DESCRIPTION: State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This abstract is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

The present proposal outlines a research project to be conducted on adolescents and young adults that have earlier been assigned diagnoses of Fetal Alcohol Syndrome (FAS) or Fetal Alcohol Spectrum Disorders (FASD). The general aim is to study the status in adolescence of these persons on many levels: educational and societal, cognitive and behavioral, as well as neurobiological. The first specific aim is to evaluate longterm outcome for FAS/FASD in Finland. Using questionnaires and in-depth interviews the education and professional activities as well as social functioning and mental well-being of the study group is reviewed. High rates of secondary disabilities have been reported for young adults with FAS/FASD in the United States. It is of interest to see whether the same difficulties appear in other cultures. Specifically, it would be of interest to know to what extent the secondary disabilities are influenced by the social context in which the children with FAS grow up. The second specific aim is to assess the neurocognitive profile of the FAS/FASD subjects. We intend to perform a comprehensive assessment of neurocognitive abilities, including attention and executive functioning, language, visual perception, motor functioning as well as memory and learning. The importance of a broad neuropsychological assessment has been stressed by us and by others since prenatal alcohol may affect many areas of neuropsychological functioning. The third specific aim is to obtain further information concerning the neurobiological pathology and structural abnormalities underlying impairments specific to FAS/FASD. Magnetic resonance spectroscopy (MRS) is carried out in order to study whether possible brain anatomic and metabolic deviance may underlie characteristic impairments of FAS/FASD. Results are compared with neuropsychological findings. Furthermore, Magnetic Resonance Imaging (MRI) is carried out in order to gather more understanding of the vulnerability of structural brain development during pregnancy.

PERFORMANCE SITE(S) *(organization, city, state)*

Folkhälsan Research Institute, Helsinki, Finland
Helsinki University Hospital, Helsinki, Finland
Teslamed, Helsinki, Finland

KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Principal Investigator. List all other key personnel in alphabetical order, last name first.

Name	Organization	Role on Project
Autti-Rämö, Ilona	Helsinki University Hospital	PI
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Disclosure Permission Statement. Applicable to SBIR/STTR Only. See instructions. ☐ **Yes** ☐ **No**

Finnish Proposal

Neurobehavioral outcome in adolescents with FAS and FASD

RESEARCH PLAN

a. SPECIFIC AIMS.

The present proposal outlines a research project to be conducted on adolescents and young adults that have earlier been assigned diagnoses of Fetal Alcohol Syndrome (FAS) or Fetal Alcohol Spectrum Disorders (FASD). The general aim of this project is to study the status in adolescence of these persons on many levels: educational and societal, cognitive and behavioral, as well as neurobiological. The project will be conducted as two separate studies with specific aims.

Specific Aim #1 is to evaluate longterm outcome for FAS/FASD in late adolescence and early adulthood in Finland (Study #1). Using questionnaires and in-depth interviews the education and professional activities as well as social functioning and mental well-being of the study group is reviewed. Further, alcohol and drug problems, inappropriate sexual behavior and trouble with the law are clarified. High rates of such secondary disabilities have been reported for young adults with FAS/FASD in the United States. It is of interest to see whether the same difficulties appear in other cultures. Specifically, it would be of interest to know to what extent secondary disabilities are influenced by the social context in which the children with FAS grow up.

Specific Aim #2 is to assess the neurocognitive profile of the FAS/FASD subjects (Study #1). We intend to perform a comprehensive assessment of neurocognitive abilities, including attention and executive functioning, language, visual perception, motor functioning as well as memory and learning. The importance of a broad neuropsychological assessment has been stressed by us and by others because prenatal alcohol may affect many areas of neuropsychological functioning. However, relatively few studies have comprehensively assessed the neuropsychological profile of the adolescents with FAS or FASD. Such studies are essential in order to improve existing methods of identifying and helping individuals affected by alcohol who are at risk for poor educational achievement and societal adjustment.

