FETAL ALCOHOL SPECTRUM DISORDERS IN FINNISH CHILDREN AND ADOLESCENTS

Diagnosis, cognition, behavior, adaptation
and brain metabolic alterations

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Åse Fagerlund

Department of Psychology and Logopedics
Åbo Akademi University
Folkhälsan Research Center
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Supervised by

Professor Marit Korkman, PhD
Institute of Behavioral Sciences, University of Helsinki
Helsinki, Finland

Research Professor Ilona Autti-Rämö, MD
The Social Insurance Institute, Research Department
Helsinki, Finland

Reviewed by

Heather Carmichael Olson, Ph.D.
Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine
Seattle Children's Research Institute, Center on Child Health, Behavior and Development,
Families Moving Forward Research Program
Fetal Alcohol Syndrome Diagnostic and Prevention Network
Seattle, U.S.A.

Jari Sinkkonen, MD
Adjunct Professor, University of Turku
Turku, Finland

Opponent

Heather Carmichael Olson, Ph.D.
Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine
Seattle Children's Research Institute, Center on Child Health, Behavior and Development,
Families Moving Forward Research Program
Fetal Alcohol Syndrome Diagnostic and Prevention Network
Seattle, U.S.A.

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ABBREVIATIONS AND DEFINITIONS

ADHD	Attention Deficit Hyperactivity Disorder
ARBD	Alcohol-Related Birth Defects
ARND	Alcohol-Related Neurodevelopmental Disorder
BMI	Body Mass Index
CBCL	Child Behavior Check List
Cho	Choline
CNS	Central Nervous System
Cr	Creatine
DTI	Diffusion Tensor Imaging
Dysmorphology	The study of human congenital malformations (birth defects), particularly those affecting the morphology (the anatomy) of the individual. Dysmorphology literally means “the study of abnormal form.”
Dysplasia	Maturation abnormality
Echo time (TE)	The echo time in MRI represents the time in milliseconds between the application of the pulse and the peak of the echo signal.
FAE	Fetal Alcohol Effects
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorders
FOV	Field of View, the size of the two or three dimensional spatial encoding area of the image. Usually defined in units of mm^2. The FOV is the square image area that contains the object of interest to be measured.
FLAIR	Fluid Attenuated Inversion Recovery, a pulse sequence used in magnetic resonance imaging to remove the effects of fluid from the resulting images.
fMRI	functional Magnetic Resonance Imaging

Hyperkinetic disorder	Hyperkinesis can be defined as an enduring disposition to behave in a restless, inattentive, distractible and disorganized fashion. Referred to in the American literature as attention deficit hyperactivity disorder (ADHD).
LIPS-R	Leiter International Performance Scale-Revised
Malformation	Deformity in the shape or structure of a part
Microcephaly	Disorder characterized by a small head; the circumference of the head is more than two standard deviations smaller than average for the person's age and sex. Microcephaly may be congenital or it may develop in the first few years of life.
MRI	Magnetic Resonance Imaging
MRM	Magnetic Resonance Microscopy
MRS	Magnetic Resonance Spectroscopy
NAA	N-Acetyl Aspartate (neuronal marker)
PFAS	Partial Fetal Alcohol Syndrome
Repetition time (TR)	The amount of time that exists between successive pulse sequences applied to the same slice.
SLD	Specific Learning Disorder
Teratogen	Any agent that can disturb the development of an embryo or fetus. Teratogens may cause a birth defect in the child or halt the pregnancy outright. Classes of teratogens include radiation, maternal infections, chemicals, and drugs.
TDS	Total Dysmorphology Score
VABS	Vineland Adaptive Behavior Scales
WISC-III	Wechsler Intelligence Scale for Children – Third Edition
WAIS-III	Wechsler Intelligence Scale for Adults – Third Edition

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SWEDISH SUMMARY - SVENSK SAMMANFATTNING

När en gravid kvinna dricker alkohol gör hennes foster det också. Eftersom det inte finns någon skyddande blodbarriär kan alkohol fritt korsa moderkakan och orsaka omfattande skador både fysiologiskt, neurologiskt och beteendemässigt på det växande fostret. Alkoholrelaterade fosterskador går under den engelska termen Fetal Alcohol Spectrum Disorders (FASD, Fetala alkohol spektrum störningar). Trots att alkoholrelaterade skador är fullt möjliga att förhindra utgör de idag en av de vanligaste orsakerna till utvecklingsstörning i västvärlden. I västländer där prevalensundersökningar har gjorts är antalet barn som föds med FASD fler än de med autismspektrumstörningar, Downs syndrom eller cerebral pares. I siffror handlar det om mellan 1 och 6 % av alla levande födda, vilket i Finland skulle innebära att 600–3600 barn föds med alkoholrelaterade fosterskador varje år. Utöver de direkta toxiska effekterna av alkohol utsätts barnen som föds med FASD ofta för en dubbel börda i livet. Dels har barnen redan vid födseln neurologiska skador, dels föds de också med stor sannolikhet in i en familj med minst en missbrukande förälder och en omgivning där de utsätts för ytterligare risker i sin utveckling. Trots detta är FASD idag en starkt underdiagnosticerad grupp inom hälso- och sjukvården.

Den här avhandlingen utgör en del av ett större multinationellt forskningsprojekt, The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), som initierades av det nationella institutet för alkoholmissbruk och alkoholism (National Institute of Alcohol Abuse and Alcoholism, NIAAA) i USA. Det huvudsakliga syftet med den föreliggande avhandlingen var att undersöka en kohort med barn och ungdomar med alkoholrelaterade fosterskador i Finland. Avhandlingen består av fem studier med ett brett fokus på diagnos, kognition, beteende, adaptiva färdigheter och avvikelser i hjärnans ämnesomsättning hos barn och unga med FASD.

Deltagarna bestod av fyra olika grupper: en grupp som varit utsatt för alkohol under graviditeten (FASD); en IQ-matchad kontrollgrupp som huvudsakligen bestod av barn med specifika inlärningssvårigheter (Specific Learning Disorder, SLD); och två grupper med normala kontroller (CON1 och CON2). Deltagarna rekryterades via genomgång av medicinska journaler, slumpmässigt urval ur det finska befolkningsregistret och e-postförfrågningar till studerande.

Med diagnoser som är såpass svåra att fastställa som de inom FASD-spektret är det av stor betydelse att de föreliggande studierna har utförts i nära samarbete med ledande experter på FASD (prof. Edward Riley och prof. Sarah Mattson från Center for Behavioral Teratology vid San Diego State University, USA och prof. Eugene Hoyme från Sanford School of Medicine, University of South Dakota, USA). Deltagarna i föreliggande studier är således mycket noggrant undersökta och diagnosticerade. I den här avhandlingen testades för första gången de amerikanska reviderade Institute of Medicines diagnoskriterier för FASD på en finsk population. Kriterierna visade sig tillförlitliga i att särskilja olika undergrupper bland alkoholskadade barn. Ett annat värdefullt hjälpmedel som användes vid diagnosticeringen var en speciellt utarbetad skala för bedömning av de specifika dysmorfa dragen vid FASD (Studie 1).

Syftet med Studie 2 var att klargöra relationen mellan alkoholrelaterade dysmorfa drag och allmän kognitiv kapacitet. Resultaten visade på en signifikant korrelation mellan dysmorfa

drag och kognitiv kapacitet, så att barn med större avvikelser i sin tillväxt och med mer dysmorfa drag också tenderade att uppvisa större kognitiva svårigheter. Sambandet var emellertid måttligt och det kan betonas att fysiologiska markörer och kognitiv kapacitet inte alls alltid går hand i hand hos individer med FASD.

Barnen och ungdomarna i FASD-gruppen uppvisade omfattande problem i beteende och mental hälsa jämfört med kontrollgruppen (CON1). I studie 3 utforskades närmare hurudana risk- och skyddande faktorer som kunde associeras med beteendeproblemen i FASD-gruppen. Studien fokuserade på diagnosrelaterade och omgivningsrelaterade faktorer. Resultaten visade att två grupper med förhöjd risk för beteendeproblem kunde urskiljas: 1) Ju längre tid ett barn hade spenderat intaget på barnhem desto högre risk för beteendeproblem och 2) ju mindre dysmorfa drag ett barn med FASD hade desto mer omfattande beteendeproblem uppvisade barnet. Resultaten understryker betydelsen av att inom hälso- och sjukvården uppmärksamma och ge vård och adekvata insatser också (eller framför allt) till mindre synligt alkoholskadade barn. Det är också av stor vikt att uppmärksamma behoven och välmåendet hos de barn med FASD som växer upp på olika former av barnhem. För dessa barn verkar kombinationen av medfödda fysiologiska och psykologiska skador tillsammans med minskad möjlighet till en nära och kontinuerlig relation till en närstående vuxen göra dem extra utsatta och sårbara i livet.

Studie 4 fokuserade på adaptiva färdigheter så som kommunikationsförmåga, förmåga att klara ett dagligt liv och sociala förmågor. Adaptiva färdigheter handlar med andra ord om förmågor som gradvis hjälper en individ att klara ett självständigt liv, upprätthålla sociala relationer och integreras i samhället. Resultaten visade att de adaptiva färdigheterna hos barn och unga som växer upp med FASD är avsevärt sämre än hos både normalt utvecklade barn och IQ-matchade barn med inlärningssvårigheter. Klart skilda adaptiva profiler uppdagades där FASD-gruppen klarade sig sämre än barnen med inlärningssvårigheter som i sin tur klarade sig sämre än barnen i den normala kontrollgruppen. Det är viktigt att poängtera att barnen med inlärningssvårigheter presterade bättre än FASD-gruppen trots att de kognitivt befann sig på samma nivå. Den här studien är den första att jämföra adaptiva förmågor hos en grupp barn och unga med FASD jämfört med både en grupp IQ-matchade barn med inlärningssvårigheter och en grupp normalt utvecklade barn.

Slutligen påvisades i studie 5 neurokemiska förändringar med hjälp av magnetisk resonans-spektroskopi (MRS) hos tonåringar och unga vuxna med FASD som kunde relateras till alkoholbruk under fosterstadiet 14–20 år tidigare. De neurokemiska förändringarna kunde påvisas i ett flertal områden i hjärnan: i den frontala och parietala hjärnbarken, i corpus callosum, thalamus, i frontala områden med vit substans samt i lilla hjärnans nucleus dentatus. Förändringarna stämmer överens med den neuropsykologiska profilen vid FASD. Glia celler (vit hjärnsubstans) verkade mer påverkade av alkohol under fosterstadiet än neuron (nervceller).

Sammantaget kan konstateras att större samhälleliga ansträngningar och resurser borde fokuseras på att känna igen och diagnosticera FASD och på att stöda speciellt utsatta riskgrupper av alkoholskadade barn och unga. Utan tillräcklig intervention och stöd löper de en stor risk för marginalisering och utslagning, vilket är kostsamt inte bara för samhället utan också för de många barn som växer upp med FASD.

FINNISH SUMMARY - TIIVISTELMÄ SUOMEKSI

Alkoholin käyttö raskauden aikana voi vaurioittaa kehittyvää sikiötä, ja nämä vauriot voivat johtaa erilaisiin fyysisisiin, neurologisiin ja käyttäytymiseen liittyviin muutoksiin. Näitä seurauksia kuvataan termillä FASD (Fetal Alcohol Spectrum Disorders). Sikiöaikainen alkoholialtistus on tällä hetkellä yksi länsimaiden suurimmista kehitysvammaisuuden syistä vaikka se on täysin ehkäistävissä. Niissä länsimaissa, joissa on tehty FASD:n prevalenssitutkimuksia, FASD:n esiintyvyysluvut ovat suurempia kuin esimerkiksi autismikirjon häiriöiden, Downin oireyhtymän tai CP oireyhtymän. Suomessa syntyy arviolta n. 600-3600 alkoholivaurioitunutta lasta joka vuosi. Alkoholin sikiöaikaisten vaikutusten lisäksi lapset ja nuoret, joilla on FASD altistuvat usein kaksinkertaisille haittavaikutuksille elämässään, sillä neurologisten vaurioiden lisäksi he joutuvat usein elämään haitallisissa elinolosuhteissa, mikä johtaa ympäristön aiheuttamiin kehityksellisiin riskitekijöihin. Merkittävä osa lapsista, joilla on FASD jää nykypäivän terveydenhoitojärjestelmässä diagnosoimatta.

Väitöskirja on osa suurempaa Yhdysvaltain alkoholitutkimuskeskus NIAAA:n (National Institute of Alcohol Abuse and Alcoholism) rahoittamaa monikansallista CIFASD-tutkimusprojektia (The Collaborative Initiative on Fetal Alcohol Spectrum Disorders). Väitöskirjan yleisenä tavoitteena on kuvata sikiöaikaisen alkoholialtistuksen aiheuttamia oireita ja muutoksia suomalaisilla lapsilla ja nuorilla. Työ koostuu viidestä osatutkimuksesta, joissa kuvataan FASD:n diagnostisia kriteereitä sekä sikiöaikaisen alkoholialtistuksen aiheuttamia muutoksia lasten ja nuorten kognitiossa, käyttäytymisessä, adaptaatiossa sekä aivojen metaboliassa.

Tutkimuksissa oli neljä osallistujaryhmää: FASD-ryhmä, joka oli sikiöaikana altistunut alkoholille; älykkyysosamäärältään vastaava verrokkiryhmä, joilla oli pääasiassa spesifi oppimishäiriö (SLD, specific learning disorder); ja kaksi tyypillisesti kehittyvää verrokkiryhmää (CON1 ja CON2). Osallistujat valittiin sairauskertomusten avulla (FASD ja SLD), satunnaisotannalla Suomen väestörekisteristä (CON1) ja opiskelijoille lähetetyillä sähköpostipyynnöillä (CON2).

Tutkimukseen osallistuneiden lasten ja nuorten FASD-diagnoosi oli huolellisesti varmistettu yhteistyössä alan johtavien asiantuntijoiden kanssa (prof. Edward Riley ja prof. Sarah Mattson, Center for Behavioral Teratology, San Diegon osavaltion yliopisto, Yhdysvallat; prof. Eugene Hoyme, Sanford School of Medicine, Etelä-Dakotan yliopisto, Yhdysvallat). Tutkimuksessa arvioitiin Yhdysvaltain lääketieteellisen instituutin (Institute of Medicine) muokattujen FASD:n diagnostisten kriteerien validiteetti suomalaisessa väestössä ja ne todettiin päteviksi erottamaan FASD:n eri alaryhmät toisistaan. Painotettu dysmorfologinen pisteytysjärjestelmä osoittautui arvokkaaksi lisäksi kasvuhäiriön ja dysmorfisten piirteiden määrittämisessä (Tutkimus 1).

Tutkimuksessa 2 pyrittiin selkeyttämään sikiöaikaiseen alkoholialtistukseen liittyvien dysmorfisten piirteiden ja yleisten kognitiivisten kykyjen välistä suhdetta. Tulokset osoittavat tilastollisesti merkittävän korrelaation dysmorfisten piirteiden ja kognitiivisten taitojen välillä. Tämä viittaa siihen, että lapset, joilla on kasvuhäiriö ja dysmorfisia piirteitä, suoriutuivat

kognitiivisissa tehtävissä heikommin. Yhteys on kuitenkin vain kohtalainen, eivätkä fyysiset piirteet ja kognitiiviset taidot ole FASD-oireyhtymässä aina toisiinsa kytkeytyneitä.

FASD-ryhmän lapset ja nuoret kokivat merkittäviä käyttäytymiseen ja psyykkiseen hyvinvointiin liittyviä ongelmia verrattuna tyypillisesti kehittyvään verrokkiryhmään. Tutkimuksessa 3 selvitettiin tarkemmin FASD-ryhmässä todettujen käyttäytymisvaikeuksien riskitekijöitä ja suojaavia tekijöitä. Tutkimuksessa keskityttiin diagnostisiin kriteereihin ja ympäristötekijöihin. Valituista muuttujista tunnistettiin kaksi tekijää, jotka lisäsivät käyttäytymisvaikeuksien todennäköisyyttä: laitoshoidossa eletyn ajan pituus ja pieni dysmorfologinen pistemäärä osoittautuivat käyttäytymisvaikeuksien suurimmiksi riskitekijöiksi. Tulokset korostavat sopivien palveluiden ja hoidon tärkeyttä sellaisten lasten hoidossa, joilla sikiöaikaisen alkoholialtistuksen aiheuttamia vaurioita ei ole helppo tunnistaa, sekä tarvetta kiinnittää entistä enemmän huomiota laitoksiin sijoitettuihin lapsiin, joilla on FASD. Epäsuotuisan kehityksen riski on huomattava, kun fyysiseen ja psykologiseen kehitykseen vaikuttavaan sikiövaurioon yhdistyy läheisen ja jatkuvan hoivan puute.

Tutkimus 4 keskittyi adaptiivisiin kykyihin kuten kommunikaatioon, yleiseen päivittäiseen elämänhallintaan ja sosiaalisiin taitoihin eli taitoihin, jotka ovat tärkeitä itsenäisen elämän asteittaisessa rakentamisessa, sosiaalisten suhteiden ylläpitämisessä ja yhteiskuntaan integroitumisessa. Tulokset osoittivat, että lasten ja nuorten, joilla on FASD, adaptiiviset kyvyt olivat huomattavasti heikommat verrattuna sekä tyypillisesti kehittyviin lapsiin että älykkyysosamäärältään vastaaviin lapsiin, joilla on oppimisen erityisvaikeus. Tutkimuksessa todettiin selkeästi erilaiset profiilit; FASD-ryhmä suoriutui huonommin kuin SLD-ryhmä, joka puolestaan suoriutui huonommin kuin normaalisti kehittyvä verrokkiryhmä. Huomionarvoista on, että SLD-ryhmän tulos adaptiivisessa käyttäytymisessä oli FASD-ryhmää parempi kognitiotasojen vastaavuudesta huolimatta. Lasten ja nuorten, joilla on FASD, adaptiivisia kykyjä ei ole aiemmissa tutkimuksissa verrattu sekä älykkyysosamäärältään vastaavaan verrokkiryhmään että tyypillisesti kehittyvään verrokkiryhmään.

Tutkimuksessa 5 saatiin aivojen magneettispektroskopian (MRS) avulla todisteita pitkäaikaisista neurokemiallisista muutoksista, jotka liittyivät 14–20 vuotta aiemmin tapahtuneeseen sikiöaikaiseen alkoholialtistukseen. Neurokemiallisia muutoksia todettiin useilla aivojen alueilla: otsa- ja ohimolohkojen kuorikerroksessa, aivokurkiaisessa, talamuksessa ja otsalohkon valkoisessa aivokudoksessa sekä pikkuaivojen dentatus tumakkeessa. Nämä alueelliset löydökset sopivat yhteen FASD:ssa todettujen neuropsykologisten löydösten kanssa. Muutokset vaikuttivat olevan selvempiä aivojen gliasoluissa (tukisoluissa) kuin neuroneissa (hermosoluissa).

Yhteenvetona todetaan, että FASD:n tunnistamiseen ja diagnosointiin sekä suuren kehityksellisen riskin omaaviin lapsiin ja nuoriin, on kohdistettava enemmän yhteiskunnan tukea ja resursseja. Ilman riittävää puuttumista Ilman riittävää puuttumista nämä lapset ja nuoret ovat suuressa vaarassa syrjäytyä, mikä tulee kalliiksi paitsi yhteiskunnalle myös monille nuorille, joille on FASD.

ABSTRACT

Alcohol consumption during pregnancy can potentially affect the developing fetus in devastating ways, leading to a range of physical, neurological, and behavioral alterations most accurately termed Fetal Alcohol Spectrum Disorders (FASD). Despite the fact that it is a preventable disorder, prenatal alcohol exposure today constitutes a leading cause of intellectual disability in the Western world. In Western countries where prevalence studies have been performed the rates of FASD exceed, for example, autism spectrum disorders, Down's syndrome and cerebral palsy. In addition to the direct effects of alcohol, children and adolescents with FASD are often exposed to a double burden in life, as their neurological sequelae are accompanied by adverse living surroundings exposing them to further environmental risk. However, children with FASD today remain remarkably underdiagnosed by the health care system.

This thesis forms part of a larger multinational research project, The Collaborative Initiative on Fetal Alcohol Spectrum Disorders (the CIFASD), initiated by the National Institute of Alcohol Abuse and Alcoholism (NIAAA) in the U.S.A. The general aim of the present thesis was to examine a cohort of children and adolescents growing up with fetal alcohol-related damage in Finland. The thesis consists of five studies with a broad focus on diagnosis, cognition, behavior, adaptation and brain metabolic alterations in children and adolescents with FASD.

The participants consisted of four different groups: one group with histories of prenatal exposure to alcohol, the FASD group; one IQ matched contrast group mostly consisting of children with specific learning disorder (SLD); and two typically-developing control groups (CON1 and CON2). Participants were identified through medical records, random sampling from the Finnish national population registry and email alerts to students.

Importantly, the participants in the present studies comprise a group of very carefully clinically characterized children with FASD as the studies were performed in close collaboration with leading experts in the field (Prof. Edward Riley and Prof. Sarah Mattson, Center for Behavioral Teratology, San Diego State University, U.S.A; Prof. Eugene Hoyme, Sanford School of Medicine, University of South Dakota, U.S.A.). In the present thesis, the revised Institute of Medicine diagnostic criteria for FASD were tested on a Finnish population and found to be a reliable tool for differentiating among the subgroups of FASD. A weighted dysmorphology scoring system proved to be a valuable additional adjunct in quantification of growth deficits and dysmorphic features in children with FASD (Study 1).

The purpose of Study 2 was to clarify the relationship between alcohol-related dysmorphic features and general cognitive capacity. Results showed a significant correlation between dysmorphic features and cognitive capacity, suggesting that children with more severe growth deficiency and dysmorphic features have more cognitive limitations. This association was, however, only moderate, indicating that physical markers and cognitive capacity not always go hand in hand in individuals with FASD.

Behavioral problems in the FASD group proved substantial compared to the typically developing control group. In Study 3 risk and protective factors associated with behavioral problems in the FASD group were explored further focusing on diagnostic and environmental factors. Two groups with elevated risks for behavioral problems emerged: length of time spent in residential care and a low dysmorphology score proved to be the most pervasive risk factor for behavioral problems. The results underscore the clinical importance of appropriate services and care for less visibly alcohol affected children and highlight the need to attend to children with FASD being raised in institutions. With their background of early biological and psychological impairment compounded with less opportunity for a close and continuous caregiver relationship, such children seem to run an especially great risk of adverse life outcomes.

