but inferior executive function scores and a trend toward lower working memory score ($p = 0.08$) and inferior general adaptive function score ($p = 0.10$), compared with the children without abnormal sleep. This indicates lower functioning during daytime in children with FASD. The fact that sleep problems can further exacerbate neurobehavioral and cognitive conditions, screening, and treatment of sleeping disturbance is of huge importance (Ipsiroglu et al., 2013). Even if sleep disturbances are described as a common problem in FASD children, it is often unrecognized (Chen et al., 2012; Hanlon-Dearman et al., 2018; Ipsiroglu et al., 2013). Our findings underline the need of sleep evaluation for all children with FASD and should be a reminder to healthcare providers regarding the high prevalence and severity of sleeping problems in these children. Clinicians should include a standardized assessment of sleep, and we recommend the use of SDSC to improve diagnosis and treatment. Larger samples and further research on this topic could aid to establish some guidelines that can help using the most effective methods of examination and intervention.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Article 2

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RESEARCH ARTICLE

ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH

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 de- velopmental, cognitive, and behavioral disabilities that occur in children exposed to alcohol prenatally. A higher prevalence of epilepsy and pathological electroencepha- lographic (EEG) features have also been reported in individuals with FASD. We exam- ined 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 un- derwent a multidisciplinary assessment and a 120-min EEG recording. Group com- parisons and regression analyses were performed to test the associations between epilepsy and pathological EEG findings, FASD subgroups and neurocognitive test re- sults 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 find- ings. 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 fron- tal EEG pathology (without epilepsy) had significantly lower scores on the IQ indices *Processing speed* and *Working memory* than FASD children without such findings, ir- respective 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 pathol- ogy, 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

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

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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Article 3

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
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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 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 ¼ 81)	FASD children without epilepsy or pathological EEG (n ¼ 63)	FASD children without epilepsy, pathological EEG, ADHD (n ¼ 30)	Control group (n ¼ 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* ¼ 79 84 (11.6)	*n* ¼ 61 84 (11.2)	*n* ¼ 28 82 (10.1)	ns
Verbal IQ (mean score/SD)	*n* ¼ 73 87 (14.4)	*n* ¼ 55 87 (13.9)	*n* ¼ 26 85 (14.4)	ns
Performance IQ (mean score/SD)	*n* ¼ 72 88 (13.6)	*n* ¼ 55 88 (14.2)	*n* ¼ 26 84.9 (14.4)	ns
Working memory (mean score/SD)	*n* ¼ 68 79 (11.6)	*n* ¼ 52 79 (9.8)	*n* ¼ 24 80 (10.5)	ns
Processing speed (mean score/SD)	*n* ¼ 69 84 (11.6)	*n* ¼ 52 85 (12)	*n* ¼ 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* ¼ 81)	Control group (*n* ¼ 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* ¼ 63)**	**Control group (*n* ¼ 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* ¼ 30)**	**Control group (*n* ¼ 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 ¼ 17) SE/ND (n ¼ 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 ¼ 0.05. R squared ¼ 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 ¼ 0.04) and *processing speed* (p ¼ 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 ¼ 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 ¼ 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 ¼0.05. R squared ¼ 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 ¼ 0.04) and the *processing speed* index (p ¼ 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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