Specific Aim #3 is to obtain further information concerning the neurobiological pathology and structural abnormalities underlying impairments specific to FAS/FASD. Magnetic resonance spectroscopy (MRS) is carried out on the older subjects in order to specifically study brain anatomic and metabolic deviance and to compare the findings with the neuropsychological findings to try to establish an understanding of the biological underpinnings of cognitive impairments not explained by structural findings only (Study #2a). Magnetic Resonance Imaging (MRI) is carried out with the entire study group as part of the CIFASD consortium in order to gather more understanding of the vulnerability of structural brain development during pregnancy (Study #2b). The results of the structural MRI findings of the brain is also compared with the detailed neuropsychological findings

b. BACKGROUND AND SIGNIFICANCE

The impetus for this project was an international research meeting in Valencia, Spain, in 2001. On this meeting, researchers from different parts of the world reviewed the present status of FAS research as well as prospectives and needs for future research. The organizer, the National Institute for Alcoholism and Alcohol Abuse (NIAAA), encouraged international research collaboration. Subsequently, an international consortium has been envisaged as organized by Dr. Edward Riley, San Diego State University, and the NIAAA.

In Finland, a longitudinal, prospective study was carried out on children exposed to alcohol *in utero*. Following the initiative mentioned above, Dr. Riley and representatives of the NIAAA visited the research team in Helsinki to review and evaluate the possibilities to conduct new fetal alcohol research in Finland as part of the consortium. The Finnish researchers were invited to submit a research proposal to the NIAAA and were encouraged to utilize some, although not all, of the possibilities that Finland may have to offer in this realm. A unique component of this proposal is that in Finland comprehensive population records permit tracing of persons that have earlier been assigned diagnoses, which facilitates a longitudinal analysis of children with various diagnoses. Neuropsychological assessment and intervention are widely practiced by many specialized clinical neuropsychologists working in the field. Finally, Finland has a strong tradition of research employing brain-imaging techniques.

A further impetus to a study in Finland is the good public health care and educational system, which may influence the outcome in FAS/FASD in a positive direction. In Finland a free public health care system ensures all citizens equal health care regardless of income or place of living. A private insurance is not necessary to be eligible for health care. During pregnancy every woman undergoes regular health controls undertaken by a nurse and a physician. Children from 0-16 years of age undergo free regular health care check-ups. All parents receive an income-based family allowance and are entitled to day-care for children under school age. Further, health controls are also well documented. With permission from parents, data from the child's health history may be retreaved from health care records.

Children between 7 and 16 years of age are by law eligible to free education within the public school system. Only a few private schools exist in Finland. The public school system provides regular health check-ups by a school-nurse and a physician of various physiological and psychological problems (e.g. impaired growth, delayed puberty, specific learning disorders or delayed development, vision and sight, anorexia), which may require further investigations within the specialized health care system. Daily consultations (acute illness or trauma) and psychological support (concerning e.g. bullying, eating disorders or other psychic disorders not requiring special services) are also offered. In addition, most schools have access to a school psychologist and/or social worker. Special education is provided when judged necessary by the teachers. Referral to a special class is based on a recommendation by a psychologist or a physician; formal diagnoses of learning disorders are not required. The resources for special education are, however, not perceived as sufficient. All special education needs are not fully met.

In a Finnish part of the collaborative project it may be possible to obtain an idea of the extent to which good public health care and education may influence the expression of secondary disabilities of prenatal alcohol damage. Finnish persons with FASD may achieve a relatively good societal adaptation, due to the good health care and educational system. Further assets provided by a Finnish setting are the strong traditions in brain imaging.

Long-term outcome of FAS

FAS is a condition that affects the individual in most aspects of life: Achievement and adaptation in an educational and professional context, the individual's neurocognitive capacities, strengths and weaknesses, and on the level of brain organization and processes. Few systematic means have as yet been validated of how to help the affected individuals to achieve a better quality of life.

The neurobiological damage caused by alcohol prenatally is not reversible and makes FAS a life-long condition. For the individual with FAS or FASD the outcome depends on many factors such as the extent of alcohol damage, genetic and individual factors as well as the kind of family the child is raised in (see for example Stratton, Howe & Battaglia, 1996; Streissguth, 1997).

Disabilities reflecting the CNS dysfunctions inherent in the FAS or FASD diagnosis are often referred to as primary disabilities. Secondary disabilities are those that an individual is not born with, and that could presumably be ameliorated through better understanding and appropriate interventions (Streissguth, Barr, Kogan & Bookstein, 1996). The largest study done with [redacted] adults with FAS/FASD.