Study 4 focused on adaptive abilities such as communication, daily living skills and social skills, in other words skills that are important for gradually enabling an independent life, maintain social relationships and allow the individual to become integrated into society. The results showed that adaptive abilities of children and adolescents growing up with FASD were significantly compromised compared to both typically-developing peers and IQ-matched children with SLD. Clearly different adaptive profiles were revealed where the FASD group performed worse than the SLD group, who in turn performed worse than the CON1 group. Importantly, the SLD group outperformed the FASD group on adaptive behavior in spite of comparable cognitive levels. This is the first study to compare adaptive abilities in a group of children and adolescents with FASD relative to both a contrast group of IQ-matched children with SLD and to a group of typically-developing peers.

Finally, in Study 5, through magnetic resonance spectroscopic imaging (MRS) evidence of longstanding neurochemical alterations were observed in adolescents and young adults with FASD related to alcohol exposure *in utero* 14-20 years earlier. Neurochemical alterations were seen in several brain areas: in frontal and parietal cortices, corpus callosum, thalamus and frontal white matter areas as well as in the cerebellar dentate nucleus. The findings are compatible with neuropsychological findings in FASD. Glial cells seemed to be more affected than neurons.

In conclusion, more societal efforts and resources should be focused on recognizing and diagnosing FASD, and supporting subgroups with elevated risk of poor outcome. Without adequate intervention children and adolescents with FASD run a great risk of marginalization and social maladjustment, costly not only to society but also to the lives of the many young people with FASD.

1. INTRODUCTION

When a pregnant woman consumes alcohol so does her unborn baby. As there is no protective blood filtration system for alcohol this substance readily crosses the placenta. Alcohol can potentially affect the developing embryo and fetus in devastating ways. Despite the fact that it is a fully preventable disorder, prenatal alcohol exposure today constitutes a leading cause of intellectual disability in the Western world. In Western countries where prevalence studies have been performed the rates of FASD exceed, for example, autism spectrum disorders, Down's syndrome and cerebral palsy (Arneson et al., 2009; Baron-Cohen et al., 2009; Marttala, Yliniemi, Gissler, Nieminen, & Ryynanen, 2010). Recent studies have revealed prevalences of fetal alcohol related damage far higher than was earlier estimated. Prevalence studies conducted in two European countries have found overall prevalence rates for fetal alcohol spectrum disorders (FASD) as high as 2.3-6.3% in Italy (May et al., 2006; May et al., 2011) and 4.1% in Croatia (diagnostic categories Fetal Alcohol Syndrome (FAS) and Partial Fetal Alcohol Syndrome, PFAS) (Petkovic & Barisic, 2010). In the U.S.A. the prevalence of FASD is similarly estimated to range between 1 or 2 - 5% (May et al., 2009; May, 2011). The Western Cape region in South Africa is thought to have among the world's highest prevalences of fetal alcohol-induced damage with *average* figures of about 7 % among the colored population (May, 2011; Viljoen et al., 2005). In a Swedish follow-up of adopted children from Eastern Europe diagnoses within the FASD spectrum were found in as many as 52% of the children (Landgren, Svensson, Stromland, & Andersson Gronlund, 2010).

To date, no population based prevalence study for FASD has been conducted in Finland, but since a liberation of the Finnish alcohol policy took place in the late 1960s overall alcohol consumption by women has risen seven-fold (Working group to ensure the care and treatment of pregnant women with substance abuse problems, 2009). A corresponding development has been seen in other Nordic countries as well (Karlsson, 2008). In addition, binge drinking has markedly increased among young people in Finland during the last four decades, especially among young women of childbearing age (15-29 year olds) (Mäkelä, Mustonen, & Tigerstedt, 2010). In the 1980s, the incidence of pregnant women with problem drinking in Finland was estimated to about 1% (Halmesmäki, 1987). More recently, two other Finnish studies have found unspecified substance dependency (including alcohol, pills and illicit drugs) among 6.4% of pregnant women (n=391) (Pajulo, Savonlahti, Sourander, Helenius, & Piha, 2001) and among 5.8% of mothers of small children (n=413) (Savonlahi, Pajulo, Helenius, Korvenranta, & Piha, 2004). The geographically and culturally closest data from a larger population based study are found in a study of pregnant women in Norway (Alvik, 2007; Alvik, Heyerdahl, Haldorsen, & Lindemann, 2006) where binge drinking on at least one occasion was reported by 59% of the women prior to pregnancy and during pregnancy weeks 0-6 by as many as 25% of the women. After pregnancy recognition, 39% of the Norwegian women were still not abstinent from alcohol. As overall alcohol consumption is clearly lower in Norway than in Finland (Documented consumption of alcoholic beverages,

100% alcohol per capita 15 years or older, 2008: Finland 10,3 l, Norway 6,8 l. Source: Nordic Alcohol Statistics 2008 THL) (National Institute for Health and Welfare, Finland, 2010), corresponding Finnish figures for drinking during pregnancy might be expected to reach the Norwegian level at the very least.

In accordance with prevalence studies on FASD from other Western societies, and a birth rate of about 60 000 children/year, an approximate estimate for Finland would be that between 600 and 3600 children are born with fetal alcohol related damage every year (1-6% prevalence rate). If this assumption holds true, the teratogenic consequences caused by prenatal alcohol consumption constitute a highly significant public health problem in Finland.

1.1 Historical background

The discovery of the effects of prenatal alcohol exposure on the developing fetus actually seems to be relatively new (Sanders, 2009). Historical records suggest a rather rudimentary awareness of an interaction between alcohol and reproduction before the 1970s. In ancient Greece and Rome, the belief was not that maternal drinking during pregnancy harmed the child, but that intoxication of the father at the moment of conception could lead to deformity of the child (Calhoun & Warren, 2007).

From antiquity until the eighteenth century, there appears to be a lack of recorded information regarding alcohol and human reproduction. However, in 18th century England some physicians showed awareness of deficits in children of alcoholic mothers, but these were non-specific and often attributed to a specific type of beverage (like gin) or to the bad genes of the lower classes or their environment (Sanders, 2009).

Probably the first true epidemiological study documenting adverse effects of maternal drinking on the developing fetus was written by William Sullivan in England in 1899 (Sanders, 2009; Sullivan, 2011). The study was conducted in the Liverpool jail on 600 children born to 120 alcoholic women. Sullivan found that infant mortality was 2 ½ times higher for the alcoholic mothers compared to their non-drinking relative controls. Further, Sullivan found that infant mortality was decreased when women were abstinent due to incarceration in prison.

In 1968 Paul Lemoine published a clinical description of 127 children born to alcoholic mothers in France noting physical malformations, developmental delays, and behavioral problems (Lemoine, Harousseau, Borteyru, & Menuet, 1968). Unfortunately, his findings documented in French were not widely acclaimed. It was not until a few years later when teratologists David Smith and Kenneth Jones in the U.S.A. described similar characteristics in eight children born to alcoholic mothers that worldwide attention was brought to the disorder (Jones, Smith, Ulleland, & Streissguth, 1973). They coined the term Fetal Alcohol Syndrome (FAS) describing the characteristic facial features of FAS, developmental delay

as well as prenatal and postnatal growth deficiency and major organ malformation. The authors concluded that "the similarity in pattern of malformation noted among these eight children suggests a singular mode of etiology related to an as yet unknown effect of maternal alcoholism. Direct ethanol toxicity is the most likely possibility." (Jones et al., 1973).

1.2 Diagnosis

Since the discovery of FAS by Jones, Smith and Lemoine, nearly four decades of research has explored the devastating effects of alcohol on the developing fetus. Clinicians soon recognized that the physical and neurobehavioral outcomes of prenatal alcohol exposure were broader than those described as FAS, and in 1978 Clarren and Smith (Clarren & Smith, 1978) introduced the term suspected fetal alcohol effects (FAE). In Germany the term alcohol embryopathy was used, classified from I-III depending on the severity of the damage (Majewski, Bierich, Michaelis, Loser, & Leiber, 1977). However, the term FAE was subsequently clinically misapplied to label any child with behavioral problems coming from families with suspected alcohol abuse and in 1995 Aase et al. (Aase, Jones, & Clarren, 1995) suggested that the term FAE should be abandoned. Instead, the continuum of effects caused by prenatal alcohol was expanded to four different diagnoses by the Institute of Medicine (IOM) in the United States (Stratton, Howe, & Battaglia, 1996). The four diagnoses were designated as FAS, partial FAS (PFAS), alcohol-related birth defects (ARBD), and alcohol-related neurodevelopmental disorder (ARND).

1.2.1 FASD

Today, it is recognized that the adverse effects of prenatal alcohol exposure on the developing fetus lie within a continuum representing a spectrum of structural anomalies as well as behavioral and neurocognitive impairments. The disorders are classified under the umbrella term Fetal Alcohol Spectrum Disorders (FASD) (Bertrand, Floyd, Weber, & Fetal Alcohol Syndrome Prevention Team, Division of Birth Defects and Developmental Disabilities, National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention (CDC), 2005; Sokol, Delaney-Black, & Nordstrom, 2003). The term FASD is not in itself intended for use as a clinical diagnosis (Bertrand et al., 2005). Several published sets of diagnostic criteria for FASD are currently being used to identify and describe individuals exposed to alcohol prenatally, including the 4-Digit Diagnostic Code (Astley & Clarren, 2000), The Revised IOM Diagnostic Classification System (Hoyme et al., 2005), the Canadian Diagnostic Guidelines (Chudley et al., 2005), and the guidelines generated by the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effects (Bertrand et al., 2005). For detailed comparisons between the diagnostic schemata please see Warren et al. (2011) and Riley et al. (2011). All guidelines rely on anomalies in three distinct areas: prenatal and/or postnatal growth deficiency; central nervous system dysfunction; and a characteristic pattern of facial characteristics. Where diagnostic guidelines differ, it is

regarding the number and content of characteristics that need to present for a particular diagnosis (Riley et al., 2011).

Below, the discussion will focus on the Revised IOM Diagnostic Classification System. This system has been field tested in a large multi-racial international cohort of children prenatally exposed to alcohol and has been found to accurately define the range of FASD (Hoyme et al., 2005). It recommends a multidisciplinary approach to ensure diagnosis including input from experienced physicians, psychologists and maternal interviewers. Other specialists, such as physical, occupational and language therapists can also add important insights in the diagnostic process. The four diagnostic entities accounted for under the heading FASD of the revised IOM diagnostic system will be described in more detail (Hoyme et al., 2005).

1.2.2 FAS

An individual diagnosed with so called full-blown FAS should show evidence of:

A. A characteristic pattern of minor facial anomalies, including *at least two* of the following:

   1. Short palpebral fissures (eye openings less than or equal to the 10th percentile, see Figure 1)

   2. Thin vermilion border of the upper lip (score 4 or 5 on the lip/philtrum guide; see Figure 1)

   3. Smooth philtrum (score 4 or 5 on the lip/philtrum guide)

B. Prenatal and/or postnatal growth retardation: height or weight less than or equal to the 10th percentile. Children born with FAS are commonly smaller than other children and often remain smaller throughout their lives.

C. Deficient brain growth or abnormal morphogenesis, including one or more of the following:

   1. Structural brain abnormalities

   2. Head circumference less than or equal to the 10th percentile

Note that a diagnosis of FAS requires *all* features A-C to be present and can be made with or without a confirmed history of maternal alcohol exposure.

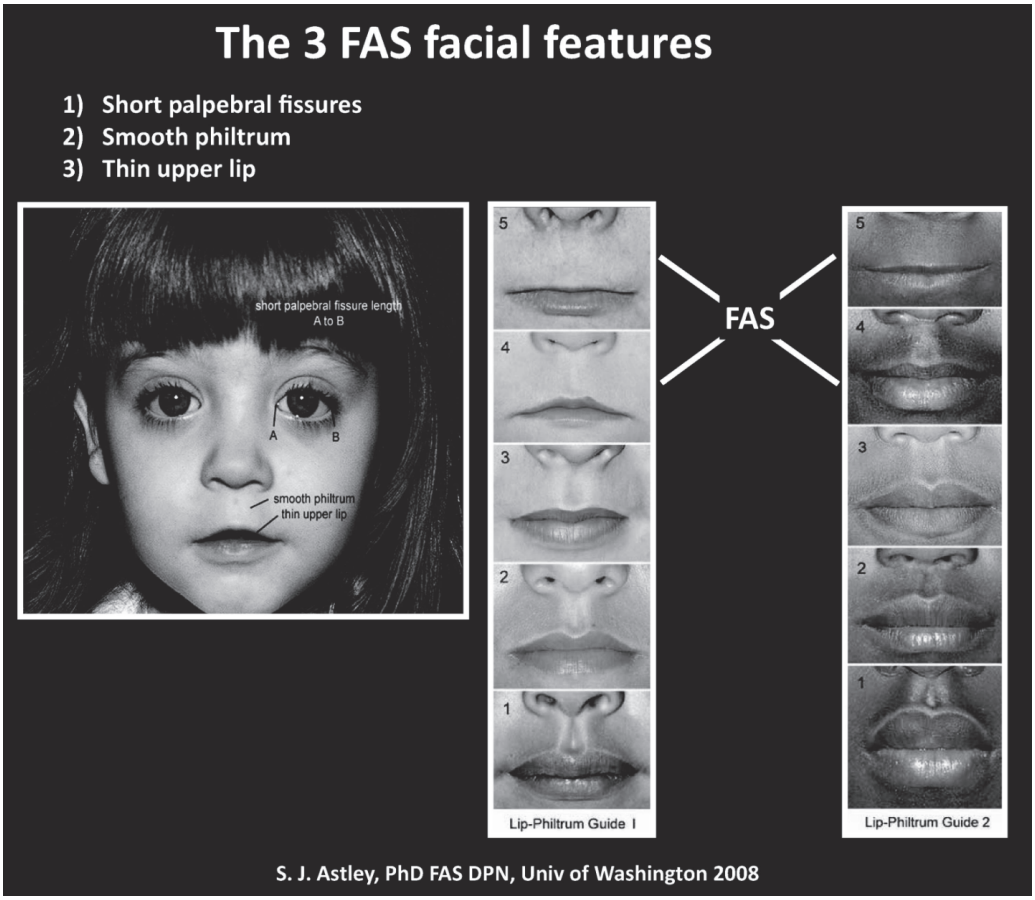

Figure 1. The 3 FAS facial features.
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1.2.3 Partial FAS (PFAS)

As with FAS, PFAS is also diagnosed with or without a confirmed history of maternal alcohol exposure. Diagnostic criteria for PFAS require:

A. Evidence of a characteristic pattern of minor facial anomalies, including *at least two* of the following:

1. Short palpebral fissures (eye openings less than or equal to the 10th percentile, see Figure 1)

2. Thin vermilion border of the upper lip (score 4 or 5 on the lip/philtrum guide; figure 1)

3. Smooth philtrum (score 4 or 5 on the lip/philtrum guide)

AND

B. Evidence of prenatal and/or postnatal growth retardation: height or weight less than or equal to the 10th percentile

OR

C. Evidence of deficient brain growth or abnormal morphogenesis, including one or more of the following:

1. Structural brain abnormalities

2. Head circumference less than or equal to the 10th percentile

OR

D. Evidence of a complex pattern of behavior or cognitive abnormalities inconsistent with developmental level and that *cannot be explained by genetic predisposition, family background or environment alone*.

Thus, for a PFAS diagnosis, the same pattern of facial characteristics as in FAS is required (A). In addition there has to be evidence of one additional set of criteria (B or C or D) pertaining to growth retardation, deficient brain growth or behavior or cognitive abnormalities. The cognitive abnormalities associated with prenatal alcohol-induced damage will be further outlined below (see 1.2.5 ARND). As for FAS, a diagnosis of PFAS can be made with or without confirmed maternal alcohol exposure.

1.2.4 Alcohol-Related Birth Defects (ARBD)

ARBD refers specifically to physical anomalies associated with prenatal alcohol exposure. A prerequisite for a diagnosis of ARBD is a *confirmed* history of prenatal alcohol exposure as well as the facial characteristics of FAS and PFAS (see category A under FAS and PFAS). In addition a diagnosis of ARBD requires specific congenital structural defects (including malformations and dysplasias) in at least *one* organ system (if the patient displays minor anomalies only, at least *two* must be present). Minor anomalies of body parts other than the face are usually less consistent than the facial anomalies, but are observed more frequently in children with prenatal alcohol exposure than in the general population (Aase, 1992). Congenital structural defects associated with maternal alcohol exposure include cardiac, skeletal, and renal abnormalities, defects in eyes and ears, as well as typical minor anomalies (e.g. hypoplastic nails, short fifth digits, “hockey stick” palmar crease). This category assumes the individual to have normal growth and intellectual/behavioral characteristics.

1.2.5 Alcohol-Related Neurodevelopmental Disorder (ARND)

A diagnosis of ARND requires confirmed maternal alcohol exposure. ARND assumes the individual to have *normal growth and structure* and at least *one* of the following:

1. Evidence of deficient brain growth or abnormal morphogenesis, including one or more of the following:

    a. structural brain abnormalities

    b. head circumference less than or equal to the 10th percentile

2. Evidence of a complex pattern of behavior or cognitive abnormalities inconsistent with developmental level that *cannot be explained by genetic predisposition, family background or environment alone*.

    This pattern includes: marked impairment in the performance of complex tasks (complex problem solving, planning, judgment, abstraction, metacognition and arithmetic tasks), higher-level receptive and expressive language deficits, and disordered behavior (difficulties in personal manner, emotional lability, motor dysfunction, poor academic performance and deficient social interaction).

ARND thus comprises a specific pattern of disordered behavior and development linked to confirmed maternal alcohol exposure among individuals with normal growth and structural development. Most importantly, *the facial features described above need not be present.* Because they exhibit none or only some of the physical features associated with prenatal alcohol exposure, individuals with ARND are more difficult to recognize and differentiate from individuals with other developmental disorders (Warren et al., 2011). In clinical practice this constitutes a major challenge as the majority of fetal alcohol-affected children may show no physical evidence of prenatal alcohol-associated birth defects (Bakhireva & Savage, 2011). In the diagnostic process, the importance of an extensive cognitive and behavioral testing is underscored.

1.2.6 Prevalence rates for the different categories of FASD

Today, a general prevalence estimate for the full FAS is 2-7/1000 live births but figures vary in different countries as well as within countries. In the Western Cape region in South Africa prevalence of FAS has been measured to be about 50/1000 among the colored population (May, 2009; May et al., 2009), in Italy 4-12/1000 (May et al., 2011), in Croatia 6.4/1000 (Petkovic & Barisic, 2010) and in the United States 2-10.2/1000 (May, 2009). Prevalence rates for FAS and PFAS combined rise to between 1 and 6 % according to recent studies (May et al., 2011; May, 2011). At present, the prevalence of ARND cannot be accurately estimated due to diagnostic challenges. In addition, the dysmorphology associated with FAS and PFAS vary across populations (May et al., 2010). For example, there is a more frequent occurrence of FASD in South African colored women who consume alcohol than in groups of American Plain Indians and Italian women. Results suggest that other factors (like nutrition, body mass and genetics, see Section 1.5 Pre – and postnatal risk factors) may play a role in the development of FASD and the severity of the dysmorphology (May et al., 2010).

1.2.7 Diagnostic challenges

Over the years it has become clear that the range of fetal alcohol-induced outcomes is far more wide reaching than those defined as FAS. A diagnostic scheme mainly based on the facial features meets the problem of poor sensitivity, as there are too many false negatives. Actually, the most profound teratogenic effects of prenatal alcohol exposure may be those it has on *brain development and the cognitive and behavioral effects that follow* (Riley et al., 2011; Streissguth & O'Malley, 2000). Already in 1981 David Smith, one of the two researchers who discovered FAS, wrote that "one extremely important concept is to speak of fetal alcohol effects rather than fetal alcohol syndrome… Of greatest concern are the effects on brain development and function including microcephaly, poor organization of brain, mental deficiency, behavioral aberration and neurological dysfunction" (Smith, 1981). Researchers today argue that the presence of the facial features of FAS do not indicate that the damage caused by prenatal alcohol exposure is necessarily any more severe than damage caused to individuals without the typical facial features (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000; Mattson, Riley, Gramling, Delis, & Jones, 1997). A proposed diagnostic goal is to recognize *FASD as a disorder of the brain* rather than one of facial/physical characteristics (Riley et al., 2011; Sampson, Streissguth, Bookstein, & Barr, 2000). In clinical practice it implicates a shift from focusing on the FAS face to a much broader focus on the effects of alcohol-related brain damage including dysmorphology, neurocognition, mental and behavioral functioning, and adaptive abilities.

Unfortunately, alcohol-affected individuals without the FAS facial characteristics are often not identified (Sampson et al., 2000). At present, fetal alcohol related disorders are vastly underdiagnosed conditions. It is estimated that only 1 out of 7-10 children (10-14%) receive their FAS diagnosis through the general health care system; and in the case of children with PFAS or ARND diagnoses are made even less often (Autti-Rämö & Ritvanen, 2005; May, 2011). The symptoms of FASD may be difficult to detect, especially regarding younger children and infants and individuals with ARND without the typical facial features (Warren et al., 2011). Consequently, many paediatricians and neonatologists do not feel confident about diagnosing FASD (Vagnarelli et al., 2011). Adolescents and adults with suspected symptoms of ARND constitute a difficult diagnostic challenge as the information on maternal alcohol consumption during pregnancy may not be available anymore or incorrectly remembered.

Another group that may exert diagnostic challenges is children adopted from abroad, especially if they lack the typical facial features associated with FAS and PFAS or represent a different race. In the case of adoptees, an often adverse environment in their country of origin, including being taken into custody and residential care, as well as adaptation to new cultural and familial surroundings in the country of adoption pose a substantially elevated developmental risk. It may be very difficult to determine to what extent disordered behavioral traits pertain to alcohol-related damage or are the results of adaptation to challenging environments. In addition, the facial characteristics may be more difficult to assess if the adoptee represents a different race. Still, adoptees are an important group to note in a discussion of diagnosing FASD as many of them may potentially suffer from alcohol-related damage (Landgren et al., 2010).

1.3 Cognitive characteristics

Extensive research during the last decades has shown that prenatal alcohol exposure is associated with widespread and generalized effects on cognitive performance (Coles, 2011; Korkman, Kettunen, & Autti-Rämö, 2003). Patterns of impairment, however, show considerable individual variability, and neurocognitive dysfunction varies from mild developmental delays to global developmental disabilities depending on the degree of the underlying alcohol-induced brain damage (Astley et al., 2009).

1.3.1 Intellectual performance

The intellectual capacity of individuals with FASD is commonly diminished, even though the majority do not have IQ scores below 70 and are thus not considered intellectually disabled. An average IQ estimate is around 70-80 for individuals with FAS and around 80-90 for alcohol exposed individuals without the FAS facial features (Mattson & Riley, 1998; Mattson, Crocker, & Nguyen, 2011; Sampson et al., 2000), but severe deficits in cognitive functioning have been observed in the entire spectrum of disability (Streissguth, Barr, Kogan, & Bookstein, 1996). Further, intellectual deficits in prenatally alcohol exposed individuals also seem to remain stable over time (Kodituwakku, 2007). Contrasting verbal and performance IQ has yielded contradictory results; children heavily exposed to alcohol prenatally sometimes score lower on both verbal and performance measures of intelligence (Aragon et al., 2008; Mattson et al., 1997) or lower on verbal or performance IQ at different age levels (Korkman, Hilakivi-Clarke, Autti-Rämö, Fellman, & Granstrom, 1994; Korkman et al., 2003; Mattson et al., 1997; Mattson, Riley, Gramling, Delis, & Jones, 1998). Of note is also that the IQ range in individuals with FASD may vary greatly. In one of the largest studies, performed on 473 individuals with FASD, IQ scores ranged from 29-120 for individuals diagnosed with FAS and 42-142 for individuals with the formerly used diagnosis FAE (Streissguth et al., 1996).

A few studies have investigated the association between physical markers of FASD and cognitive function. The results have been contradictory: some have been unable to find significant differences in cognitive function among children with and without the physical features of prenatal alcohol exposure (Mattson et al., 1997; Mattson et al., 1998; Veltheim & Ylitalo, 1998). Other researchers have demonstrated a relationship between physical markers of FASD and cognitive function (Astley & Clarren, 2001; Roussotte et al., 2012). To date it is not completely clear to what extent the full range of dysmorphology associated with prenatal alcohol exposure relates to brain functioning or cognitive capacity.

1.3.2 Learning and memory

Both verbal and spatial memory are commonly affected by prenatal alcohol exposure (Kodituwakku, 2007; Manji, Pei, Loomes, & Rasmussen, 2009; Richardson, Ryan, Willford, Day, & Goldschmidt, 2002). A continuum of effects of prenatal exposure to alcohol have been shown where more dysmorphic individuals perform worse on memory tests than non-dysmorphic alcohol-exposed individuals (Coles, Lynch, Kable, Johnson, & Goldstein, 2010). More specifically, several studies have documented problems with encoding of verbal

information in individuals with FASD (Coles et al., 2010; Kaemingk, Mulvaney, & Halverson, 2003; Mattson & Roebuck, 2002). To reach the level of mastering a learning task an individual with FASD may require many repetitions and/or different teaching methods. It seems that information is processed more slowly, employment of adequate learning strategies is deficient and awareness may be lacking as to what level of effort is required to resolve a task (Coles, 2011). However, once information has been encoded satisfactorily, it seems to be retained as well in individuals with FASD as in typical individuals (Kaemingk et al., 2003; Mattson & Roebuck, 2002). A clear discrepancy between children with FASD versus children with ADHD was revealed in one recent study (Crocker, Vaurio, Riley, & Mattson, 2011) where the children with FASD displayed inefficient *encoding* or learning of verbal material in contrast to children with ADHD who had difficulty retaining information over time, reflecting a deficit in *retrieval* of learned material. It is less clear whether retention of nonverbal material is intact or impaired because results are mixed and studies limited (Mattson et al., 2011).

1.3.3 Executive function and attention

Prenatal alcohol exposure consistently affects executive functioning regardless of the diagnosis within the FASD continuum (Korkman et al., 2003; Mattson et al., 2010; Mattson et al., 2011; Rasmussen, 2005). Executive functions refers to cognitive abilities involved in planning and guiding efficient goal-directed behavior (Best, Miller, & Jones, 2009; Kodituwakku, Kalberg, & May, 2001; Romine & Reynolds, 2005). Alcohol-exposed children show marked deficits in the ability to hold and manipulate information in working memory (Connor et al., 2000; Rasmussen, 2005). They also experience difficulties with planning, fluency, solving problems and modifying their behavior in response to changing environmental conditions (Mattson, Goodman, Caine, Delis, & Riley, 1999; Mattson et al., 2011; Olson, Feldman, Streissguth, Sampson, & Bookstein, 1998; Rasmussen, 2005). A child or adult with FASD may not be able to sustain attention or shift attention appropriately and may instead persevere with incorrect responses (Connor et al., 2000; Rasmussen & Bisanz, 2009; Schonfeld, Mattson, Lang, Delis, & Riley, 2001). It is not uncommon that the child with FASD also fulfills the diagnostic criteria for ADHD even though evidence suggests that ADHD and FASD are characterized by separate neurobehavioral profiles (Coles, 2001; Mattson et al., 2011). It is also possible that symptoms of inattention discriminate children with FASD from typically-developing children better than does hyperactivity (Aragon et al., 2008; Kodituwakku, 2007).

Further, the deficits in executive function predict poorer social adaptation and more high risk behaviors (Connor et al., 2000; Rasmussen & Wyper, 2007; Schonfeld, Paley, Frankel, & O'Connor, 2006). The ability to control impulses, solve problems flexibly and monitor emotional responses also predicts the success of interventions targeting improved social skills in children with FASD (Schonfeld, Paley, Frankel, & O'Connor, 2009).

1.3.4 Language and arithmetics

Children with FASD are commonly described as open and talkative, but their seemingly good expressive language abilities may mask both deficient language comprehension

and production (Church & Kaltenbach, 1997; McGee, Bjorkquist, Riley, & Mattson, 2009; Streissguth et al., 1994) as well as functional deficits in social communicative abilities (Coggins, Timler, & Olswang, 2007) compared to controls. Not all studies, however, find language impairments in children with FASD (see Greene, Ernhart, Martier, Sokol, & Ager, 1990 for an example). Plausible explanations may be that language impairments are apparent only when prenatal alcohol exposure has been heavy (Korkman et al., 2003) or when the language tasks are more complex involving working memory (Kodituwakku, 2007; Mattson et al., 2011).

Particular and pronounced difficulties in calculation and arithmetic have been seen in alcohol-exposed individuals in the form of auditorily processed mental computations as well as with problems in cognitive estimation tasks (Kopera-Frye, Dehaene, & Streissguth, 1996; Rasmussen & Bisanz, 2011; Streissguth et al., 1994).

1.3.5 Visual-spatial skills

Several measures of spatial abilities have been shown to distinguish alcohol-exposed individuals from unexposed controls, including spatial working memory, spatial learning, spatial recognition memory and visual-motor integration (Mattson et al., 2010; Olson et al., 1998; Uecker & Nadel, 1996). Children with FASD are also impaired at place learning (D. A. Hamilton, Kodituwakku, Sutherland, & Savage, 2003). On the other hand, facial recognition tests have shown no difference between FASD and controls (Uecker & Nadel, 1996), suggesting that the impairment may lie in more complex visual perceptual tasks demanding integration of information (Kodituwakku, 2007).

1.3.6 Motor function and timing accuracy

Children with prenatal alcohol-related damage frequently present with both fine and gross motor delays (Autti-Rämö & Granström, 1991; Kalberg et al., 2006; Mattson et al., 2011) even though the delays could probably best be described as “mild” compared to the more severe deficits that characterize cerebral palsy and related conditions affecting gross motor performance (Coles, 2011). In young children with FASD fine motor skills are more delayed than gross motor skills (Kalberg et al., 2006). That said, effects of prenatal alcohol exposure have been detected in numerous areas of motor function, e.g. eye and hand coordination (Adnams et al., 2001), balance, clumsiness and abnormal gait (Coles, 2011). Further, timing accuracy has proven difficult, such as in the ability required to produce accurate and consistent motor responses to a moving target like a football (Wass, Simmons, Thomas, & Riley, 2002).

1.3.7 Neurobehavioral profile

Emanating from the research described above, the first attempts to define a neurobehavioral profile for FASD have been published (Mattson et al., 2010; Mattson & Riley, 2011; Mattson et al., 2011). The task is difficult as prenatal alcohol exposure presents with a considerable variability of neurobehavioral outcomes and, possibly, multiple profiles may need to

be defined. Dose and pattern of alcohol consumption as well as timing of exposure can influence the severity of the brain damage and thus the outcome. Still, qualitatively similar patterns of deficits are seen across the FASD spectrum (Riley et al., 2011).

To date, attempts to delineate a neurocognitive profile related to prenatal alcohol exposure characterize individuals with FASD by:

- General deficits in intellectual ability.
- Relative deficits in verbal and nonverbal learning, executive function, visual attention, and, motor function.
- Areas of relative sparing or lack of impairment can be seen in auditory attention, basic language skills and retention of verbal information (Mattson et al., 2010; Mattson et al., 2011).

It has been suggested that the essence of a cognitive phenotype associated with FASD could be a generalized deficit in processing complex information with the assumption based on diminished intellectual functioning, slow information processing, and difficulty with complex tasks (Kodituwakku, 2007).

1.4 Mental and behavioral functioning

For individuals exposed to alcohol in utero mental and behavioral problems have been reported in several domains. On an externalizing continuum, various forms of attention disorders are commonly described (Fryer, McGee, Matt, Riley, & Mattson, 2007; Steinhausen, Willms, Winkler Metzke, & Spohr, 2003) as well as oppositional defiant behavior and conduct disorders (D'Onofrio et al., 2007; Fryer et al., 2007). Internalizing behaviors such as depressive symptoms (O'Connor & Paley, 2006) and anxiety (Steinhausen et al., 2003) are also reported. Among children with FASD it has been shown that girls with high levels of alcohol exposure whose mothers are depressed have the highest levels of depressive symptoms (O'Connor & Kasari, 2000). Further, prenatal alcohol may in itself be associated with more negative affect in the child. In turn, mothers of more negative children are less emotionally connected to them, and those children have higher levels of depressive symptomatology (O'Connor & Paley, 2006).

The psychopathology in FASD seems to have a strong persistence over time (Spohr & Steinhausen, 2008; Streissguth & O'Malley, 2000; Streissguth et al., 2004). Interviewing a large sample of 473 3-51 year-old North American subjects who were prenatally exposed to alcohol, Streissguth et al. (1996) found mental health problems affecting over 90% of their sample. Mental health related problems included attention deficit problems, depression, panic attacks, as well as suicide threats and attempts. Further, many of the subjects had histories of disrupted school (60% of subjects 12 and over), trouble with the law (60% of subjects 12 and over), confinement (50% of subjects 12 and over), inappropriate sexual

behavior (50% of subjects 12 and over) and alcohol/drug problems themselves (30% of subjects 12 and over) (Streissguth et al., 1996; Streissguth et al., 2004). Of the adult women with FASD in this group who had become parents, as many as 40% had been drinking during pregnancy. Around 30% of their children had received a diagnosis or suspected diagnosis within the FASD spectra. In Germany, a longitudinal study started in 1977 following 158 children with FASD. They have reported high rates of hyperkinetic disorder, behavioral and emotional problems, sleep disturbances, abnormal habits and stereotypies (Spohr & Steinhausen, 2008; Steinhausen & Spohr, 1998; Steinhausen et al., 2003). All in all, serious and pervasive behavioral consequences often accompany FASD, limiting the chances of successes and independence in life.

1.5 Pre- and postnatal risk factors

Many prenatal risk factors may influence the degree and type of brain damage alcohol induces. The amount of alcohol (number of doses) consumed is naturally an important determinant of the expression of FASD (Autti-Rämö & Granström, 1991; Sood et al., 2001). Other factors include pattern of alcohol consumption (e.g. a glass a day or many at a time), developmental timing of exposure, genetic variability, metabolism, maternal smoking and other drug use, poor nutrition, maternal age and, BMI (Autti-Rämö et al., 1992; Guerri, Bazinet, & Riley, 2009; May, 2011; Sampson et al., 2000) In addition, there may be detrimental effects of maternal prenatal stress affecting neurodevelopment (Mathews & Janusek, 2011; Talge, Neal, Glover, & Early Stress, Translational Research and Prevention Science Network: Fetal and Neonatal Experience on Child and Adolescent Mental Health, 2007. For a more substantive review see Kobor & Weinberg, 2011 or May, 2011). Although alcohol can induce severe damage during the entire pregnancy, the prenatal period most sensitive to alcohol's adverse effects appears to be around weeks 3 to 8, when cells are differentiating to form organs (Kobor & Weinberg, 2011). Importantly, this is a period when many women are not yet aware of their pregnancy. Another important aspect of timing relates to the facial features of FAS which in animal models have been shown to be time limited to exposure during a small window of vulnerability in early gestation (days 7-9 in the mouse embryo, equivalent to weeks 3 to 4 in human pregnancy) (Sulik, Johnston, & Webb, 1981; Sulik, 2005).

Alcohol consumed in large amounts at a time, binge drinking, has been found to be the most damaging form of alcohol consumption on embryonal and fetal development because it produces the highest peak blood alcohol concentrations, which affect the fetus most negatively (May & Gossage, 2011). In one study from Norway pregnant women's report of binge drinking only during weeks 1-6, that is, before the mothers even knew they were pregnant, was linked to difficult temper in the children (Alvik, Torgersen, Aalen, & Lindemann, 2011).

1.5.1 Risk regarding low and moderate alcohol consumption

Harm is well established for heavy drinking during pregnancy, and has also been demonstrated at moderate levels of exposure (30-40 g per occasion and no more than 70 g per week)

(O'Leary & Bower, 2012). There is a lack of consensus, however, on whether small doses of alcohol during pregnancy may affect child cognition and behavior. Sood et al. (2001) found maternal alcohol consumption at low levels to be adversely related to child behavior. The effect was observed at average levels of exposure as low as one drink per week. In contrast, a prospective study by Robinson and colleagues (Robinson et al., 2010) came to the conclusion that low to moderate consumption of alcohol in pregnancy did not appear to be a risk factor in the epidemiology of child behavioral problems. A similar view was taken by Kelly et al. (2009) who found a J-shaped relationship between mothers drinking during pregnancy and the likelihood of behavioral and emotional problems at 3 years of age. Children born to light drinkers (1-2 drinks per week) were actually less likely to score above cut-off compared to children of abstinent mothers. On the other hand, children born to heavy drinkers were more likely to experience behavioral problems than children of abstaining mothers. Recently, a series of studies carried out in Denmark (Kesmodel et al., 2012; Skogerbo et al., 2012; Underbjerg et al., 2012) claimed that low to moderate alcohol consumption did not affect general intelligence, executive function or attention in 5-year-old children.

These studies, however, have been criticized regarding the validity of the findings. Test instruments used may not have been sensitive enough to the effects of prenatal alcohol and do not preclude the existence of other types of harm (European FASD Alliance, 2012; Kodituwakku & Ceccanti, 2010). In addition, as the European FASD alliance points out (European FASD Alliance, 2012), human observational studies cannot be used to determine a safe dose of alcohol for several reasons. First, humans are very diverse genetically, and, second, pregnant women are heterogeneous in age, health, parity and nutritional status, making it impossible to draw any definitive conclusions. Children in several of the above mentioned studies may also have been too young to measure the full impact alcohol may have had on their brains. In a large study based on 2,600 children from the U.S. half of the children diagnosed with full FAS had developmental scores in the normal range as pre-schoolers, but all of them had confirmed signs of severe brain dysfunction by age 10. Similarly, only 10% of the children with FAS had attention problems by age 5, but 60% showed attention problems by age 10 (Grant & Astley, 2012). In addition, collective evidence from animal studies strongly suggests that moderate prenatal alcohol exposure can persistently alter multiple neurotransmitter and neuromodulatory systems throughout the brain, leading to significant neurobehavioral alterations in animal offspring (Valenzuela, Morton, Diaz, & Topper, 2012). In order to determine safe doses of alcohol for the fetus, participants would have to be randomly divided into control (no alcohol) and experimental groups (alcohol exposure), an obviously unethical experiment. Actually, there are animal studies showing that as little as a single drink can cause apoptosis in the developing brain (Young & Olney, 2006). According to standard safe exposure limits to chemicals, food additives and so forth, in humans even one tenth or one hundredth of a drink could then not be considered safe for pregnant humans (European FASD Alliance, 2012).

With so many uncertain factors regarding the effects of alcohol on a particular fetus and such small margins before there is an apparent risk, the policy advice that pregnant women should abstain from alcohol should be maintained (O'Leary & Bower, 2012).

1.5.2 Psychosocial risk factors

Children with the more severe forms of FAS and PFAS have often been identified most frequently in lower socioeconomic categories in society (May & Gossage, 2011). Prenatal alcohol exposure may also be combined with disordered family conditions. Women who drink heavily during pregnancy are likely to have been raised in families with heavy drinking (May et al., 2005). Their partners also tend to be heavy drinkers. Smoking and other drug use in combination with alcohol is common. In addition, domestic violence such as spousal abuse and poor relations between parents have been shown to be significantly higher in families with children diagnosed with FASD (May et al., 2005; May et al., 2008). Thus, individuals with FASD often have to face a double hazard. Not only are they born with alcohol-induced brain damage, but they are also often born into families where at least one parent continues to abuse alcohol. Many of the children experience unstable and chaotic rearing environments. They may at some stage be taken into custody and placed in residential care units and/or foster care (Astley, 2010; Sarkola, Kahila, & Halmesmäki, 2007). This event in combination with its preceding stressful family conditions is in itself a considerable risk factor. A study from Finland indicated that 50% of children born to alcohol and drug abusing mothers were taken into custody for some duration over a 12 year follow-up (Sarkola et al., 2007). Generally, children in foster and residential care are at increased risk for behavioral and psychiatric problems (Maclean, 2003; Vinnerljung & Sallnäs, 2008), attachment disorders (Rutter et al., 2007), as well as with criminality and poor academic performance in school (Vinnerljung & Sallnäs, 2008). Taken together, children growing up with FASD may face accumulating risk environments during development, increasing their vulnerability with respect to behavioral problems.

Relatively few studies have explored the effects of postnatal risk and protective factors influencing the adverse development in FASD, particularly with respect to effects of the social environment on ultimate functioning. In one large study (Streissguth et al., 1996), protective factors associated with relatively better outcomes were an early diagnosis and a diagnosis of FAS rather than FAE, where the individual does not display all of the physical features of FAS. Both the early diagnosis and the clearer abnormality in FAS may make the need for early intervention more obvious and thus exert a protective influence. Other protective factors were no experienced violence, staying in each living situation for more than 2.8 years, experiencing a good quality home from age 8-12, having been found eligible for developmental disabilities services, basic needs met for at least 13% of life and a stable and nurturing home for over 72 % of life (Streissguth et al., 1996; Streissguth et al., 2004). On the other hand, Spohr et al. found that although almost all of the aforementioned protective factors were present for their subjects, the outcome in their sample was nevertheless significantly impaired (Spohr, Willms, & Steinhausen, 2007). The researchers concluded that their results did *not* corroborate the benefits of the protective function of the factors cited by Streissguth et al. Children exposed to alcohol raised in their biological families have also been compared to alcohol exposed children raised in foster homes. These studies tentatively indicate early foster placement as a protective factor with respect to psychosocial problems (Aronson, Kyllerman, Sabel, Sandin, & Olegard, 1985; Aronson & Olegard, 1987; Aronson & Hagberg, 1998; Koponen, Kalland, & Autti-Rämö, 2009).

1.6 Adaptive abilities

Given the load of biological and environmental risks children and adolescents growing up with FASD face, an important question is how well they will be able to adapt to the world around them, develop skills to cope with everyday demands and learn to live independently.

Adaptive behavior can be defined as the performance of daily activities required for personal and social self-sufficiency or the ability to respond successfully to everyday demands (Sparrow, Balla, & Cicchetti, 1984). In other words, adaptive abilities are about developing skills that gradually enable an individual to lead an independent life, maintain social relationships, and to become integrated into society. According to the Vineland Adaptive Behavior Scales (VABS), adaptive abilities can be conceptualized in three domains: communication (receptive, expressive and written), daily living skills (how an individual eats, dresses, performs household tasks, uses time, money, the telephone and performs at work), and socialization (how an individual interacts with others, plays and uses leisure time, as well as the development of coping skills, i.e., how an individual demonstrates responsibility and sensitivity to others) (Sparrow et al., 1984).

Deficits in adaptive behavior are observed in different groups of children with developmental difficulties, e.g., autism (Liss et al., 2001), intellectual disability (Tremblay, Richer, Lachance, & Cote, 2010) and ADHD (Crocker, Vaurio, Riley, & Mattson, 2009). The relatively few studies performed on adaptive abilities in children with prenatal exposure to alcohol show somewhat mixed results. According to Coles et al. (1991), prenatal alcohol exposure in the absence of the typical somatic features and the mental retardation associated with full FAS does not impair social and adaptive abilities. In contrast, Carr et al. (2010) argue that adaptive difficulties are found regardless of the diagnosis received under the FASD umbrella.

If we are to delineate a specific adaptive profile for children with FASD, their adaptive behavior has to be contrasted with that of other groups of children. Using the Scales of Independent Behavior-Revised (SIB-R) Jirikowic et al. (2008) compared 5-8-year-olds with FASD to same aged typically-developing children and found clear differences with regard to adaptive skills. Crocker et al. (2009), comparing adaptive behavior in 6-13-year-olds with FASD and ADHD using the VABS, came to the conclusion that *both* groups were impaired on adaptive behavior, but that children in the FASD group were significantly more impaired than the ADHD group in the daily living skills domain. However, in these studies the children were not matched on IQ (even though Crocker et al. managed to match a small subgroup of their sample on IQ and found results pointing in the same direction). If IQ is not taken into account the possibility that differences between groups are a consequence of a lower IQ in the FASD group cannot be excluded. Accordingly, Whaley et al. (2001) also using the VABS found *no* significant differences between 2-10-year-old alcohol-exposed children versus a very heterogeneous group of non-exposed clinical control children when the groups were matched on IQ.