Neuropsychological strengths and weaknesses

Prenatal alcohol exposure seems to have relatively widespread effects on neuropsychological development. In several studies (Korkman, Autti-Rämö, Koivulehto & Granström, 1998; Korkman, Kettunen, Autti-Rämö, 2002; Riley et al., 2003) children and young adolescents with FAS have demonstrated deficits in all cognitive domains compared to control children. Impairments have been found in attention and executive functioning (Connor, Sampson, Bookstein, Barr & Streissguth, 2000; Kodituwakku, Kalberg & May, 2001; Mattson, Goodman, Caine, Delis & Riley, 1999; Riley et al., 2003), calculation and estimation (Kopera-Frye, Dehaene & Streissguth, 1996), visual-motor production, naming and receptive language (Korkman, Autti-Rämö, Koivulehto & Granström, 1998). Certain domains seem to be somewhat more strongly affected than others. In one longitudinal study (Riley et al., 2003) impairment of language and executive functions was significant across age levels. The results in the visuomotor domain and in the memory and learning domains were somewhat less consistent. Evidently, various types of tasks may be differentially sensitive at different age levels. On the whole, FAS individuals tend to perform somewhat worse on complex tests involving executive control processes than on relatively simple tests (Riley et al., 2003). In contrast to the deficits, long-term memory as well as sensorimotor differentiation and precision seem to constitute relative assets (Korkman, Autti-Rämö, Koivulehto & Granström, 1998).

The above studies are as yet preliminary. More data should be obtained from comprehensive neuropsychological assessments to obtain a full overview of neurocognitive strengths or weaknesses characteristic of individuals with FAS or FASD. If only selective instruments are used impairments on these may be taken to indicate specific impairments even if greater problems would exist in other areas of performance. Only comprehensive neurocognitive studies can reveal whether the individuals with FAS or FASD have characteristic patterns of strengths or weaknesses or a generalized cognitive impairment. The possibility also exists that impairments at a later stage of development may turn out to be simply reflections of a generalized cognitive impairment. In a follow-up of the children in the study by Korkman et al. (1998) the finding of a lower VIQ than a PIQ had been reversed. Furthermore, impairments were found on some tasks of memory and learning (Korkman, Kettunen & Autti-Rämö, 2002).

In one study from the United States (Streissguth, Barr, Kogan, & Bookstein, 1996), psychometric IQ of individuals with FAS was on average 79. In a Russian sample mean IQ was 67.9 (Riley et al., 2003). In individuals diagnosed with FAE (Fetal Alcohol Effects) an average IQ of 90 has been reported (Streissguth, Barr, Kogan, & Bookstein, 1996). Following this, most of the FAS/FASD children at least in the United States do not qualify for special education. It would be important to clarify typical specific weaknesses of these individuals. Such a clarification could facilitate their identification and direct attention to the special educational needs of this population. In addition, it is important to clarify how general intellectual ability and environmental factors influence the neuropsychological features seen in children with FAS. By better understanding these influences, it should be possible to better identify strengths and weaknesses that are specific to this population and not secondary to other factors (Riley et al., 2003)

Behavior and psychosocial functioning

Prenatal alcohol exposure has been shown to result in significant impairments of parent-rated behavioral and emotional problems (Mattson & Riley, 2000; Steinhausen, Willms, Metzke & Spohr, 2003). Particular difficulties have been seen in social, attention and aggressive domains on the Child Behavior Checklist (CBCL) that could not be explained entirely by the presence or absence of facial dysmorphology, general intellectual functioning, or demographic factors. The data was, however, based solely on the parent-report and did not include the self-report or the collateral report. It is possible that the parents do not accurately represent the behavior difficulties experienced by their children.

Behaviorally, children with FAS have been compared to children with attention disorders such as Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity Disorder (ADHD). Coles (2001) and Coles et al. (1997) reported that alcohol affected children did not have the same behavioral characteristics as children diagnosed with ADHD. Other data (Roebuck, Mattson & Riley, 1999) shows that alcohol exposed children, as a group, do not have the same pattern of personality traits when measured on the Personality Inventory for Children (PIC) as ADHD children. But although their overall profiles differed from ADHD groups, a large portion of the children in an alcohol exposed group may exhibit behaviors typically associated with ADHD.