The studies also vary as to which adaptive domain is most affected in alcohol-exposed children. While one study shows the weakest scores on daily living skills and best scores on

social skills (Crocker et al., 2009) the opposite is true in another (Streissguth et al., 1991). There is more agreement on the fact that impairments in social skills are apparent in both younger and older age groups (Spohr et al., 2007; Streissguth et al., 1991). Some studies even suggest that the social difficulties become more marked with age in the FASD group (Crocker et al., 2009; S. E. Thomas, Kelly, Mattson, & Riley, 1998; Whaley et al., 2001). While most of the above mentioned studies have used the VABS or VABS-II to measure adaptive behavior (Becker-Weidman, 2009; Crocker et al., 2009; Streissguth et al., 1996; Thomas et al., 1998; Whaley et al., 2001), the Adaptive Behavior Assessment System- II (ABAS-II) (Carr et al., 2010), Scales of Independent Behavior – Revised (SIB-R) (Jirikowic et al., 2008) as well as a coded item list based on an interview (Spohr et al., 2007) have also been used, which possibly may have had an impact on the varied results.

As children with FASD not only bear the burden of neurological sequelae, but also may experience an adverse rearing environment, the reasons behind difficulties with adaptive behavior could hypothetically be twofold: stemming from neurocognitive difficulties, a non-optimal environment or, most likely, a combination of both. Especially difficulties with executive functions may be linked to impaired adaptive behavior as it is likely that an individual experiencing difficulty with modifying behavior in response to changes in the environment, solving problems, or having problems focusing and shifting attention would also experience challenges in everyday adaptive functioning. Recently, nonverbal (but not verbal) measures of executive functions have been linked to adaptive functioning (Ware et al., 2012).

Rearing environment and out of home placement may also play a role in the adaptive abilities of children with FASD. In support of this notion, maltreated children with a diagnosis of reactive attachment disorder showed developmental delays in all adaptive domains (Becker-Weidman, 2009). To our knowledge, however, no study has taken rearing environment into account when reporting on adaptive skills in the FASD group.

To date no clear adaptive profile distinguishing individuals with FASD from other groups with developmental diagnoses has been demonstrated, even though social impairments generally seem to be a characteristic of this group. Samples are often small and there is a lack both of comparisons to other developmental disorders as well as incomplete matching of groups on important variables such as IQ and/or caregiving environment.

1.7 Brain functioning and brain metabolism

1.7.1 Mechanisms of alcohol teratogenicity

In concert with the widespread neurocognitive sequelae often seen in individuals with FASD, abnormalities in brain structure and function related to fetal alcohol exposure have been detected in multiple cortical areas and in white matter connecting these regions (Nuñez, Rousotte, & Sowell, 2011). Prenatal alcohol may in fact affect all stages of brain development from neurogenesis to myelination, through a variety of mechanisms. First, alcohol may induce cell death through apoptosis and damaging cell membranes by causing oxidative

stress (Goodlett & Horn, 2001; Wozniak et al., 2004). Through generation of reactive oxygen species prenatal alcohol can interfere with the functioning of the mitochondria and cause both apoptosis and necrosis (Kroemer, Zamzami, & Susin, 1997). Generation of new cells or cell division rate can be affected (Goodlett & Horn, 2001). It has also been suggested that glial cells may be a primary target of ethanol toxicity during brain development (Guerri & Renau-Piqueras, 1997; Guerri, 1998; Guerri, Pascual, & Renau-Piqueras, 2001; Valles, Pitarch, Renau-Piqueras, & Guerri, 1997). Guerri and Renau-Picqueras have shown ethanol induced alterations in astrocyte cell maturation, proliferation and differentiation in rat studies (Guerri & Renau-Piqueras, 1997). Following the alcohol insult, the degree of brain damage among individuals with FASD may range from microcellular and neurochemical aberrations to gross structural anomalies (Astley et al., 2009). For more substantive reviews see Goodlett et al. (2005 and 2001).

1.7.2 Human studies

The teratogenic effects of alcohol tend to be widespread, affecting almost the entire brain. Subsequently, one of the most common findings in children with heavy prenatal alcohol exposure is reduced overall brain volume (smaller head size and a small brain) (Lebel, Roussotte, & Sowell, 2011; Nuñez et al., 2011). However, certain areas of the brain appear to be especially vulnerable to alcohol insult. In accordance with neurocognitive studies reporting executive dysfunction and working memory deficits, volume reductions and increased abnormal cortical thickness of certain areas in the *frontal lobes* have been found across the whole FASD spectrum (Sowell et al., 2008). Also the *parietal lobes* commonly seem to be affected by prenatal alcohol, which may relate to problems with visuospatial skills and attention regulation (Sowell et al., 2002). *Temporal lobe* findings are more inconsistent in FASD (Archibald et al., 2001; Sowell et al., 2008) and the occipital lobe seems to be relatively spared (Lebel et al., 2011). Despite their smaller brains, inferior performance of individuals with FASD is commonly characterized by cortical thickness excesses compared to controls, suggesting that they may have “too much” grey matter in relation to their brain size (Nuñez et al., 2011; Sowell et al., 2008). Other studies on intellectually disabled children and adolescents correspondingly show reduced overall brain volumes and white matter volumes, but not significantly reduced grey matter volumes (Mannerkoski et al., 2009; Spencer et al., 2006). In contrast, a thinner cortex (a thinner layer of grey matter) has been associated with better performance on verbal intellectual performance and verbal learning in typically developing, intellectually intact children (Sowell et al., 2008). More mature grey matter tends to be “thinner” (more myelinated) in relation to brain size and with fewer synapses, explaining why individuals with lower grey matter volumes relative to brain size may perform better on neurocognitive tests (Sowell, Delis, Stiles, & Jernigan, 2001). So as “more” grey matter apparently does not indicate better performance in the above mentioned studies for individuals with FASD, the findings suggest that pruning and myelination processes as well as brain-behavior relationships somehow develop abnormally following a prenatal alcohol insult (Nuñez et al., 2011; Sowell et al., 2008).

Other common findings following prenatal alcohol exposure are malformations of the corpus callosum, including agenesis, decreased local volumes, and other developmental anomalies (Archibald et al., 2001; Autti-Rämö et al., 2002; Bookstein, Sampson, Streissguth, & Connor, 2001; Bookstein, Streissguth, Sampson, Connor, & Barr, 2002; Riikonen, Salonen, Partanen, & Verho, 1999; Sowell et al., 2001). Researchers have also found decreased volumes of the thalamus (Mattson et al., 1996), hippocampus (Archibald et al., 2001; Autti-Rämö et al., 2002) and basal ganglia related to motor control and learning (Archibald et al., 2001; Cortese et al., 2006). Specifically, a decrease of the volume of the caudate nucleus in the basal ganglia, important for set learning, mental flexibility and behavioral inhibition has been detected in FASD (Archibald et al., 2001; Cortese et al., 2006; Roussotte et al., 2012). Further, abnormalities have also been seen in displacement of the anterior cerebellar vermis (Archibald et al., 2001; Autti-Rämö et al., 2002) as well as in cerebellar hemispheres (Autti-Rämö et al., 2002; Riikonen et al., 1999).

1.7.3 Animal studies

Studies on humans are, however, inevitably limited by factors such as restricted ability to evaluate structural and functional damage and difficulty in controlling variables like alcohol consumption, nutrition and genetics (O'Leary-Moore, Parnell, Lipinski, & Sulik, 2011; Wilson & Cudd, 2011). To solve the limitations of human studies, animal models as well as cell and tissue culture experiments play an important role in clarifying the effects of prenatal alcohol exposure. Animal studies lend support to and extend the understanding of a variety of the structural and functional changes shown in humans such as facial and forebrain deficiencies (Godin, Dehart, Parnell, O'Leary-Moore, & Sulik, 2011) and regional brain volume reductions in the hippocampus and cerebellum (Parnell et al., 2009).

Using laboratory animals, researchers have tried to identify the stage(s) in development when the immature brain is most sensitive to the neurotoxic effects of alcohol, and to gain insight into the underlying mechanisms (Olney, Wozniak et al., 2002). For example, during the human equivalent of the third trimester in pregnancy one single ethanol intoxication (alcohol binge) can trigger a massive wave of apoptotic neurodegeneration (cell death) in the brains of developing rats, mice and nonhuman primates (macaques)(Farber, Creeley, & Olney, 2010; Olney et al., 2002; Olney, Wozniak et al., 2002). This apoptotic cell loss as well as alcohol-induced reduced cell proliferation in the developing CNS have been linked to the smaller brains of children with FASD (Olney, Wozniak et al., 2002). In fact, a laboratory study on mice has shown that a rise in blood ethanol to a level as low as 50 mg/dl for a duration of 30 to 45 minutes seems to be sufficient to trigger significant neuroapoptosis (Young & Olney, 2006). Blood ethanol levels of this magnitude are commonly achieved in human social contexts, implying that pregnant women with only moderate drinking habits might expose the fetus to detrimental alcohol levels on multiple occasions during pregnancy. As different combinations of neuronal groups become more sensitive to ethanol toxicity at different times during development the timing of the alcohol exposure will determine which neuronal groups will be deleted from the brain, from which it follows that alcohol has the potential to produce a great variety of neurobehavioral disturbances (Karacay, Li, & Bonthius, 2008; Olney, Wozniak et al., 2002).

In infant mice the apoptopic neurodegeneration has been linked to impaired hippocampal-dependent behavior such as profound spatial learning and memory deficits (D. F. Wozniak et al., 2004) with effects persisting on to adult hippocampal neurogenesis (Hamilton et al., 2011; Klintsova et al., 2007). In addition, animal studies have shown that because of genetic differences some fetuses are much more susceptible than others to alcohol-induced brain injury (de Licona et al., 2009). Finally, animal studies have been used to develop approaches to reduce the impact of prenatal alcohol exposure. For example, Klintsova and colleagues have shown how *complex* motor skills training in rats improves motor performance deficits despite a permanent loss of cerebellar neurons induced by neonatal alcohol exposure (Klintsova et al., 1998; Klintsova, Goodlett, & Greenough, 2000; Klintsova et al., 2002). Challenging motor skills intervention stimulates synaptogenesis and prove a substantial experience-induced plasticity in the cerebellar Purkinje neurons that have survived an alcohol insult (Klintsova et al., 2000; Klintsova et al., 2002).

1.7.4 Brain imaging and brain metabolism

Apart from structural findings as detected by Magnetic Resonance Imaging (MRI) and Magnetic Resonance Microscopy (MRM, currently in use in animal studies), several new neuroimaging techniques can detect effects of prenatal alcohol-induced damage. Imaging methods in use in the area of FASD include functional Magnetic Resonance Imaging (fMRI), Diffusion Tensor Imaging (DTI) and ^{1}H Magnetic Resonance Spectroscopy (^{1}H MRS). Of these, fMRI can measure the effects of prenatal alcohol on brain activation (Coles & Li, 2011) and DTI provides data on the effects of prenatal alcohol exposure on white matter development (Wozniak & Muetzel, 2011). The living biochemistry and metabolic abnormalities in targeted brain regions can be examined through ^{1}H MRS, where the integrity of both neuronal and glial markers can be evaluated. In the ^{1}H MRS spectrum recorded with so-called long echo time, the most dominant resonances originate from N-acetylaspartate (NAA), choline-containing compounds (Cho), and creatine and phosphocreatine (Cr). NAA is a cerebral amino acid and serves as a marker of neuronal/axonal density and viability (Hammen, Stefan, Eberhardt, W-Huk, & Tomandl, 2003; Ross & Bluml, 2001). More specifically, NAA can be taken as a marker of functioning neurons rather than as a mere indicator of the presence of nerve cells (Pouwels et al., 1999). A loss of NAA is seen in diseases which are associated with neuronal loss or axonal degeneration (Hammen et al., 2003). Choline-containing compounds are involved in membrane synthesis and degradation, and creatine reflects high-energy phosphate metabolism (Rotondo, Bruschetta, Sacca, Bramanti, & Di Pasquale, 2003). Choline compounds of intact membranes are not visible in MRS, but precursors and breakdown products of phospholipids involved in membrane metabolism can be detected. Therefore, an increase of Cho is typically seen in both acute and chronic membrane pathology of myelin and glial cells that undergo slow degradation and/or present with altered turnover (Castillo, Kwock, & Mukherji, 1996; Ross & Bluml, 2001). Creatine is commonly used to normalize metabolite concentrations across subjects and groups. Further, there are regional differences in metabolite concentrations between grey matter and white matter, the former having a higher Cr content in accordance with its

higher metabolic activity, and the latter having a higher Cho content due to the multiple phospholipid layers of myelin (Pouwels & Frahm, 1998).

Compared to other neuroimaging techniques, MRS has been relatively underutilized in studying FASD (Nuñez et al., 2011); ^{1}H MRS reports on alcohol teratogenicity are scarce and results inconclusive. Cortese et al. (2006) found effects of prenatal alcohol exposure, regardless of diagnostic category, in the left caudate nucleus. An elevated NAA/Cr ratio was found in the FASD participants compared to controls. An analysis of absolute metabolite concentrations revealed that this was due to an increase in the neuronal marker NAA alone. Astley et al. (2009) reported that choline concentration in one frontal white matter region was significantly lower in individuals with FAS and PFAS relative to healthy controls and alcohol exposed children with neurobehavioral disorder but no facial features of FAS. In the FAS/PFAS group choline levels were low and correlated with their smaller frontal white matter volume and shorter corpus callosum. Results were interpreted as reflecting white matter deficits among FAS/PFAS. In this study NAA and Cr did not vary significantly between groups.

As has become emphasized throughout this introduction, prenatally alcohol-induced damage is a complex and multi-faceted area of research. To promote our understanding of FASD a broad focus on physiological, genetic as well as on psychological and social aspects is warranted both in research and in the clinical practice.

2. AIMS

The general aim of the present thesis was to examine a cohort of children and adolescents growing up with fetal alcohol-related damage in Finland. The thesis had a broad focus on diagnosis, cognition, behavior, adaptation and brain metabolic alterations in children and adolescents with FASD, more specifically described in the following aims:

1. To examine a genetically homogeneous cohort of Finnish children and adolescents with FASD, delineating the clinical spectrum of FASD in terms of history and morphometric data, and to compare the phenotype with that described in other populations. At the same time the validity of the revised IOM criteria for FASD was tested. (Study 1)

2. To examine the utility of a broad weighted dysmorphology score for potential use as a clinical and research adjunct when fetal alcohol exposure is suspected. (Studies 1,2 and 3)

3. To investigate the extent to which prenatal alcohol-induced dysmorphic features and growth deficiency are associated with general cognitive capacity. (Study 2)

4. To examine potential risk and protective factors for behavioral adaptation in children and adolescents with FASD focusing on diagnostic and environmental factors. (Study 3)

5. To compare adaptive behavior in children and adolescents with FASD with two contrast groups: an IQ-matched group of children with specific learning disability (SLD) and a group of typically-developing children (CON1). (Study 4)

6. To investigate the possible effects of fetal alcohol exposure on brain metabolism using three-dimensional proton magnetic resonance spectroscopic imaging (3D 1H MRS). (Study 5)

3. MATERIALS AND METHODS

The background of the present study was an international collaboration initiated by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) in the United States. An international research meeting was arranged in Valencia, Spain, where researchers from different parts of the world reviewed the status of research on FASD as well as prospectives and needs for future research. Subsequently, an international consortium, the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), was envisaged as organized by Dr Edward Riley, San Diego State University, and the NIAAA. Through Dr Ilona Autti-Rämö, Finland was invited as one of the countries to apply for funding. Other countries participating in the CIFASD are the U.S.A., South Africa, Italy, Russia, and the Ukraine. Further information regarding the consortium can be obtained at www.cifasd.org. The present thesis was conducted as the Finnish part of the CIFASD project. The PI of the Finnish project was Dr Ilona Autti-Rämö and Co-PI Dr Marit Korkman. Åse Fagerlund was the project coordinator and doctoral student. The studies were performed in close collaboration with Dr H. Eugene Hoyme, Sanford Research Center, U.S.A. and Prof Sarah N. Mattson from San Diego State University, U.S.A.

3.1 Participants

The participants in the five studies included in this thesis consisted of four different groups: one group with histories of prenatal exposure to alcohol, the FASD group; one IQ matched contrast group consisting of children with mostly specific learning disorder (SLD); and two typically-developing control groups (CON1 and CON2). An overview of the participants in the different studies is detailed in Table 1.

Table 1. An Overview of Participants and Measures/Assessments in the Original Studies.

Study	Participants (N)	Age of participants	Females/males	Measures/Assessment
I	FASD (77)	8-21	47/30	Dysmorphology exam
II	FASD (48)	8-16	28/20	Dysmorphology exam WISC-III
III	FASD (73) CON1 (40)	8-21	44/29 22/18	Dysmorphology exam LIPS-R CBCL
IV	FASD (73) SLD (30) CON1 (40)	8-21	44/29 16/14 22/18	Dysmorphology exam WISC-III/WAIS-III, LIPS-R, VABS
V	FASD (10) CON2 (10)	14-21	9/1 9/1	Dysmorphology exam (not CON2)

Note. FASD = Fetal Alcohol Spectrum Disorders; SLD= Specific Learning Disorder; CON= typically-developing controls; WISC-III= Wechsler Intelligence Scale for Children - Third Edition ; WAIS-III= Wechsler Adult Intelligence Scale– Third Edition; LIPS-R= Leiter International Performance Scale-Revised; CBCL= Child Behavior Checklist; VABS=Vineland Adaptive Behavior Scales.

3.1.1 The FASD group (Study I-V)

All children diagnosed as FAS or FAE born between 1984 and 1996 were identified from the medical records of the Hospital for Children and Adolescents, University of Helsinki, or from the Folkhälsan Rehabilitation Center, Helsinki. In total 104 children were ascertained, 60 girls and 44 boys. Of these 77 agreed to participate in the study. Reasons for not participating in the study (n=27) were biological parent not interested/giving permission for participation (n=9), child not interested (n=4), child too old to fit the sample (n=4), child dead (n=1), child adopted from abroad (n=2), other diagnosis than FASD according to parent (n=2), family had moved too far away (n=1), interviewer was not able to get in touch with the family (n=4). Of those who chose not to participate the gender distribution was even; 13 were girls and 14 were boys. Maternal alcohol consumption during pregnancy was confirmed for all cases by review of patient records from the time of birth and/or other reliable collateral sources, including interview of biological parents and/or guardians. To ensure diagnosis, all participants were assessed by an experienced dysmorphologist (H. Eugene Hoyme) and were assigned diagnoses: FAS (n=41), PFAS (n=23); ARND (n=9), and other (n=4), according to the revised IOM diagnostic criteria for FASD (Hoyme et al., 2005). The category 'other' included participants who had features of other unrecognizable malformation syndromes inconsistent with the teratogenic effects of alcohol. Participants were also assigned a dysmorphology score, a weighted quantitative measure of associated major and minor anomalies (see Section 3.3. Assessments and measures and Table 3).

In Study 1 a clinical delineation of all 77 participants was made, but as participants with a diagnosis other than FASD (n=4) were subsequently excluded from the study, a total of 73 participants were included in the analyses. In Study 2 a subgroup of 48 younger subjects (age range 8-16) were analysed. Study 3 and 4 included all participants who had received a diagnosis within the FASD spectra (n=73). Finally, in Study 5, participants were a subgroup of older subjects (age range 14-21 years) supposedly able to lie still for the required time in the magnetic resonance (MR) scanner (n=10).

3.1.2 The SLD group (Study IV)

In order to determine which neurodevelopmental and adaptive characteristics were specific to FASD we included a contrast group of children with specific learning difficulties (SLD) but with comparable cognitive level. In clinical practice patients with SLD constitute an important comparison group to FASD as they come to the same neurological examination units and are evaluated for similar rehabilitation procedures and special education. The SLD group was matched with the FASD group on IQ, age and sex (Table 2). To enable IQ matching, 8 children had an IQ below 70 and the remaining children (n=22) an IQ above 70. They were recruited from the same hospitals in the Helsinki area as the FASD group.

The children and adolescents in the SLD group had been diagnosed with either mixed specific developmental disorder (coded F83 according to the ICD-10 (World Health

Organization, 2009) or specific developmental disorder of scholastic skills (F81 according to the ICD-10 (World Health Organization, 2009). Mixed specific developmental disorder, F83, is described as a category in which there is a mixture of specific developmental disorders of speech and language, of scholastic skills, and of motor function, but in which none predominates sufficiently to constitute the prime diagnosis. The disorder is usually, but not always, associated with some degree of general impairment of cognitive functions (World Health Organization, 2009). Specific developmental disorder of scholastic skills, F81, is a disorder where the normal pattern of skill acquisition regarding reading, spelling, writing, and arithmetical skills is disturbed from the early stages of development. This should not simply be a consequence of a lack of opportunity to learn, not solely a result of mental retardation, and not due to any form of acquired brain trauma or disease (World Health Organization, 2009).

For patients diagnosed with F83 or F81 every effort to exclude FASD was done by strict inclusion criteria: 1) no history of maternal alcohol abuse in the medical records, 2) no clinical signs including facial features suggestive of prenatal alcohol exposure in the medical records, 3) normal somatic growth according to growth charts, 4) maternal confirmation of no alcohol consumption during pregnancy. In total 59 possible participants were contacted; 30 agreed to participate and 29 did not. All participants who agreed to participate underwent clinical examination by two experienced dysmorphologists (H. Eugene Hoyme and Luther K. Robinson). Every case was checked for concordance between the raters and any ambiguities were discussed until consensus was reached regarding examination results.

3.1.3 The CON1 group (Study III-IV)

Next, a typically-developing control group (n=40) was recruited through random sampling from the Finnish national population registry. Seventy-two potential participants were contacted and 40 agreed to participate. CON1 participants were matched to the participants with FASD on age, sex and geographical region (Table 2). As in the SLD group all participants were examined by two dysmorphologists (H. Eugene Hoyme and Luther K. Robinson). Parents were questioned about alcohol intake during pregnancy and any mention of alcohol intake during pregnancy was an exclusion criterion in the CON1 group.

3.1.4 The CON2 group (Study V)

As stricter matching criteria were applied, a new group of controls was recruited specifically for the MRS study (Study 5). This control group consisted of typically-developing adolescents and young adults who volunteered for the study. Participants were recruited through an email inquiry to university students in Helsinki. Exclusion criteria were any kind of learning disorder and a history of medication affecting the Central Nervous System (CNS). Each CON2 participant was individually matched with one participant with FASD on sex, age, handedness, body mass index (BMI), and head circumference (Table 2). Age ranged from 14 to 21 (M=18.8) and most participants were female (F/M=9/1, Table 1).

Table 2. Matching Criteria for SLD, CON and CON2 Groups Versus the FASD Group.

	FASD
SLD	Sex, age, IQ , and subgroup on living environment
CON1	Sex, age, geographical region
CON2	Sex, age, handedness, body mass index, head circumference

Note. SLD= Specific Learning Disorder; CON=Typically-developing Control

3.2 Procedures

3.2.1 Study I-IV

With the exception of the CON2 group all selected participants or their parents/foster parents/legal guardians were initially contacted by phone. Those interested in participating received a letter with further information regarding the study. After a few days a research assistant contacted them again for a brief telephone interview and to schedule an appointment at the Folkhälsan Research Center in Helsinki. At the clinic all participants (caregivers as well as the children) read and signed forms of informed consent or assent agreements prior to examinations. They were informed of study proceedings by a clinical psychologist and by an assisting nurse.

The children and adolescents were examined by one or two experienced dysmorphologists (H. Eugene Hoyme and Luther K Robinson) together with their parents/legal guardians, a nurse and a clinical psychologist who served as interpreter when needed, as the dysmorphologists spoke English and no Finnish or Swedish. Each child was then tested by a clinical psychologist while the caregiver was interviewed in a separate room by a nurse experienced in working with FASD. By the end of the testing, children and adolescents were given 20 euro compensation in the form of a gift card. During the interview an extensive family history was taken and the Vineland Adaptive Behavior Scales (VABS) interview was conducted. Finally, the parents/guardians were administered questionnaires.

Later, a report with a summary of the test results were sent to the caregivers of participants 8-17 years old and to the participants themselves if they were 18 years or older.

The tests, interviews and questionnaires included in this thesis formed part of a larger neurocognitive and behavioral test battery designed by the CIFASD consortium. However, the Wechsler Intelligence Scale for Children - Third Edition (WISC-III), Wechsler Adult Intelligence Scale – Third Edition (WAIS-III), VABS, the Life History Interview (LHI) and the telephone interview were solely used in the studies carried out in Finland.

3.2.2 Study V

Participants in Study V were a subgroup of adolescents (n=10) from the FASD group who were willing to be examined in the MR scanner as well as a typically-developing control group (CON2).The CON2 group was recruited through email among normally developing

adolescents and young adult students volunteering for the study. Interested students were then contacted by email and/or phone to check if they fulfilled the matching criteria for the study.

Participants in both groups were given appointments at the Helsinki Medical Imaging Center at the Helsinki University Hospital. Prior to examinations, participants read and signed forms of informed consent or assent agreements. They were informed of study proceedings by a clinical psychologist and by an assisting nurse. The MR scanner time lasted for approximately 60 minutes. Participants were given 15 euro compensation in the form of a gift card. Later, participants were given feedback of their results in a personal letter.

3.3 Assessments and measures

3.3.1 Dysmorphology (Study I-V)

With the dysmorphologist, participants and their parents or guardians underwent a standard interview regarding family, medical and developmental histories. Anthropometric measurements were recorded. Height, weight and head circumference were transformed into age and sex specific centiles according to Finnish norms (Sorva, Lankinen, Tolppanen, & Perheentupa, 1990). Palpebral fissure measurements were obtained using a rigid ruler, marked in millimeters, with the examiner directly seated in front of the subject, recording the distance from the medial canthus to the lateral canthus. Due to the lack of Finnish norms, American norms (Thomas, Gaitantzis, & Frias, 1987) were used for palpebral fissure length. The morphology of each subject's upper lip and philtrum was scored utilizing the lip philtrum guide (Astley, Bailey, Talbot, & Clarren, 2000) as presented by Hoyme et al. (2005) (Figure 1). A physical examination was performed to assess major and minor anomalies. In addition, all children in the FASD group were assigned a dysmorphology score, a weighted quantitative measure of associated major and/or minor anomalies according to the method of Hoyme et al. (2005). The dysmorphology scoring system is detailed in Table 3. The total dysmorphology score (TDS) ranges from 0-36 and a higher score is associated with a larger number of dysmorphic features commonly observed in FASD, as well as growth deficiency and/or microcephaly. Finally, the children were assigned diagnoses according to the revised IOM criteria for FASD (Hoyme et al., 2005).

Table 3: Dysmorphology Scoring System (Hoyme et al, 2005)

Feature	Points
Height <10%	1
Weight<10%	2
Occipitofrontal Circumference<10%	3
Inner Canthal Distance<10%	0
Palpebral Fissure Length<10%	3
Attention Deficit/Hyperactivity	1
Fine Motor Dysfunction	1
Midfacial Hypoplasia	2
"Railroad Track" Ears	1
Strabismus	0
Ptosis	2
Epicanthal Folds (non-racial)	1
Flat Nasal Bridge	1
Anteverted Nares	2
Long Philtrum	2
Smooth Philtrum	3
Thin Vermilion Border of Upper Lip	3
Prognathism	0
Cardiac Murmur	1
Cardiac Malformation (Confirmed)	1
Hypoplastic Nails	0
Decreased Pronation/Supination of Elbow	2
Clinodactyly of Fifth Fingers	1
Camptodactyly	1
"Hockey Stick" Palmar Creases	1
Hirsutism	1
Total Possible Dysmorphology Score	**36**

Note. The Dysmorphology Score is a weighted calculation based on assigning points to clinical findings characteristic of FASD (the highest point values are assigned to the cardinal findings of FAS, i.e., growth deficiency, microcephaly, short palpebral fissures, smooth philtrum and a thin upper lip). The score is an objective method of quantifying dysmorphology, but is ***not*** used in assigning clinical diagnoses in the FASD continuum. The Dysmorphology Score was originally developed by Dr John Aase. Reprinted with permission.

3.3.2 Cognitive capacity (Study II-IV)

Cognitive capacity was evaluated with an abbreviated form of the Finnish version of the Wechsler Intelligence Scale for Children - Third Edition (WISC-III) or the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) (Wechsler, 1991; Wechsler, 1997) or/and with the Brief IQ Screener of the Leiter International Performance Scale-Revised (LIPS-R) (Roid & Miller, 1997b).

The WISC-III and WAIS-III are the most widely used standardized tests for assessing cognitive abilities (Wechsler, 1991; Wechsler, 1997). The WISC-III is intended for use with children aged 6-15 years and the WAIS-III for 16 year olds and above. In this study a shortened version of the Finnish standardized versions of the tests were used. The subtests included three verbal tests and three performance tests: Information, Vocabulary and Comprehension for verbal IQ and Picture Completion, Picture Arrangement, and Block Design for performance IQ. These subtests were chosen due to their strong correlations with the respective verbal IQ (VIQ) and performance IQ (PIQ).

The LIPS-R (Roid & Miller, 1997b) was developed and standardized in the U.S.A. to assess nonverbal cognitive capacities in individuals 2–20 years of age. The LIPS-R is completely nonverbal and does not require verbalization from either examiner or child, therefore it was appropriate for the CIFASD consortium project where participants came from several countries and spoke different languages. Also, the child is not required to read or write any material. The LIPS-R is correlated with other frequently used measures of ability, including the WISC-III (r=0.85).The LIPS-R Brief IQ Screener consists of four subtests and provides an assessment of nonverbal cognitive ability with an emphasis on fluid reasoning and visual-spatial abilities (Roid & Miller, 1997a).The subtests used were Figure Ground, Form Completion, Sequential Order and Repeated Patterns.

The WISC-III was used in Study II, LIPS-R in Study III and WISC-III/ WAIS-III and LIPS-R in Study IV.

3.3.3 Behavioral problems (Study III)

The number and degree of behavioral problems was determined from the Child Behavior Checklist (CBCL) for ages 6-18, translated to Finnish and Swedish (Achenbach & Rescorla, 2001). Parents rated 113 items on a three point Likert scale (0=not true, 1=somewhat or sometimes true and 2=very true or often true). The CBCL has proved to be a valid and reliable instrument, widely used and translated to at least 61 languages (Achenbach & Rescorla, 2001). It provides a syndrome profile from which two broad dimensions can be scored. Problems mainly within oneself such as anxiety, depressive symptoms, social withdrawal and somatic complaints are drawn together under *internalizing* problems. *Externalizing* problems comprise symptoms involving conflicts with other people and with inappropriate behavior such as rule-breaking and aggressive behavior. The CBCL also includes scales for social problems and problems with thought and attention categorized as neither internalizing nor externalizing, but included in the score for *total* behavior problems. T scores were derived from the summary scores, and internalizing, externalizing, and total behavior problems extracted using a computer scoring system. Higher T scores indicate more behavioral problems. For externalizing, internalizing and total problem scale scores, T scores below 60 are considered to be in a normal behavioral range. Scores from 60 to 63 are classified as borderline and scores above 63 fall into the clinical range. American norms were used, but the clinical range cut-off has earlier been found to be similar in American and Finnish population samples (Almqvist, Bredenberg, Suominen, & Leijala, 1988). As CBCL is normed for ages 6-18 and a few of the participants (n=8) of the FASD group were older than 18, we checked for age related bias by dividing the sample into two age groups: 8-18 year olds and 19-21 year olds. Using independent samples t-tests no significant differences were found for any of the CBCL scales between the groups.

3.3.4 Risk and protective factors (Study III)

Information on risk and protective factors for the participants was collected through interviews with the accompanying adult. Both the initial telephone interview and an extensive in-person interview on risk/protective factors developed for the FASD population,

the Life History Interview (LHI) (Streissguth et al., 1996; Streissguth et al., 2004), were used for this purpose. The LHI is a structured interview comprising questions about past and current events covering family history, personal development, independent living, education, employment and various problems areas. For this study, two areas of interest were chosen based on earlier research (Steinhausen & Spohr, 1998; Steinhausen et al., 2003; Streissguth et al., 1996; Streissguth et al., 2004) on risk and protective factors in FASD: diagnostic factors and living environment/home placement. In addition, the effect of remedial help in school was explored, as it may be assumed that support in school might also affect the outcome. Diagnostic factors were type of diagnosis within the FASD continuum, dysmorphology score (see Table 3) and age at diagnosis. Factors relating to living environment were length of time spent in different placements: with biological parents, foster or adoptive parents as well as in residential care units. Also included was the total number of home placements or, in other words, how many times the child had moved back and forth between different placements. The third area comprised of special education and classroom aide provided in school. Through ameliorating learning difficulties, remedial help in school was entered as a potential protective factor for diminishing behavioral problems.

3.3.5 Adaptive abilities (Study IV)

The Vineland Adaptive Behavior Scales (VABS) were developed as a standardized measure to assess an individual's level of adaptive daily functioning from birth to 18 years 11 months old or a low functioning adult (Sparrow et al., 1984). In this study the VABS Interview Edition-Survey Form was used, administered in the form of a semi-structured interview with a parent or caregiver. The VABS assess adaptive behavior in three domains, each of which is divided into three subdomains: communication (receptive, expressive and written), daily living skills (personal, domestic, and community) and socialization (interpersonal relationship skills, play and leisure time, and coping skills). In addition, an adaptive behavior composite score can be derived from the three domains.

3.3.6 MRI and MRS imaging (Study V)

Magnetic resonance imaging (MRI) is an imaging technique that allows for in vivo measurement of brain structures. With magnetic resonance spectroscopy (MRS), on the other hand, it is possible to assess a number of neurochemicals in the brain and detect subtle changes in brain metabolism. In the present study, MRI and 3D ^{1}H MRS studies were performed with a clinical 1.5 T MR-system (Siemens Magnetom Sonata, Erlangen, Germany) equipped with a standard head coil. Fluid Attenuated Inversion Recovery (FLAIR) images, that is, sequences of radio frequency pulses to remove the effects of fluid from the resulting images, covering the whole brain were obtained for the FASD and CON2 groups. FLAIR imaging parameters were as follows: echo time (TE, the time in milliseconds between the application of the pulse and the peak of the echo signal) 119 ms; repetition time (TR, the amount of time that exists between successive pulse sequences applied to the same slice) 9500 ms; inversion time (TI, the time period between the inversion pulse and the

excitation pulse in an inversion recovery pulse sequence - the inversion time controls the signal of different tissues) 2500 ms; field-of-view (FOV, the square image area that contains the object of interest to be measured.) 201 mm x 230 mm; matrix size 448 x 512; and slice thickness 3.0 mm. The MRIs were evaluated by a neuroradiologist blinded to the drug-exposed status. One of the FASD adolescents had a slight deformation on the lateral ventricle on the left and one had an exceptionally small vermis. The controls had normal brain MRIs.

Technical details of the ^{1}HMRS measurements were as follows:

Three-dimensional ^{1}H MRS measurements were performed using the PRESS method (Bottomley, 1987; Luyten, Marien, & den Hollander, 1991) with TE of 288 ms, TR of 1500 ms, and 2 averages. The 3D MRSI FOV of 16 cm (RL) x 16 cm (AP) x 12 cm (SI) was covered with 16 x 16 x 8 phase steps. To reduce the measurement time, weighted/elliptical *k*-space scanning was used. In the spectral dimension 512 complex points were used to cover the spectral width of 1000 Hz. The volume-of-interest (VOI) size was 10 cm (RL) x 10 cm (AP) x 6 cm (SI) for the cerebrum and 8 cm (RL) x 6 cm (AP) x 8 cm (SI) for the cerebellum (illustrated in Figures 2 and 3). The VOI were positioned using oblique axial, coronal, and sagittal T_1-weighted gradient echo MR-images. Before Fourier transformation in the spatial dimensions, the ^{1}H MRS data matrix was filtered with Hamming filter and zero filled up to 16 x 16 x 16 points. The resulting nominal voxel size was 1 x 1 x 0.75 cm. These data were transferred to an in-house-built program running on Matlab 6.5 (MathWorks, Natick, MA, U.S.A.) to construct and analyse the spectral data. Before Fourier transformation, the time domain data were zero filled up to 1024 points and apodized using a Hamming function with full-width-at-half-maximum of 350 ms. After automatic phase (zero- and first-order phases) and baseline corrections, the intensities of NAA, Cr, and Cho signals were determined using Gaussian lineshape fitting. The analysis program automatically corrects the data for possible differences in coil loading and nominal voxel size.

Representative voxels in the temporal, parietal, and lateral frontal cortices; corpus callosum; frontal white matter; basal ganglia; hippocampi; cerebellar vermis; hemispheres; and dentate nucleus were selected by 2 MR-spectroscopists (S.H., N.L) blinded to exposure group (Figure 3). Metabolite data for all subjects were gathered using the same MRS slice levels and voxel locations whenever possible. For small anatomical structures (e.g. thalamus, hippocampi), 1 to 2 voxels and for larger structures (e.g. white matter) 1 to 6 voxels with data of only target tissue were chosen. Frequently, voxels from 2 adjacent MRSI slices were used for larger structures. Low-quality spectra were omitted. The cerebrum data of one of the FASD patients were extremely noisy due to either a scanner problem or subject movement and were not usable. Therefore, only data from 9 FASD and 9 CON2 were included for the cerebrum analysis. Representative spectra showing NAA, Cho and Cr are shown in Figure 5.

The average metabolite ratio values NAA/Cr, NAA/Cho, and Cho/Cr were calculated for each anatomical structure presented in Figure 3. Left and right hemispheres were analysed separately. Using NAA/Cr, NAA/Cho and Cho/Cr ratios eliminates the need to correct for CSF volume in the MRSI voxel. In addition, ratios are not affected by possible instrument instabilities, differences in coil loading, RF-field inhomogeneity, or RF-coil sensitivity differences due to intersubject alteration in head position/head size within the coil.

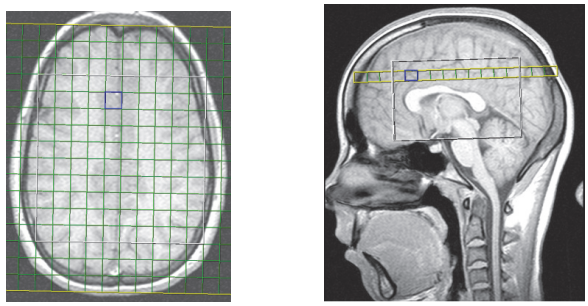

Figure 2. Sagittal and axial images showing the locations of cerebral VOIs.

The absolute metabolite signal intensities (corrected for coil loading) were used to aid in interpreting the findings based on the metabolite ratios. For this analysis, the data of one participant with FASD and two CON2 participants were omitted due to systematically lower absolute intensity (30%) compared with other participants with FASD and controls. This phenomenon is occasionally encountered with our scanner and has no effect on the ratios. Absolute metabolite signal intensities in each region were compared between FASD and CON2 groups and expressed in percentages, $(I_{mean(FASD)}-I_{mean(CON2)})/I_{mean(CON2)}X100$, where *I* is the mean regional metabolite intensity: for further details see Study 5.

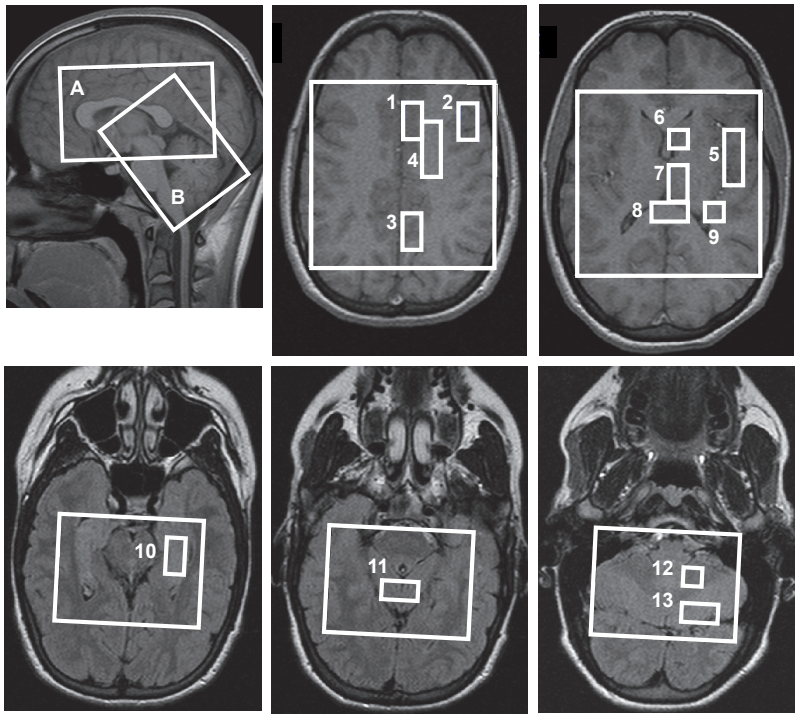

Figure 3. Positioning of 1H MRS volumes-of-interest (VOI) to cover the cerebrum (A) and cerebellum (B) on a mid-sagittal MR-image, and voxel locations on axial MR images. The largest rectangles show the VOI locations and the small rectangles represent voxel positions used to collect the MRS data: anterior cingulate (1), lateral frontal cortex (2), parietal cortex (3), frontal white matter (4), insular cortex (5), caudate nucleus (6), thalamus (7), corpus callosum (8), temporal white matter (9), hippocampus (10), cerebellar vermis (11), dentate nucleus (12), and cerebellar cortex (13).

3.4 Ethical considerations

The present studies were reviewed and approved by the Coordinating Ethics Committee at the Hospital District of Helsinki and Uusimaa, the Ethical Board of the Finnish Ministry of Social Affairs and Health, as well as by the Institutional Review Boards of San Diego State University and Stanford University School of Medicine in the United States. Regular progress reports have been sent to the Coordinating Ethical Committee at the Hospital District of Helsinki and Uusimaa.

The children and their parents/guardians were advised that participation in the study was voluntary and that the decision to participate did/would not affect the participants' relationships with the institutions involved in the research project. Written consent was obtained separately from the children and their guardians. Information about the research project and the physical and psychological examinations was given individually and the participants were given opportunity to ask questions. The participants were informed that they were allowed to discontinue assessments at any time. Test data and completed interview and questionnaire forms were kept confidential.

3.5 Statistical Analysis

All data were entered, and statistical calculations performed, using SPSS for Windows software packages/ IBM SPSS Statistics, versions 12.0 – 19.0. The significance level in all studies was set at $p<0.05$.

In Study I descriptive statistical methods were used (frequencies, means, standard deviations, range of outcomes) to clinically characterize the children and adolescents with FASD. In Study II descriptive statistics (mean, SD, range, frequencies), pairwise t-tests and univariate analysis of variance (ANOVA) were used to describe dysmorphic features and cognitive function in subgroups of FASD (FAS, PFAS and ARND). Associations between total dysmorphology score (TDS) and cognitive function (Full scale IQ, Verbal IQ, Performance IQ) were analysed using correlations, independent samples t-tests and cross-tabulation.

In Study III, the number of potential predictors of risk and protective factors was high in relation to the number of participants and it was not possible to include all predictors simultaneously in a single regression analysis. Therefore, the potential risk and protective factors were grouped into three categories: diagnostic factors, living environment and remedial help in school (see Table 7) and separate linear regression analyses including predictors from one category at a time were conducted. In this way the number of predictors never exceeded the recommended ratio between predictors and cases. The separate regression analyses were then followed by a similar linear regression analysis in which the significant predictors from the separate regressions were included simultaneously. This procedure was followed for each of the three dependent variables, that is, internalizing, externalizing and total problem scale scores from the CBCL. The linear regression analyses

were conducted using a simultaneous method (variables in a block were entered in a single step). To control for age, sex and IQ these variables were always entered together as Block 1 (not reported in tables 3-4 for sake of brevity) and risk/protective variables as Block 2 in each analysis.

In Study IV on adaptive behavior, descriptive statistics were calculated for the FASD, SLD and CON1 groups separately. Matching criteria was controlled using one way analysis-of-variance (age, IQ) and the chi-square test (sex). In the subgroup analysis of the FASD and SLD children matching criteria was controlled using independent sample t-tests (age, IQ) and the chi-square test (sex). Pearson correlations were performed to correlate IQ and adaptive behavior. One way analyses of variance were used to compare the three groups on adaptive behavior and to compare adaptive skills within the FASD group. A subgroup analysis between the FASD and SLD children raised in biological families was performed with the nonparametric Mann-Whitney U Test.