Thus, it seems that prenatal alcohol exposure is related to significant impairments in psychosocial functioning, and that these impairments span various developmental or age levels. Although alcohol exposed children may share some behavioral characteristics with children diagnosed with attention deficit disorders, current reports on the behavioral profile of alcohol-exposed children are not conclusive. Further data, gathered from multiple sources (i.e. parent and teacher reports as well as self-reports), is needed to clarify the psychosocial functioning of individuals affected with FAS.

Structural and Neurobiological Aspects

Neuropathological studies have revealed no consistent alcohol-induced morphological alterations in the developing nervous system of infants with FAS though various midline anomalies are markedly overrepresented (Jones &Smith, 1973; Clarren et al., 1978; Pfeiffer et al., 1987; Pfeiffer et al., 1979; Jellinger et al., 1982; Ronen & Andrews, 1991; Schaefer et al., 1991). Neither have the brain imaging studies on children with FAS/FASD been able to report consistent findings. A few CT studies report cortical or subcortical dysplasia but most CT studies have been normal (Cremin & Jaffer, 1981; Schaywitz et al., 1981; Neri et al., 1988; Riikonen et a., 1993). The MRI studies have further increased the variation of structural abnormalities in FAS/FASD children. The areas of special vulnerability are suggested to be corpus callosum (Mattson et al., 1992; Riley et al., 1995; Swayze et al., 1997), vermis and/or cerebellum (Sowell et al., 1995; Hannigan et al., 1995; Autti-Rämö et al., 2002), basal ganglia (Mattson et al., 1994; Archibald et al., 2001) and parietal lobes (Archibald et al., 2001; Autti-Rämö et al., 2002). A volumetric study revealed that in addition to general hypoplasia (microcephaly) the white matter volumes seem to be more affected than gray matter volumes (Archibald, 2001).

Traditionally, glial cells were thought to have a role mainly as supportive tissue in the brain. However, later research has put in evidence that they may play an active role also in the development and metabolism of the grey matter. Glial cells serve as guiding neurons for the migration and lamination of neurons. They participate in the control of the survival of neurons through trophic factors. Recent findings have indicated that they may give rise to postnatally formed neurons in the hippocampus. Furthermore, they may promote active brain processes by serving as contacts that shuffle nutrients and metabolites between blood vessels and neurons. They may even participate actively in the neural processes by integrating neurotransmitter input and through releasing neurotransmitters of their own (see review by Kurosinski & Götz, 2002).

On a behavioral level, poorly developed white-matter structures have been thought to underlie many types of impairments of cognitive development, with arithmetic ability and many aspects of nonverbal processing being particularly affected, a so-called non-verbal learning disorder (NLD; Rourke, 1995). A suboptimal development of white-matter structures in the brain is thought to stem from an impairment of the integration of separate cortical processes into interactive neural networks (Rourke, 1995). FAS is one of the syndromes that is thought to be characterized by NLD and white-matter hypoplasia (Don & Rourke, 1995). The recent finding of Archibald et al. 2001 that the white matter volume is more affected than grey matter volume supports this hypothesis. There are, however, also other possible mechanisms of influence of glial hypoplasia on cognitive processes, including disordered neuronal migration with dysplasias as consequences, as well as an influence on on-line metabolism during cognitive processes.

The hypothesis of a white-matter hypoplasia as one cause of cognitive impairment has received much attention in the neuropsychological literature, but very little substantive evidence has been obtained. Recent methodological developments, including applications of the spectroscopy methods, might permit a more reliable separation of white and grey matter. Magnetic Resonance Spectroscopy (MRS) is a new technology with the capacity of measuring molecular and also metabolic underpinnings of brain development and neurocognitive functioning (Minshew & Pettigrew, 1996). With MRS it is possible to study the relationship between glial and grey matter structures (Kurosinski & Götz, 2002; Moreno, Roos & Bluml, 2001).