In Study V on MRS, all FASD participants were paired together with a matched CON2 group member for analysis. The distributions of the biochemical variables did not deviate significantly from normality (Kolmogorov-Smirnov, $p>0.05$). On the basis of correlation analyses between the ratios, repeated-measures multivariate analysis of variance (MANOVA) was used to analyse NAA/Cho and NAA/Cr between the FASD and CON2 groups. Cho/Cr ratios were analysed using paired-samples ANOVA. Absolute metabolite intensities were analysed using t-tests (2-tailed, assuming unequal variances).

4. RESULTS

4.1 Clinical delineation of the FASD group (Study I-III)

4.1.1 Demographic characteristics and revised IOM diagnostic category assignment

In the FASD group 60.3% (n= 44) of the participants were female and 39.7% (n=29) were males. Age ranged from 8 to 21 years, with a mean of 13 years. The majority (n=48, 65%) had been diagnosed with FAS or FAE before their first birthday and by 3 years of age 83.3% (n=60) had a diagnosis. As part of the present study a new diagnostic evaluation was performed. Of the 77 participants evaluated, 73 (95%) proved to have an FASD diagnosis, whereas 4 (5%) had features of other unrecognizable multiple malformation syndromes inconsistent with the teratogenic effects of alcohol. These 4 subjects were excluded from further analysis. Of the remaining participants 53% (n=41) were assigned a diagnosis of FAS, 30% (n=23) a diagnosis of PFAS and 12% (n=9) a diagnosis of ARND. No participants were diagnosed as having ARBD.

4.1.2 Family history

95% of the participants were racially Finnish Caucasian; no consanguinity was reported. A family history of genetic disorders, birth defects or mental retardation was rare. However, 42% reported first degree relatives with learning disabilities and/or attention deficit hyperactivity disorder and 43% reported a sibling who also had been diagnosed with FASD.

4.1.3 Prenatal/birth history

11% of the participants were born prematurely (less than 36 weeks gestation). 70% demonstrated prenatal growth deficiency and 45% were microcephalic at birth. Although other potentially teratogenic exposures were rare, 89% of the women for whom prenatal data were available smoked cigarettes throughout pregnancy. The participants were generally diagnosed with FASD at an early age (mean age for diagnosis 1 year, 6 months, SD 2.9, range 1-11 years).

4.1.4 Major and minor malformations

The dysmorphic features observed in the FASD cohort are listed by order of frequency in Table 4. The mean total dysmorphology score (TDS) for the entire cohort was 15.7 (SD=6.2, median=17, range 2-29); for children with FAS 19.8 (SD=3.6, median=19, range 12-29), PFAS 12.4 (SD=3.7, median=12, range 5-19) and ARND 5.3 (SD=2.3, median=5, range 2-10). There was a significant difference in the TDS between all three groups $F(2, 72)=75,46$, $p< 0.001$.

The presence of the cardinal facial features of FAS and PFAS was very high in this Finnish cohort of children and adolescents with FASD: 77% of all children in the FASD group had philtrum scores of 4 or 5 and 87% had vermilion scores of 4 or 5 on the lip/philtrum guide

(Astley & Clarren, 2000). Midfacial hypoplasia, long philtrum and anteverted nares were also common features, observed in nearly half of the children.

The most common morbidity in an organ system was with vision (refractive errors in 40% and strabismus in 38% of the children), followed by gastrointestinal malformation (26%), genitourinary (22%) and skeletal (21%) malformations. 18% suffered from congenital heart disease and 16 % of the participants had hearing impairments.

Table 4: Dysmorphic Features by Order of Frequency.

Dysmorphic Feature	Percent
Vermilion score 4 or 5	87
Short palpebral fissures (<10%)	78
Philtrum score 4 or 5	77
Epicanthal folds	68
Anteverted nares	56
Camptodactyly	55
Long philtrum	47
Midface hypoplasia	45
Dental crowding	43
Nail hypoplasia	38
Hockey stick palmar crease(s)	30
Altered palmar crease(s) (other)	21
Limitation in radioulnar rotation	16
Ptosis	14
Clinodactyly	12
Flat nasal bridge	10
Railroad track ear	5

4.1.5 Clinical characteristics

Most of the children with FASD had lived the majority of their lives in a foster or adoptive home (68.5%) followed by biological parents' homes (17.8%) and residential care (8.2%). At the time of the study, 64% lived with a foster family or had been adopted, 16% were staying in residential care, 16% resided with a biological parent and 4% lived independently. Over 90% had been offered some form of special education and almost 20% had had a personal aide at some stage of their education.

According to informants 11% (n=8) had suffered from serious depression and had threatened suicide. One participant (1.4%) had made a suicide attempt and two (2.7%) had had panic attacks. The majority was described as having attention deficit problems (n=44, 60.3%), but only 6 (8.2%) had been prescribed stimulant medication. Twelve participants (16.4%) had attended some form of psychotherapy.

4.2 Cognitive functioning (Study II-IV)

Intellectual performance of the FASD, SLD and CON1 groups is detailed in Table 5. Groups differed significantly for IQ according to matching criteria ($F_{(2,140)}$=41.81, p<0.001; FASD and SLD < CON). Corresponding figures within the FASD group is depicted in Table 6 for FAS, PFAS and ARND, respectively. No significant differences for IQ were found between the diagnostic subgroups of FASD.

Table 5. IQ Performance on the WISC-III/WAIS-III and LIPS-R by FASD, SLD and CON Groups.

	WISC-III/WAIS-III		LIPS-R	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**
FASD	79,34 (17,27)	37-120	90,12 (16,04)	50-127
SLD	80,23 (15,86)	51-103	87,0 (14,13)	60-111
CON1	107,33 (14,49)	70-134	108,15 (12,69)	77-129

Note. The WISC-III and WAIS-III test scores according to Finnish standardized test norms. LIPS-R scores according to American norms.

Table 6. IQ Performance on the WISC-III/WAIS-III and LIPS-R by FAS, PFAS and ARND Groups.

	WISC-III/WAIS-III		LIPS-R	
	Mean (SD)	**Range**	**Mean (SD)**	**Range**
FAS	75,35 (18,63)	37-120	87,58 (17,08)	50-127
PFAS	84,78 (14,12)	51-106	93,55 (14,22)	70-120
ARND	83,63 (14,59)	54-107	92,67 (15,32)	76-117

Note. The WISC-III and WAIS-III test scores according to Finnish standardized test norms. LIPS-R scores according to American norms.

4.2.1 Cognitive functioning and dysmorphic features

In Study II the intellectual performance of a younger subsample of the FASD group was correlated to their degree of dysmorphic features (TDS). Significant negative correlations were found between the TDS and full scale IQ (FSIQ, $r(48)$=-0.34, p<.05), and between TDS and performance IQ (PIQ, $r(48)$=-0.34, p<0.05), suggesting that more severe growth deficiency and dysmorphic features were associated with poorer cognitive capacity. The correlation between the TDS and verbal IQ (VIQ) did not reach significance.

The association between the TDS and IQ was further investigated with an independent samples t-test. On the basis of the median value of the TDS (17, range 5–29), a dichotomous variable was created, with one value corresponding to scores 17 and above and the other corresponding to scores 16 and below. Participants with a TDS score less than 17 showed significantly higher level of cognitive functioning than participants with higher TDS scores ($t(46)$=2.51, p<0.05). Significant differences were also found on VIQ ($t(46)$=2.25, p<0.05) and PIQ ($t(46)$=2.15, p<0.05).

Next, correlations between cognitive capacity and the single variables of the TDS were carried out. The strongest correlations were found for head circumference, which correlated

significantly with FSIQ (r(48)=0.34, p<0.05), VIQ (r(48)=0.30, p<0.05), and PIQ (r(48) =0.29, p< 0.05). Camptodactyly correlated significantly with VIQ (r(48)=0.29, p<0.05). With a Bonferroni correction the latter correlation was not significant. The other correlations did not reach significance.

4.3 Behavioral problems (Study III)

4.3.1 Comparison of the FASD and CON1 groups on the CBCL

The FASD group differed significantly from the CON1 group on internalizing, externalizing and total problem scale scores on the CBCL. In the FASD group 42.2% of the participants scored in the clinical or borderline ranges on total number of problems. In the CON1 group none scored in the clinical range and only 2.5% in the borderline range. A pattern in the same direction was seen for internalizing (FASD: 29.6% in borderline/clinical ranges, CON1: 7.5%) and externalizing problems (FASD: 26.8% in borderline/clinical ranges, CON1: 5%).

4.3.2 Living environment and behavioral problems in the FASD group

Of all the participants in the FASD group, 61.6 % (n=45) had lived with their biological parents at some stage in their lives; 80.8 % (n=59) had lived for at least some time in residential care, and 74% (n=54) had experienced a foster family (see further Table 7). There was a

Table 7. Descriptive statistics for diagnostic factors, living environments and remedial help in school for the FASD participants (N=73).

Diagnostic factors	
IOM diagnosis[a]	
FAS, n(%)	41 (56,2)
PFAS, n(%)	23 (31,5)
ARND, n(%)	9 (12,3)
TDS[b], range 2-29, median 17, M(SD)	15,7 (6,2)
Age for FASD diagnosis[b], median 0 years, range 0-11 years, M(SD)	1,6 (2,9)
Living environments	
Length of time lived with biological parents[c] Range 0-207, 25%=1, 50%=17, 75%=48, M(SD)	33,8 (45,5)
Length of time lived with foster or adoptive parents[c] Range 0-210, 25%=0, 50%=84, 75%= 124, M(SD)	76,7 (62,4)
Length of time lived in residential care[c] Range 0-162, 25%=6, 50%=12, 75%=24, M(SD)	27,2 (40,0)
Number of different living environments during the first 17 years Range 1-6,median=3, M(SD)	3,1 (1,0)
Remedial help in school	
Special education, 0-10 years[d], M(SD)	2,9 (3,1)
Classroom aide, 0-6 years[d], M(SD)	0,9 (1,7)

Note. [a] FAS= Fetal Alcohol Syndrome, PFAS=Partial Fetal Alcohol Syndrome, ARND=Alcohol Related Neurodevelopmental Disorder ; [b] Dysmorphology score, a weighted quantitative measure of associated major and minor anomalies, scale range 0-36 (Hoyme et al.2005); [c] Time in months; [d]Time in years and months.

significant positive correlation between number of different placements and length of time in residential care (r=0.34, p,<0.01), implying that children with FASD who had moved back and forth between different placements also tended to have spent longer time in residential care.

When asked about the longest placement in their lives so far, there were significant effects of the longest living environments (biological parents, n=12, foster/adoptive home, n=49, residential care, n=6) on behavioral problems in the FASD group: CBCL Total problems $F_{(2,64)}$=4.55, p<0.05; CBCL Internalizing problems $F_{(2,64)}$=5.89, p<0.01; CBCL Externalizing problems $F_{(2,64)}$=3.35, p<0.05. Participants whose longest placement had been in residential care experienced increased *total* problems and *internalizing* problems when compared to participants whose longest placement had been with biological parents or foster/adoptive parents (p<0.05). Longest placement in residential care was also associated with increased *externalizing* problems when compared to longest placement in foster/adoptive homes (p<0.05). There were no significant differences in behavioral problems between longest placement in foster/adoptive home and biological parents.

4.3.3 Risk- and protective factors association with behavioral problems

Of the nine potential risk and protective factors presented in Table 7, two yielded significant effects on the outcome variables: TDS and length of time spent in residential care. The TDS was negatively associated with externalizing problems. Thus, a lower number of visible dysmorphic signs was associated with more rule-breaking and aggressive behavior. IOM diagnosis and age at diagnosis were not significantly associated with behavioral problems. In the domain of living environments, longer time spent in *residential care* predicted more internalizing, externalizing, and total problems on the CBCL. Time spent in foster- and/or adoptive home(s) and fewer living placements were, however, not significant protective factors. Similarly, the length of time spent with biological parents or a high number of living placements were not risk factors for behavioral problems in this sample. Furthermore, remedial help in school was not significantly associated with behavioral problems.

In a final regression analyses we included the TDS and the time spent in residential care, as they were significantly associated with behavioral problems. After controlling for age, sex and IQ, the *TDS score* was negatively associated with internalizing (r_p-0.357**, β-0.289, p<0.05) and total problem scale scores (r_p-0.229*, β-0.267, p<0.05). Longer the time spent in *residential care* resulted in more problems in internalizing (r_p0.353**, β0.267, p<0.01), externalizing (r_p0.342**, β0.308, p<0.05) and total problem scale scores (r_p0.327**, β0.273, p<0.05). Age, sex and gender did not significantly affect the outcome variables.

4.4 Adaptive Behavior (Study IV)

4.4.1 Comparison of FASD, SLD and CON1 groups on adaptive behavior domains and subdomains

Separate analyses were conducted to evaluate the effect of group (FASD, SLD, CON1) on the VABS composite score, three domains and nine subdomains. Significant differences among the groups were revealed for all three domains on the VABS: Communication, Daily Living Skills and Socialization. Scores on the subdomains also revealed significant group differences for all scales but receptive communication. Results are presented in full in Study 4. As can be seen in Figure 4, a clear pattern was revealed on the domain level: the typically-developing controls scored better than the children with specific learning disorders, who in turn scored better than the alcohol-exposed children. On the subdomain level, the FASD group scored worse than both other groups on most scales.

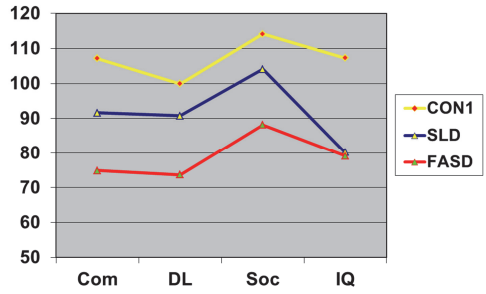

Figure 4. Adaptive Behavior Performance for FASD, SLD and CON Groups as Measured by the VABS

4.4.2 Combined influences of group and age on adaptive behavior

To address the broader question of whether age influenced adaptive behavior skills, the sample was divided into two age groups; 8-12 year olds and 13-21 year olds. A two way analysis of variance (General Linear Model) was performed combining age and group. Results revealed a significant two way interaction for the socialization domain. In the FASD group socialization skills were worse in the older age group (13-21 year olds) compared to the younger children (8-12 year olds). In the SLD group on the other hand, socialization skills improved with age and approached the typically-developing control children.

4.4.3 Influence of caregiving environment between the FASD and SLD groups

As the FASD group consistently performed less well on adaptive behavior skills compared not only to typically developing controls but also to their IQ-matched peers in the SLD group, we wanted to explore whether caregiving environment affected this relationship. Most children in the FASD group had at some stage been taken into custody and thus had been separated from their biological family. At the time of the study, 75.3% (n=55) of them lived in foster- or adoptive homes with a continuous caregiver, 16.4% (n=12) lived in residential care with alternating caregivers and 8.2% (n=6) had been able to stay with their

biological families. Differences between these groups on adaptive behavior skills did not reach significant levels.

We then compared the subgroup of children with FASD living with their biological families (n=6) with a corresponding group of SLD children living with their biological families (n=28, excluded in the analysis were one child in the SLD group who lived with foster parents and one who was in residential care). The groups were still similar with respect to sex [χ^2 (df =1)=0.551, p=0.458], age [t(32) =0.342, p=0.734] and IQ [t(32) =-0.738, p=0.466] but now also on caregiving environment (being raised in one's biological family). As the number of participants in the FASD group was very small the analysis was performed using the nonparametric independent samples Mann-Whitney U Test. Even though absolute numbers indicated lower scores in the FASD group compared to the SLD group, the results did not show any significant differences between the two groups on the VABS composite score, domain or subdomain scores (for detailed results see Study IV).

4.4.4 Adaptive behavior skills in the FASD group

Finally, to further examine the adaptive skills within the FASD group separate analyses were performed for diagnostic subgroups (FAS, n=41, PFAS, n=23, ARND, n=9). Significant differences were found on the adaptive behavior composite score ($F_{(2,70)}$=3.43, p=0.038, FAS and PFAS performed worse than ARND) as well as on the domain scores of communication ($F_{(2,71)}$=4.12, p=0.020, FAS and PFAS performed worse than ARND) and daily living skills ($F_{(2,71)}$= 3.92, p<0.024, FAS performed worse than ARND). Diagnostic category was not associated with socialization scores.

4.5 Alcohol-induced metabolic alterations (Study V)

4.5.1 Metabolite ratios

The metabolite ratios NAA/Cho and NAA/Cr were lower in the FASD group than in the CON2 group in several brain areas, but there was no difference in Cho/Cr. NAA/Cho and NAA/Cr were significantly lower in the FASD group than in the CON2 group in the anterior cingulate and in the parietal cortex and NAA/Cho was lower in the lateral frontal cortex. NAA/Cho and NAA/Cr were lower in the FASD group compared to controls in frontal white matter and NAA/Cr was lower in the corpus callosum. NAA/Cho was lower in the thalamus in the alcohol exposed group compared to controls. Finally, NAA/Cho and NAA/Cr were lower in the alcohol exposed group compared to controls in the dentate nucleus of the cerebellum. For the full range of results please see Study V.

4.5.2 Absolute metabolite signal intensities

The absolute metabolite signal intensities differed between the two groups. The overall NAA intensity was 7% (range -5%-23%) greater and overall Cho and Cr intensities were 14% and 15% greater (ranges 3%-31% and 3%-39%) in the FASD than in the CON2 group. There

were significant differences in Cho and Cr in several white matter and cortical and deep grey matter locations.

To illustrate the results, representative magnetic resonance spectra for one FASD and one CON2 participant are depicted in Figure 5.

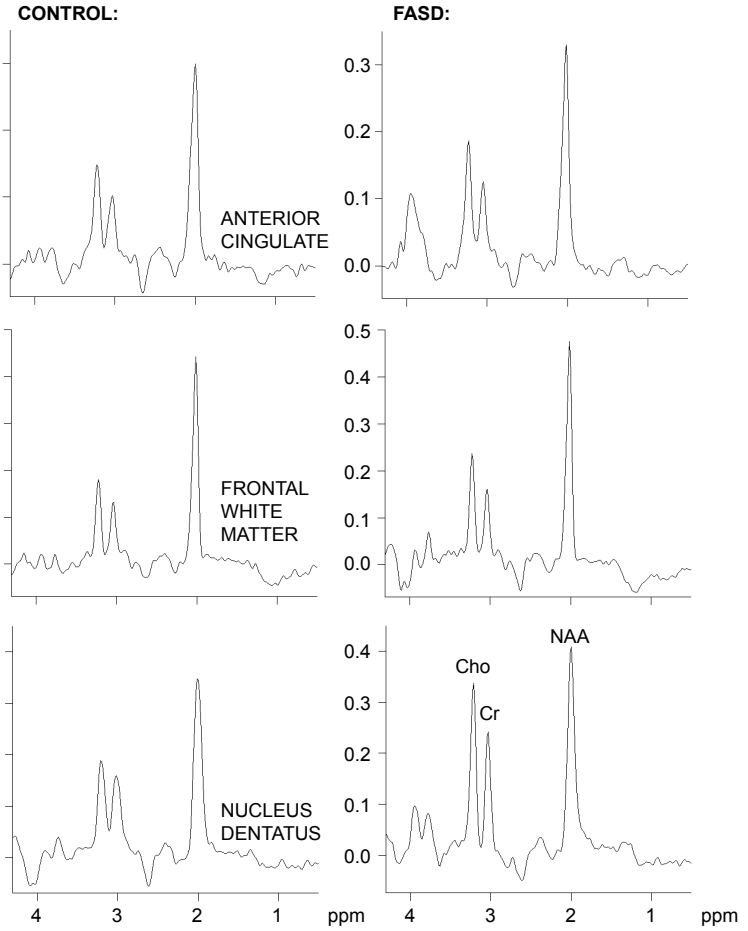

Figure 5. Representative 1H MR spectra from the left anterior cingulate, frontal white matter, and dentate nucleus of an FASD patient and of a control subject. The FASD spectrum and corresponding control subject spectrum are plotted using similar scaling. Brain metabolite signal assignments are NAA (N-acetylaspartate), Cho (choline-containing compounds) and Cr (creatine and phosphocreatine).

5. DISCUSSION

5.1 Main findings

In the present thesis, fetal alcohol spectrum disorders were examined in a cohort of Finnish children and adolescents. The five studies included had a broad focus on diagnosis, cognition, behavior, adaptation and brain metabolic alterations. Importantly, the participants in the present studies comprise a group of very carefully clinically characterized children with FASD as the studies were performed in close collaboration with leading experts in the field (Prof. Edward Riley and Prof. Sarah Mattson, Center for Behavioral Teratology, San Diego State University, U.S.; Prof. Eugene Hoyme, Sanford School of Medicine, University of South Dakota, U.S.).

The main research findings were the following:

- The revised IOM criteria for FASD were tested and found to be a reliable tool for differentiating among the subgroups of FASD in Finland.
- A weighted dysmorphology scoring system proved a valuable additional adjunct in the assessments of children with FASD.
- A significant correlation between dysmorphic features and cognitive capacity was found, suggesting that children with more severe growth deficiency and dysmorphic features have more cognitive limitations.
- Behavioral problems in the FASD group proved substantial compared to typically developing peers.
- Children and adolescents exposed to alcohol in utero faced greater risk of substantial behavioral problems 1) if they were less visibly alcohol affected and 2) the longer the time they had spent in residential care.
- When children with FASD were compared to IQ-matched children with SLD and typically-developing controls a clear pattern emerged where the children with FASD performed worse than the SLD children who in turn performed worse than the typically-developing controls for adaptive behavior skills.
- Evidence of longstanding neurochemical alterations were seen in adolescents and young adults related to alcohol exposure in utero 15-20 years earlier. The neurochemical alterations were seen in several brain areas and seemed to affect glia more than neurons.

5.2 The clinical spectrum of FASD

In clinical practice FASD is often associated with certain facial/physical characteristics in combination with learning disability. This constitutes a major challenge as the majority

of fetal-alcohol affected children may show no facial characteristics or other physical evidence of prenatal alcohol-associated birth defects (Bakhireva & Savage, 2011). In fact it has been suggested that the most profound effects of prenatal alcohol exposure may be on the developing brain and the cognitive and behavioral effects that ensue (Riley et al., 2011). It implicates a shift from a focus on the FAS face to a broader focus on prenatally alcohol-induced damage including dysmorphology, neurocognition, mental and behavioral functioning, and adaptive abilities. In addition, the individual variability of fetal-alcohol induced damage is broad. To give an example, the current FASD group comprises children with an IQ range of 37-120.

For many children growing up with FASD, an often unstable living environment may have profound effects on development in combination with the prenatally alcohol-induced brain damage. At the time of the study, only 6.8 % (n=5) of the children with FASD in our cohort lived with their biological family, 17.8 % (n=13) were living in some form of residential care with turnover of caregivers or in family group homes and the rest in foster/adoptive homes or independently (75.3%, n=55, but one adolescent who lived independently had been raised in a biological family). In other words, over 90% (n=67) of the children and adolescents with FASD in this Finnish cohort had been removed from their birth families at some stage and been taken into custody, an event necessarily preceded by some form of child maltreatment, neglect or an environment where the child's development was endangered.

The family histories of our participants with FASD were remarkable for a high rate of learning and behavior problems among first degree relatives of the probands. This was unrelated to alcohol exposure and suggests that at least some of the behaviors observed in our FASD group may have a genetic basis. In addition, for nearly half of the participants with prenatal alcohol exposure a sibling with an assigned diagnosis of FASD could be identified, a finding previously documented in a retrospective review of the medical literature on FAS (Abel, 1988). The high prevalence of FASD in siblings of affected probands is particularly important in terms of prevention, since identifying women who have had one child affected with FASD and focusing efforts on treating their alcoholism and/or improving their birth control practices (if they continue to drink) may potentially have a large impact on the occurrence and recurrence of this disorder in a given population.

5.3 The utility of the revised IOM criteria and a broad weighted dysmorphology score in the diagnosis of alcohol-exposed individuals

The revised IOM criteria require a multidisciplinary evaluation of the child. In the present thesis the children were recruited based on medical records including confirmed maternal alcohol intake during pregnancy and had already been diagnosed with FAS or (suspected) FAE by a Finnish physician. To increase reliability for the present studies, the FASD group was re-examined by an experienced dysmorphologist. The two main control groups (CON1 and SLD) were examined by two experienced dysmorphologists. A psychologist and a skilled

maternal interviewer also participated in the diagnostic process, adding to the reliability and validity of the overall measurements.

The revised IOM criteria were originally tested on 6 Native American communities in the United States and 1 community in the Western Cape Province of South Africa (1500 cases evaluated, 164 children with a potential FASD diagnosis) (Hoyme et al., 2005). With the current data the Revised IOM Diagnostic System was further tested on a white Caucasian population with a northern European cultural background. In total 147 additional cases were evaluated, of whom 77 had an earlier diagnosis of FAS/FAE. As such, the Revised IOM Diagnostic System was found to be a reliable tool to differentiate among the various diagnostic groups within the FASD continuum in Finnish children, increasing content validity of the Revised IOM Diagnostic System. The ARBD diagnostic group was, however, not found in our sample.

In the present thesis the revised IOM criteria were compared to earlier diagnostic schemes for diagnosing alcohol exposed children with FAS/FAE in Finland (Rosett, 1980 and later with a Finnish revision to the original IOM criteria, Autti-Rämö, 2000; Stratton et al., 1996), but not to any other diagnostic system in current use. Of the 77 children with earlier diagnoses of FAS/FAE 73 were, according to the Revised IOM Diagnostic System, considered to have diagnoses within the FASD spectra. The remaining 4 children presented with symptoms of other malformation diseases and were referred for genetic testing. Thus, compared to earlier diagnostic schemes used in Finland, the Revised IOM Diagnostic System can be said to have increased the *specificity* (reducing false positives) among the diagnoses.

In comparison with other diagnostic schemes, the revised IOM criteria have been criticized for requiring less rigorous inclusion criteria for the FAS and PFAS categories than the 4-Digit code or the Canadian guidelines (Astley, 2006). For example, in the Revised IOM Diagnostic System 2 of 3 cardinal facial features (palpebral fissure length, thin vermillion border of upper lip, smooth philtrum, all ≤10th percentile) have to be present for a diagnosis of FAS compared to all 3 facial features (≤ 2 SDs or ≤2,5th percentile) as in the 4-Digit code or the Canadian Guidelines. Thus if we had used the 4-Digit code or the Canadian guidelines our sample might have presented with fewer participants in the FAS and PFAS groups and more participants diagnosed with ARND or other functional deficits (static encephalopathy/ alcohol exposed or neurobehavioral disorder/alcohol exposed). On the other hand, our goal was a practical diagnostic tool suitable for clinical practice. In contrast, the 4-Digit diagnostic code offering 256 diagnostic combinations collapsed into 22 diagnostic categories, has been considered confusing and impractical for routine use in clinical practice (Hoyme et al., 2005; Watkins et al., 2012).

Common to all diagnostic guidelines for FASD, neuropsychological testing constitutes a key role in the process as the majority of individuals with fetal-alcohol related damage may show no physical evidence of their disorder. From the point of view of the psychologist or neuropsychologist, knowledge of the specific cognitive characteristics in FASD together

with extensive neuropsychological testing including adaptive behavior and a behavioral evaluation are important. For example, the revised IOM criteria specify a complex pattern of behavior or cognitive abnormalities inconsistent with developmental level including marked impairment in the performance of complex tasks, higher-level receptive and expressive language deficits, and disordered behavior as one of the criteria for PFAS and ARND (Hoyme et al., 2005). In the 4-Digit code probable brain damage (static encephalopathy) is described as substantial deficiencies (≤ 2 SDs) or discrepancies across three or more areas of brain performance such as cognition, achievement, adaptation, neurological 'soft' signs, and language (Astley & Clarren, 2000).

An apparent problem applying any of the diagnostic schemes to Finland, but especially the 4-Digit Code or Canadian Guidelines as they require all facial features to be present for FAS diagnoses, is that we lack norms for palpebral fissure length. For the current thesis American norms were used for this purpose, but we cannot be sure of their accuracy in the Finnish population. Further, the *sensitivity* of all diagnostic systems to detect prenatal alcohol-related damage if present may pose a challenge as many of the alcohol-affected children may present with less visible or no apparent visible signs of damage. In addition, the full range of a prenatal alcohol-related disability may sometimes not be apparent before adolescence or young adulthood. Hopefully, diagnostic methods for FASD will be facilitated and refined by improvements in medical technology and understanding of the deficits (Astley, 2006; Watkins et al., 2012).

As no prevalence study on FASD has been performed, we do not know the exact distribution of different diagnostic categories (FAS, PFAS, ARND, possibly ARBD) in Finland, nor do we know the ratio of girls versus boys suffering from FASD. But we do consider the children and adolescents with FASD participating in the present thesis typical of the Finnish population and as typical representatives of how prenatal alcohol-related damage manifests in the Finnish population. Based on the current data, it is our experience that the Revised IOM Diagnostic Classification System worked well as a practical clinical tool in detecting and defining documented prenatal alcohol exposure. The adoption of these criteria in Finland requires, however, a change in current practice and national education to reduce confusion among paediatric care providers.

Further, there is no consensus as to the number and type of minor physical anomalies that should be assessed in a structured dysmorphology checklist. Studies in children with fetal alcohol exposure have used varying, often self-constructed scales (Autti-Rämö, Gaily, & Granstrom, 1992; Day et al., 1991; Majewski, 1978; Tennes & Blackard, 1980; Vitez, Koranyi, Gonczy, Rudas, & Czeizel, 1984). For this study we used a weighted dysmorphology score first developed by Dr. Jon Aase of the University of New Mexico (Hoyme et al., 2005). In this scale, particular weight is given to those features which are most prevalent in children with FASD (i.e., the three cardinal facial features, head circumference, height and weight). The timing and pattern of alcohol consumption may also have a large role in the development of specific malformations. In retrospect, it was not possible to obtain information on pattern of alcohol consumption during pregnancy for the children with

FASD included in these studies, and thus we were not able to analyse time or pattern specific malformations.

We also evaluated whether differences exist in terms of the prevalence of certain minor anomalies among children with FASD by comparing our findings in Finnish children with those from other racial and ethnic groups. The methodology set forth in the CIFASD consortium (of which this study forms part) has also been applied in dysmorphology assessment of children with FASD in Native American and Cape Coloured communities in the Upper Great Plains of the United States and the Western Cape Province of South Africa (Hoyme et al., 2005; May et al., 2000). The weighted dysmorphology scores were higher in Finnish children in every diagnostic subgroup than in those previously reported in Native Americans and South Africans (Hoyme et al., 2005). The validity of this score has now been evaluated and confirmed in three different racial and genetic backgrounds. A significant difference in the weighted dysmorphology scores among the diagnostic subgroups in FASD was also observed. The results of the current studies indicate that the weighted dysmorphology score is a useful adjunctive tool in clinical and/or research assessment when fetal alcohol exposure is suspected. But although the dysmorphology score is a useful tool for quantifying major and minor anomalies it is not in itself sufficient for assigning clinical diagnoses within the FASD continuum.

Our results strongly support the use of the lip/philtrum guide (Astley & Clarren, 2000) in the clinical assessment of children with FASD: The majority of the children in the FASD group had scores of 4 or 5 as is one of the requirements for a diagnosis of FAS or PFAS. Midfacial hypoplasia, a long philtrum and anteverted nares may also be useful features indicative of fetal alcohol exposure as they were observed in nearly half of the Finnish children with FASD. In an earlier study of Finnish children epicanthal folds were the most frequently observed dysmorphic feature in non-alcohol exposed children (Autti-Rämö et al., 1992), and although present in nearly 70% of alcohol exposed children in this study, the prevalence in normal Finnish children suggests that it is not useful as a sign of FASD. A “railroad track” configuration of the ear, reported to be a common minor anomaly in children with FASD in other populations (Hoyme et al., 2005; Jones et al., 2010), was a rarity in Finnish children, but minor anomalies of the extremities (camptodactyly, nail hypoplasia, altered palmar creases including the “hockey stick” crease and clinodactyly) were observed frequently in the present study.

5.4 General cognitive capacity in FASD and associations with dysmorphic features

The mean IQ of 79 in the Finnish FASD cohort corresponded to earlier reports (Mattson & Riley, 1998; Mattson et al., 2011) and clearly differed from the typically-developing control children (mean IQ 107). It is of note that among the subgroups of FASD no significant differences in IQ was found, even though absolute numbers indicated lower scores in the FAS group (mean IQ 75) compared to PFAS (mean IQ 85) and ARND (mean IQ 84) groups. In

practice, this indicates that an individual with no physical signs of FASD may function on a similar cognitive level as someone with clear physical characteristics associated with FASD (Mattson et al., 1998).

It is also important to note that the range of IQ scores in FASD may be wide: in our FAS group IQ ranged from 37-120 as measured by WISC-III/WAIS-III and 50-127 as measured by LIPS-R. Similar IQ ranges were seen in PFAS and ARND groups. This is in accordance with earlier research on FASD (Streissguth et al., 1996). Thus, despite a diminished intellectual capacity on average, the individual variability may be high in individuals with fetal alcohol-related diagnoses.

An association between dysmorphic features/growth deficiency and general cognitive capacity was found, so that in children with FASD having more dysmorphic features were related to poorer cognitive capacity. The association seems logical, since both types of variables may be influenced by significant exposure of the fetus to alcohol. It should be noted, however, that this association was only moderate, i.e., physical markers of FASD and limited cognitive capacity do not always go hand in hand.

Despite the intuitive link between facial dysmorphology and CNS structure and function, no single dysmorphic feature was found to correlate significantly with IQ in the present data; rather it was the total sum of dysmorphic features that displayed the inverse relationship. Of the single features, the strongest correlation was found between small head circumference at present and poor cognitive capacity. However, small head circumference at birth was not significantly associated with cognitive deficits later in life.

Albeit significant, the relationship between the total dysmorphology score (TDS) and cognitive functioning was only moderate. When children were categorized into those with TDS's above and below the median value, only 11 children with obvious physical stigmata showed marked cognitive deficits (IQ<70). In fact, there were 16 children with obvious physical stigmata who had a normal IQ. Conversely, there were 5 children with subnormal IQ who had fewer stigmata. The moderate association between the TDS and cognitive capacity suggests that the presence of dysmorphic features might be an early clue for cognitive limitations. However, this is not always the case: children with more marked dysmorphic features may well function within the normal cognitive range and vice versa.

This moderate relationship is of significance in clinical practice. Dysmorphic features characteristic of FASD, including the distinctive facial features, do not reliably predict a child's cognitive development. Similarly, absence of physical markers is no guarantee of normal cognitive capacity. Test administrators should be careful not to be influenced by clear physical markers in their decision to administer psychological assessments or in expectations concerning the child's capacity. Results also underscore the importance of the (neuro)psychologist through thorough cognitive and behavioral testing in the diagnostic process.

5.5 Risk factors for behavioral problems in FASD

It was expected that children with FASD living in foster or adoptive homes would show fewer behavioral problems compared to children with FASD living with their biological parents or in residential care. We found that childhood environment did exert the strongest influence on behavioral outcome; however, it was the time spent in residential care that was the most significant risk factor. Although the groups were small and results are tentative, children living in foster homes and with biological parents did not differ significantly with respect to behavioral outcome. Second, we had expected that an early diagnosis and a diagnosis of FAS rather than PFAS and ARND would be protective factors. It turned out that diagnosis *per se* did not affect behavioral outcome. But *lower* dysmorphology scores were associated with higher scores indicating behavioral problems. We had also tentatively expected that remedial help in school might exert a protective influence. This intervention did not show any effect.

A substantial number of the children and adolescents with FASD scored in the borderline and clinical ranges on the CBCL; 42% on total problems, 29% on internalizing problems and 27% on externalizing problems. The figures were high in comparison with the typically-developing controls (clinical and borderline range scores 2.5% on total problems, 5% internalizing problems and 5% on externalizing problems). Clearly, behavioral problems in the FASD group proved substantial compared to typically developing peers.

The result that individuals affected by FASD who have fewer dysmorphic features are likely to have more behavioral problems (total problems and internalizing problems) is in line with Streissguth and colleagues' conclusion that having a diagnosis of FAS compared to alcohol exposed individuals without full-blown FAS actually constitutes a protective factor (Streissguth et al., 1996). It can be speculated that the more dysmorphic signs, including growth retardation, an individual with FASD displays, the better her/his needs are recognized and the more help and understanding he/she receives. Conversely, an individual appearing more physically "normal" may be less likely to be identified as requiring assistance and fail to comply with expectations in school and society in general.

While number of dysmorphic features was associated with outcome, the actual IOM diagnosis did not predict behavioral problems. This is consistent with the findings of Spohr et al. (2007) and Koponen et al. (2009) who found no differences in behavioral, emotional and neurocognitive abilities between groups of children with FAS compared to alcohol exposed children not fulfilling the FAS diagnosis. The results from the present study stress the clinical importance of attending to prenatal alcohol exposure *per se* and particularly children displaying fewer dysmorphic features, especially those with ARND.

Length of time spent in residential care turned out to be the strongest predictor of behavioral problems. Specifically, our findings indicated that more time spent in residential care was associated with more problems on internalizing, externalizing, and total problem scale scores on the CBCL. This may be seen as a parallel to the findings by Streissguth et al. (2004) that good quality and stable homes were protective factors in children with FASD. In Finland,

1.3% of all children under the age of 18 were placed outside the home in 2008, the highest percentage being among adolescents (STAKES, 2009). Children may be placed in residential care units for protection when the child's home is not safe or when the child's behavior is a safety risk. Today, the need for adequate foster family care is not met in Finland. As the biological parents also have to agree to foster care, not all children can be moved to foster homes but have to remain in residential care. Residential care units in Finland are restricted to a maximum of seven children/unit and a minimum of seven employees in a caregiving function per unit (Taskinen, 2008). In a study from the U.K., Roy and colleagues concluded that despite regulations enforcing an adequate caregiver to resident ratio, residential institutions still tend to be characterized by larger units compared to family environments, less individualized caregiving, more turnover of caregivers, as well as more changes in the group within which the children are reared (other children coming and going from the unit) (Roy, Rutter, & Pickles, 2000). The residential setting itself does not necessarily provide possibilities for individualized and sensitive caregiving (Vorria et al., 2003).

A substantial body of research from different countries has described various behavioral and emotional problems in institutionalized children in general (Min, Ullrich, Roberts, & Coid, 2007; Roy et al., 2000). There is a strong implication that the pattern of rearing influences psychopathology and it seems likely that the major discontinuities in individualized caregiving inherent in residential care constitute at least part of the risk (Roy et al., 2000). Attachment models emphasize that children are adversely affected by the absence of a close and continuous relationship with a caregiving adult (Bowlby, 1988). Institutionally reared children are often described as attention seeking with a somewhat indiscriminate friendliness, a relative lack of differentiation in response to different adults, a tendency to go off readily with strangers and a lack of checking back with parents/adults in anxiety-provoking situations (Rutter et al., 2007). In terms of attachment theory these types of behaviors are characterized as reactive attachment disorder – disinhibited type or nonattachment with indiscriminate sociability (Vorria, Rutter, Pickles, Wolkind, & Hobsbaum, 1998; World Health Organization, 1992; Zeanah & Boris, 2000). Interestingly, children and adolescents with FASD are often described as overly friendly and indiscriminate in their social relationships, reminiscent of the description of the attachment difficulties of institutionally reared children. Given that a substantial portion of these children prenatally exposed to alcohol may spend some time in an institutional setting or at least experience discontinuities in rearing moving from one family environment to another, the rearing environment of these children should be taken into account as a contributing factor to their specific behavioral traits. Further, in a Finnish study on international adoptees, children from Eastern Europe showed the highest risks for symptoms of reactive attachment disorder compared for example to children adopted from Asia (Raaska et al., 2012). But it has also been shown that symptoms of FASD abound in children adopted from Eastern Europe (Landgren et al., 2010). How can we ascertain that symptoms of indiscriminate sociability pertain to prenatal alcohol related damage or to non-optimal rearing experiences or to a combination of both? A prenatally alcohol exposed child, already at high risk both biologically and with respect to

early environment, may be even more sensitive to the additional environmental risk of an institutional rearing (Hellemans et al., 2010).

For children prenatally exposed to alcohol, however, longer time spent with biological parents does not necessarily lead to more secure attachment or fewer behavioral problems. Insecure attachment has been rated as high as 70-80% in children with FASD living with their biological mothers (O'Connor, Kogan, & Findlay, 2002). A Swedish study by Aronson and Hagberg (1998) concluded that early foster care did not appear to eliminate the harmful effects of prenatal alcohol exposure, but that a placement in a foster home may lead to improved performance and a better quality of life for the child with FASD.

In the current study there were no significant differences with respect to magnitude of behavioral problems between the groups of children who had been living the longest part of their lives with foster/adoptive parents compared to those living with their biological parents. Rather, differences were observed when children in residential care were compared to those living with biological parents or in foster/adoptive environments. It must be noted, however, that the groups might not be comparable primarily, as the gravest abusing biological families are more likely to lose custody of their children (Sarkola et al., 2007). In addition, as a biological family in Finland has to agree to foster care of their child, it is also possible that children of less cooperative birth parents are the ones that tend to remain in residential care.

The CBCL profile of the FASD group cannot be said to be specific to this population. Internal and/or external problems are also found in other neuropsychiatric categories such as ADHD (Fussell, Macias, & Saylor, 2005; Hudziak, Copeland, Stanger, & Wadsworth, 2004), autism spectrum disorders (Bauminger, Solomon, & Rogers, 2010) and mental retardation (Koskentausta, Iivanainen, & Almqvist, 2004). Children under child protection service are also a highly vulnerable group exhibiting high percentages of behavioral problems (Hukkanen, Sourander, Bergroth, & Piha, 1999). The underlying mechanisms may, however, be partly different as the problems of children with FASD may reflect both a neurobiological susceptibility to impaired behavioral control and coping, and a non-optimal rearing environment. Children under child protection service may run a comparable environmental risk (Hukkanen et al., 1999), but for these children the neurobiological contribution to the behavioral problems is not as clear as in FASD.

5.6 Adaptive behavior among FASD, SLD and CON1 groups

Clearly different adaptive profiles among children and adolescents with FASD, SLD and typically-developing controls (CON1) were revealed. The FASD group performed worse than the SLD group, who in turn performed worse than the CON1 group on the adaptive behavior composite, all domains (communication, daily living skills and socialization) and most subdomains on the VABS. Importantly, the SLD group outperformed the FASD group on adaptive behavior in spite of comparable cognitive levels. This is the first study to compare

adaptive abilities in a group of children and adolescents with FASD relative to both a contrast group of IQ-matched children with SLD and to a group of typically-developing peers.

This study supports the view that typically-developing children outperform children with FASD on adaptive skills (Jirikowic et al., 2008), and extends the understanding of adaptive abilities in FASD compared to IQ-matched children and adolescents with SLD. Earlier work on adaptive abilities in FASD has shown mixed results both within the FASD group (Carr et al., 2010; Coles et al., 1991) and, in a limited fashion, in comparison to other clinical groups (Crocker et al., 2009; Whaley et al., 2001). In one study where children with FASD were compared to a diverse group of IQ-matched clinical controls results showed no differences on adaptive abilities between groups (Whaley et al., 2001). In contrast, the clearly differential adaptive profiles of children with FASDs compared to children with SLD in the present study may result from the combination of the well-defined IQ-matched comparison group and the inclusion of older participants in this study. It has been suggested that difficulties with adaptive abilities in FASD may become more prominent with age (Thomas et al., 1998; Whaley et al., 2001).

In clinical practice, SLD is an important comparison group to FASD as these children often come to the same developmental neurology units where both groups may present with similar difficulties with learning. As diagnoses within the FASD continuum are difficult to make, children with FASD remain remarkably underdiagnosed (May et al., 2009; Vagnarelli et al., 2011). However, as children with FASD and SLD show differential patterns of adaptive skills regardless of IQ, the importance of accurately and differentially diagnosing FASDs is underscored.

Further analyses combining effects of age and group showed lower socialization skills in the adolescents with FASD (13-21 year olds) compared to the younger children (8-12 year olds). In contrast to this, the socialization skill scores of children in the SLD group were better in the older age group; as adolescents their level of social skills approached that of the CON1 group. The results thus support the theory that the relative deficits in social skills may increase with age among individuals with FASD (Crocker et al., 2009; Thomas et al., 1998). Typically, during late childhood and adolescence there are important changes in social awareness associated with a comparatively late development of brain regions regulating social processes. The theories on the development of social decision-making suggest an interaction between an innate, emotion-inducing system and an acquired, emotion-regulating system gradually developing over time. Possible regulatory mechanisms pertain to the development of cognitive control (the ability to keep relevant information in an active state and exert goal-directed behavior), future orientation (the ability to anticipate future consequences of actions) and perspective taking (consider the thoughts and perspectives of other people) which are thought to be regulated by different neural networks in the brain and gradually mature during late childhood and adolescence (Crone & Westenberg, 2009). According to these theories, social deficits in FASD might be associated with either a later than normal maturation of one or more of these regulating systems, (partly) deviantly functioning systems, or a combination of both.

Caregiving environment also seemed tied to level of adaptive skills, although results are very tentative as the analysis was performed on a small subgroup and the statistical power is low. When children with FASD and SLD living in their birth families were compared the developmental gap between groups diminished considerably, supporting the notion that adaptive impairments in individuals with FASD cannot be explained by neurological sequelae alone but are also influenced by the rearing environment. In the FASD group the children *not* living with their biological parents had all been taken into custody and subsequently placed in foster/adoptive homes with continuous caregivers or in residential care with turnover of caregivers. As reasons behind child welfare actions in Finland pertain to circumstances endangering the child's development, the children had experienced adverse family environments such as alcohol abuse and/or violence prior to intervention by child welfare.

5.7 Brain metabolic alterations in FASD

This study was among the very first to provide evidence for in vivo brain metabolic alterations among adolescents and young adults with FASD. To date, only two other MRS studies on humans with FASD have been published, focusing on one or two brain regions (Astley, Richards et al., 2009; Cortese et al., 2006). In the present study the FASD participants showed lower NAA/Cho and NAA/Cr in several cerebral and cerebellar locations compared to controls. Alterations were seen in frontal and parietal cortices, frontal white matter, corpus callosum, thalamus and cerebellar dentate nucleus. These findings suggest that long-standing or permanent biochemical alterations can occur in response to prenatal exposure to alcohol.

5.7.1 Neuronal and glial effects

The finding of lower NAA-containing ratios but no difference in the Cho/Cr in the FASD group could be interpreted either as lower levels of NAA (neuronal hypothesis), higher levels of Cho and Cr (membrane or glial hypothesis), or both. From the ratio data it is not possible to conclude whether one or both of these mechanisms could be active. The ratio approach corrects for all known error sources but it does not tell in which direction individual metabolites change. However, in the absolute metabolite signal intensity analysis, Cho and Cr were higher in several locations in the FASD group, but there was little or no difference in NAA. Since the absolute measurements of metabolite intensities were subject to error sources, we interpret them with caution and do not use them for regional analysis. Still, the absolute signals are helpful in assessing the direction of the metabolite change. However, they point towards a metabolic alteration in the glial cell population rather than in the neuronal cell population. The ethanol induced alterations in developing astrocytes (Guerri et al., 2001) may be long-standing or even permanent in nature. The damaged glial cell population may suffer from poorer membrane stability that manifests as enhanced turnover of the Cho-containing membrane constituents. This view finds support from studies that report such stability alterations after long-term exposure to alcohol both in humans (Chin

& Goldstein, 1977; Lee, Friedman, & Loh, 1980) and in rats (Grieve, Littleton, Jones, & John, 1979; Littleton, 1979). Our data do not show a decrease in the neuronal marker NAA and thus do not lend support to the neuronal hypothesis.

Previously, volumetric neuroimaging studies have also shown that in brains of individuals with FASD, white matter structures have suffered larger losses than grey matter structures (Riikonen et al., 1999; Sowell, Thompson et al., 2001; Sowell et al., 2002). High resolution 3D MRI and whole-brain surface-based image analysis procedures (Sowell et al., 2002) have shown increased grey matter density and decreased white matter density bilaterally in posterior temporal and inferior parietal regions in alcohol exposed subjects, suggestive of abnormal myelination. These results imply that myelin producing glial cells or their precursors may be predilection structures for alcohol effects during fetal development.

The energy supply of neurotransmission is largely provided by astrocytes (Magistretti, Pellerin, Rothman, & Shulman, 1999) and a malfunctioning astrocytic cell population cannot fully meet the energy demands of the firing neurons. We propose that behavioral and cognitive dysfunctioning in FASD subjects may arise from a failure of this astrocytic function. This view finds support in the evidence of the effects of alcohol on astroglia development (Guerri & Renau-Piqueras, 1997; Guerri et al., 2001). An alternative or additive explanation could be a defective myelin sheath.

Of the two other MRS studies conducted on humans with FASD, Astely et al. (2009) targeted two brain regions: a right frontal/parietal white matter region and a left hippocampus/basal nuclear region. They found *lower* Cho concentrations in the frontal/parietal white matter region in FAS and PFAS groups compared to healthy controls and alcohol exposed children with neurobehavioral disorder. The hippocampus voxel did not reach significant differences between groups. Despite the fact that Cho levels point in the opposite direction compared to the present study, Astley et al. also come to the conclusion that their results reflect white matter deficits among FAS/PFAS. The participants in the two studies are, however, not necessarily comparable. Participants in the Astley et al. study were younger (8-15 years) than in the current study (14-21 years) and they were not matched on head circumference, BMI or handedness as in the current study. Further, Astley et al. base their results on one single frontal/parietal region whereas in the present study a broad range of brain regions were compared.

The other human study on FASD and MRS compared metabolism in the caudate nucleus in FAS, FAE and non-exposed controls (Cortese et al., 2006). In the left caudate nucleus *NAA/Cr was elevated* in the FAS and FAE groups compared to controls. In contrast to the results of the present study, Cortese et al. interpreted their results as an increase in the neuronal marker NAA. The groups in this study were, however, very small (FAS=7, FAE n=4, controls n=4) and, as suggested by Astley et al. (2009), the samples may have been too small to provide clinically or statistically meaningful results. In addition, groups were not matched on gender, handedness or head circumference. Compared to the present study, participants were also younger (14-21 year olds in the present study compared to 9-12 year olds in the study by Cortese et al.).

5.7.2 The relation of metabolic alterations to neuropsychological deficits

MRS has a role in revealing altered metabolism when structural alterations cannot be seen in persons with cognitive defects. In our MRS study, all 10 participants with FASD had learning difficulties but only two showed structural abnormalities. In neuropsychological studies, children with FASD have been found to have cognition-based executive dysfunction in real life situations indicative of frontal dysfunction. Typically, these individuals have difficulties with problem-solving, abstract thinking, planning and flexibility of thought processes (Kodituwakku et al., 2001; Mattson, Schoenfeld, & Riley, 2001). The NAA/Cr and NAA/Cho alterations in the lateral frontal cortex, anterior cingulate and frontal white matter are compatible with such executive dysfunction.

Our results also showed low NAA/Cho and NAA/Cr in the right parietal cortex. The parietal cortex guides spatial behavior (Kolb & Wishaw, 2003). In FAS, human place learning has been shown to be impaired (Hamilton et al., 2003) which agrees with our metabolic findings.

Further, this study demonstrated metabolic alterations in the corpus callosum even in the absence of visible structural abnormalities. Children with prenatal exposure to alcohol have been shown to display subtle deficits in interhemispheric transfer tasks (Roebuck, Mattson, & Riley, 2002), as well as in bimanual coordination tasks (Roebuck-Spencer, Mattson, Marion, Brown, & Riley, 2004), presumably dependent on a dysfunctional corpus callosum.

Animal studies (Dikranian, Qin, Labruyere, Nemmers, & Olney, 2005; Green, Rogers, Goodlett, & Steinmetz, 2000; Green, Tran, Steinmetz, & Goodlett, 2002) confirm that prenatal alcohol may induce damage to cerebellar deep nuclei as was also observed in this study. The cerebellar circuit is thought to be intimately involved in planning and mental rehearsal of complex motor actions and in the conscious assessment of movement errors (Kandel, Schwartz, & Jessell, 2000). The extent to which cerebellar metabolic abnormality is related to behavioral deficits is, however, difficult to estimate.

5.8 Limitations and suggestions for future research

A few potential limitations of this group of studies should be considered. First, although participants in the CON1 and SLD groups were assessed by two experienced dysmorphologists to exclude the possibility of fetal alcohol-related pathology, data on the dysmorphology scoring system was not available for these groups. Data on the prevalence of dysmorphic features in the SLD and CON1 groups would have provided a firmer basis for establishing dysmorphic features in the present FASD group. However, earlier studies have shown that multiple dysmorphic features are very rare in non-alcohol-exposed Finnish children (Autti-Rämö et al., 1992). The lack of exact norms for the TDS also made it difficult to specify cut off points for sub-dividing children into higher and lower scores on the TDS. The median value used for analysis in Study 2 does not correspond to any external criterion. It only indicates that some children have more and some fewer dysmorphic features. In the future it would

be of interest to compare TDS with other more specific neuropsychological measures such as executive function skills.

Second, in the SLD group we have a well-matched comparison group on cognitive level, but we have no control group matched to the FASD group on social and environmental background. In Study 4 we managed to match a subgroup of children with SLD on caregiving environment, but the group was small. In fact, very little is known about the double hazard for individuals growing up with FASD of neurocognitive sequelae in combination with a psychosocially high risk environment. This needs to be better accounted for in future studies on children growing up with FASD through inclusion of comparison groups matched on social environment. A prenatally alcohol-exposed child, already at high risk biologically, may be very sensitive to additional environmental risk. This is often the case when a child with FASD is born into an alcohol abusing family with high psychosocial risk.

Third, we found that longer placement in residential care was associated with more behavioral problems, but we cannot exclude the possibility that the sample that remained longer in residential care was biased. As age and intelligence were controlled for statistically, this group could have comprised children who, due to behavioral problems or less cooperative biological parents, were harder to place in foster families. Because children in residential care are characterized by behavioral and psychiatric problems, it is difficult to determine which problems might be due to prenatal alcohol exposure *per se* versus rearing environment and adverse life experiences. Although we have a good sample size of FASD participants, it is clear that its size is only moderate for the regression analyses which may have resulted in all actual effects of the risk and protective factors not having been identified.

Fourth, the limitation of the MRS study was the relatively small sample size; larger studies are needed to validate the results. Only participants who were able to stay motionless for over an hour in the MR scanner could be included. Since severe FAS is often characterized by restlessness and hyperactivity, the adolescents and young adults participating in this study don't represent the most severe end of the fetal alcohol spectrum. Possibly, metabolic abnormalities may be even more prominent in severe FASD. In future studies it would be of interest to use contrasting groups of adolescents with ADHD and/or other learning disorders to ascertain that the results are specific to prenatal alcohol damage. Measuring the entire frontal lobes (including the orbitofrontal and dorsolateral frontal cortices) is also of interest, as the FASD group is characterized by executive dysfunction indicative of frontal dysfunction. Metabolic data should be compared to neuropsychological deficits.

Finally, to improve diagnosis and adequate support for children with FASD, the profiling of FASD against other developmental diagnoses need to continue. The present thesis compared children with FASD and SLD. Other studies have compared FASD to ADHD and a few to undefined IQ matched control groups (Crocker et al., 2009; Crocker et al., 2011; Whaley et al., 2001). Ideally, to delineate distinct neurobehavioral profiles for FASD both IQ and caregiving environment should be fully accounted for.

6. CONCLUSIONS AND CLINICAL IMPLICATIONS

The current thesis presents a comparatively large group of carefully diagnosed children and adolescents across the continuum of FASD compared to an IQ, age and sex-matched contrast group of children with SLD as well as to typically-developing peers. The studies cover a broad area of functioning in the area of FASD, including diagnosis, cognition, behavior, adaptation and brain metabolic alterations, shedding light on the conditions under which children and adolescents with FASD grow up.

Meeting a child with FASD we face someone whose development has been adversely affected by alcohol in utero. The alcohol insult may have affected neurocognitive abilities and caused somatic health problems, but it should not be forgotten that the child with FASD is often born into a high risk environment where at least one parent continues to abuse alcohol and other psychosocial risks abound. An adverse environment in combination with a vulnerable damaged brain creates a double hazard for the child growing up with FASD and may induce unreasonable obstacles for a good quality independent life.

Drinking among women of reproductive age has increased in Finland and only one in ten is abstinent. In addition, binge drinking has increased, especially among young women (Mäkelä et al., 2010). As prevalence figures from other Western countries imply, as many as 1-6 % of all children may be affected by alcohol-induced brain damage (May et al., 2009; May et al., 2011; May, 2011). In Finnish figures this would translate to between 600 and 3600 children born with FASD every year, with between 10800–64800 1-18-year-old children and adolescents suffering from FASD in Finland. If the prevalence of fetal alcohol-induced damage in Finland equals that of other Western countries FASD is no less than a significant public health problem warranting attention and resources.

FASD is not a temporary condition. It is a lifelong disability which may require medical treatment, family support, special education, and other community support services. Research has shown that adolescents and adults with FASD often face a dependent living situation and have problems with employment (Spohr et al., 2007; Streissguth et al., 2004). Young adults with FASD also experience serious problems with their own experience of parenthood (Spohr et al., 2007; Streissguth et al., 1996; Streissguth et al., 2004). The adult lives of many are characterized by alcohol and drug problems, trouble with the law and disrupted school experiences (Streissguth et al., 1996).

The costs attributed specifically to FASD are difficult to assess as a consequence of a disability might not always be apparent. For example, additional costs due to the diagnosis at the work place or in prison for an adult with FASD may be hard to count. With these limitations in mind, the direct *lifetime cost* per person with FASD has been estimated to about US$ 1.4 million and CA$ 1.8 million (1.1-1.4 million euro) in North America (Amendah, Grosse, & Bertrand, 2011; Lupton, Burd, & Harwood, 2004; Thanh, Jonsson, Dennett, & Jacobs, 2011), and the *annual* cost per person with FASD to about CA$ 25000 (20 000 euro)

(Amendah et al., 2011; Thanh et al., 2011). In the U.S.A. children with FAS incur annual medical expenditures nine times as high as those of children without FAS (Amendah et al., 2011). When considering the amount of resources required for the prevention of FASD, these efforts should be assessed in relation to the annual and lifetime costs for FASD. The effect on an affected individual in terms of human cost may be immeasurable. In clinical practice every effort has to be made to intervene and find ways to improve the lives of all children growing up with FASD.

6.1 Societal and clinical implications of FASD in Finland

6.1.1 Prevalence study

As FASD most likely constitutes as serious a problem for public health in Finland as in other Western countries, there is a need to conduct a prevalence study for FASD in Finland. The experience from other studies recommends prevalence studies to be conducted as in-school studies where a whole population of children are screened in a certain area (Aragon et al., 2008; May et al., 2011). The examinations are performed with a team of experts trained in FASD; a dysmorphologist/neurologist/paediatrician in collaboration with a (neuro)psychologist and a social worker. The optimal age for examination and an accurate diagnosis of FASD is around 6-7 years, since dysmorphology and growth are well known at that age, and neurobehavioral testing can begin to discriminate a complex array of cognitive sequelae (Aragon et al., 2008; May et al., 2011; May, 2011).

6.1.2 Information on risks with alcohol during pregnancy

Further, it would be important to implement effective strategies to inform about risks of alcohol during pregnancy, especially regarding early stages of pregnancy when many women are not yet aware of their pregnancy. As alcohol freely crosses the placenta and there is no established safe limit for alcohol consumption during pregnancy, the recommendation should still be to abstain from alcohol when planning pregnancy as well as during the entire pregnancy (European FASD Alliance, 2012; O'Leary & Bower, 2012). And while studies sometimes yield conflicting messages, the message to women should be simple and straightforward: to have the healthiest baby possible, don't drink alcohol when trying to get pregnant or during pregnancy (Grant & Astley, 2012).

6.1.3 Improving diagnostic practices

FASDs are difficult diagnoses to make which make them vastly underdiagnosed conditions (May, 2011). To accurately assess the outcomes of Finnish drinking practices during pregnancy, it is essential that an *accurate and population-tested diagnostic methodology for FASD be employed*. In this group of studies the revised IOM criteria for FASD were tested and found to be a reliable tool for differentiating among the various diagnostic groups within the FASD continuum. The adoption of these criteria requires, however, a change in current practices and national education to reduce confusion among paediatric care providers. Data

from our study cohort indicate that the lip/philtrum guide should be used for screening of FAS/PFAS in Finnish children. In addition, because of their particular prevalence in children with FASD in the Finnish population, special emphasis should be given to identifying minor anomalies of the extremities. Our studies also indicate that the weighted dysmorphology score may be a valuable tool in clinical assessment and research in children with prenatal alcohol exposure. The recognition of children with ARND remains a significant clinical challenge.

To enhance diagnostic practices *clinics specialized in FASD should be established in Finland* (Autti-Rämö, Gissler, & Ritvanen, 2011). The teams working with diagnoses, treatment and public information on FASD should include a neurologist/paediatrician especially trained in FASD (diagnosis), a neuropsychologist (neurobehavioral testing, educative input for special needs of individuals with FASD in schools/work places), a psychologist and/or social worker (parental interview, familial and social support). Ideally, the team should also be complemented with other specialists such as a special education teacher, physiotherapist, eye specialist (Stromland, 2004) and a neuropsychiatric coach. Regular screening with validated instruments should be implemented to enhance detection of developmental delays and social-emotional problems among the children (Jee et al., 2010; Jee, Szilagyi et al., 2010).

By profiling FASD against other developmental diagnoses, as in the present thesis, it has been shown that a diagnosis of FASD cannot simply be replaced by a descriptive diagnosis of ADHD, attention deficit disorder (ADD) or SLD. For fear of labeling a child or through insecurity regarding diagnosis many clinicians may avoid a diagnosis of FASD. It could be questioned, however, whether the unfair labeling is actually what happens when a child's problems are not understood due to the lack of an appropriate diagnosis. On the contrary, *a warranted diagnosis of FASD may enhance understanding and support for the child with FASD*. The results of the present thesis point in this direction as children and adolescents with ARND face more behavioral problems than children with more visible signs of their diagnosis. As the present thesis and other studies show, a child growing up with FASD faces unique challenges that have to be considered as such. Diagnostic practices should include not only dysmorphic and physical examinations, but also neurobehavioral testing, assessment of adaptive abilities as well as assessment of the child's psychosocial living environment. Following this practice should be recommended to rehabilitation teams nationwide.

6.1.4 Attending to FASD groups with enhanced risk

In particular, the FASD groups identified with enhanced risk for mental and behavioral problems in the current thesis should receive clinical attention. The groups are 1) children and adolescents with less visible signs of their diagnosis and, 2) children with FASD growing up in residential care.

The results have important implications for clinical practice, as they underscore the importance of appropriate services and care for less visibly affected children with FASD. To

improve recognition of these individuals a thorough follow-up including neuropsychological testing is warranted in cases where prenatal alcohol abuse is known but no apparent physical signs characteristic of FAS/PFAS can be detected. Likewise, children with learning-, attention- and psychosocial problems reminiscent of the neurocognitive profile for FASD should be checked for FASD. Clearly, this requires enhanced awareness and knowledge regarding FASD among health care practitioners and educators all over the country.

Furthermore, the results highlight the need to attend to children with FASD being raised in institutions. With their background of early biological and psychological impairment, compounded with less opportunity for a close and continuous caregiver relationship, such children seem to run an especially great risk of adverse life outcomes.

6.1.5 Rehabilitative support ameliorating the effects of FASD

The Finnish children examined in this thesis fared about equally well in (sufficiently recovered) birth families compared to foster/adoptive homes and it may be argued that efforts should be made to support birth families with FASD to recover. Several promising approaches to support disadvantaged and/or substance-abusing parents exist; Minding the Baby (Slade, 2002), The Mothers and Toddlers Program (MTP) (Suchman, Decoste, Castiglioni, Legow, & Mayes, 2008) and the Parents First program (Goyette-Ewing et al., 2002; Pajulo et al., 2008) among others. The Parents First program, originally developed at the Yale Child Study Center in the U.S.A., and directed towards enhancing parental reflective capacity or mentalizing, has been successfully tested with substance-abusing mothers and is at present being implemented in adapted form for first time parents in Finland on a large scale (Pajulo, Suchman, Kalland, & Mayes, 2006; Pajulo et al., 2008). Another incentive to direct support towards birth families with FASD is the fact that there is a major risk for more children being born with FASD into the same family. In the present thesis nearly half of the participants identified a sibling with an FASD diagnosis. However, if the birth family, despite extensive support, is unable to take care of their child with FASD, the child should be moved to a foster/adoptive family permanently. The results of the current thesis support the view that residential care tends not to be a suitable placement for a child with FASD. Further, foster families raising children with FASD should receive adequate support (education on FASD, support groups, consultations with specialists).

For the children and adolescents growing up with FASD every effort should be made to ameliorate the effects of the alcohol-induced brain damage. Intervention for children with FASD should be offered in clinical practice as needed. In relation to the vast amount of neurocognitive research on FASD, surprisingly little is actually known about intervention. A review from 2011 lists only 12 papers on empirically based interventions for children with FASD (Kodituwakku, 2010). These intervention projects have aimed to improve cognitive or adaptive skills in children with FASD including literacy, mathematics, working memory, self-regulation, behavior and social skills (Bertrand & Interventions for Children with Fetal Alcohol Spectrum Disorders Research Consortium, 2009; Coles, Kable, & Taddeo, 2009; Keil, Paley, Frankel, & O'Connor, 2010; Kodituwakku, 2010; Kodituwakku & Kodituwakku,

2011). In short, it seems important to combine parental support and direct interventions with children. The parental support may include increasing positive interactions with the child and reducing parental stress. The child focused part of the intervention benefits from being specifically tailored to the child's specific cognitive-behavioral profile. It seems that effects of attention and self-regulation training are more far-reaching than more domain-specific training (e.g. literacy or math) (Kodituwakku, 2010). Another promising area of intervention is parent-assisted social skills training for children (Bertrand & Interventions for Children with Fetal Alcohol Spectrum Disorders Research Consortium, 2009; Keil et al., 2010). Addition of pharmacological agents for controlling mood and hyperactivity may also be necessary. In the future dietary supplements (like choline) or cognition-enhancing drugs may be an option (Kodituwakku & Kodituwakku, 2011). For reviews on intervention in FASD see Kodituwakku and Kodituwakku (2010, 2011) and Bertrand (2009).

From a societal point of view, the goal should be to offer children growing up with FASD as favorable an environment as possible: good quality living environments with close stable caregivers, and adequate treatment including neurocognitive and psychosocial support. Through enhancing adaptive abilities of adolescents with FASD, training their social skills, daily living skills and communicative skills, a more independent life might be achieved.

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