Clinical observations of individuals with FAS/FASD would suggest that these individuals may have a poor ability to cope with the demands put by society on general orientation, decision making, and judgement. Such impairments have been found to be part of a pattern of generalized impairment (Korkman et al., 2002). Although the executive functions impairments may thus not be clearly more impaired than other domains of cognition, they may actually be particularly incapacitating in adolescence and early adulthood when people are required to acquire functional and economic independence. In view of the clinical indications of frontal lobe dysfunction it is of interest to evaluate whether the clinical expression of executive functions in young persons with FAS/FASD are related to possible frontal metabolic abnormality using the MRS technique. It would also be a new perspective in the studies concerning the neural bases of cognitive disorders in general.

c. PRELIMINARY STUDIES.

In an earlier prospective longitudinal study children exposed to alcohol *in utero* for varying durations were assessed. Pregnant women who reported consumption exceeding 140 g alcohol per week were recruited to a study and 82 gave their permission for a follow-up of their children (Halmesmäki, 1985, Halmesmäki et al., 1986; 1987). The children were subsequently followed until early adolescence. They were seen by the principal investigator, Ilona Autti-Rämö at the ages of 4 months, 6 months, 12 months and 18 months (Autti-Rämö et al., 1991a,b). At the age of 2 years a dysmorphological assessment was performed by a blind evaluator (Autti-Rämö et al., 1992). At the ages of 2 years, 7 years and 12 to 14 year the examinations also included comprehensive neuropsychological studies (Autti-Rämö et al., 1992; Korkman et al., 1994; 1998; 2003; Riley, 2003). The neuropsychological findings indicated widespread and relatively diffuse impairment that was particularly evident in the children that had been exposed throughout pregnancy. Impairments were seen on subtests from all domains of neurocognitive development. Yet, certain domains seemed to be somewhat more strongly affected than others were. Impairment of language and of attention and executive functions was significant across age levels. The results in the visuomotor domain and in the memory and learning domains were somewhat less consistent. Across the studies, the effects of duration of alcohol exposure were clear. The children to mothers who continued to drink throughout pregnancy were most affected. In contrast, the groups of children exposed only during trimesters I and II performed in the low average to average range. Considering the possibility of variations in task sensitivity the most robust finding of the follow-up was that of relatively widespread and diffuse neurocognitive effects of alcohol exposure *in utero*.

Marit Korkman has been responsible for the neuropsychological parts of the study. She is the senior author of a neuropsychological assessment which is in wide use in the United States and internationally, the NEPSY—A Developmental Neuropsychological Assessment (Korkman, Kirk & Kemp, 1997, 1998). She has also conducted a number of studies on various groups of children with compromised neurocognitive development (Korkman, Granström, Appelqvist & Liukkonen, 1998; Korkman & Häkkinen-Rihu, 1994; Korkman & Peltomaa, 1991; 1993; Korkman & Pesonen, 1994; Korkman, Liikanen & Fellman, 1996; Korkman, Renvaktar & Sjöström, 2001; Korkman & von Wendt, 1995), as well as on normal neuropsychological development (Korkman, 2001; Klenberg, Korkman & Lahti-Nuuttila, 2001; Korkman, Barron-Linnankoski & Lahti-Nuuttila, 1999, Korkman, Kemp & Kirk, 2001). Further, she has participated in neural imaging studies on children (Autti-Rämö et al., 2002; Olsén et al., 1998; Paetau et al., 1999), and contributed on assessment issues to international special journal issues and textbooks (e.g., Korkman, 1995; 1999a; 1999b; in press; Kemp, Kirk & Korkman, 2001).

Further, MRI examinations were undertaken on part of the children with school problems (Autti-Rämö, 2002). 17 children with the diagnosis of FAS (5), FAE (7) or ARNDB (5) from a prospective follow-up study volunteered to participate. In 11 children abnormalities of vermis were observed, other abnormalities (hypoplasia of corpus callosum, small hippocampi, enlarged liquor spaces) were less common. The manual motor tasks correlated with head circumference. No other structural finding correlated with the neuropsychological findings.

Two of the consultants - neuroradiologist Nina Lundbom and chemist Sami Heikkinen have a large experience in MRS studies (Aitio, Annila, Heikkinen, Thulin, Drakenberg & Kilpeläinen, 1999; Heikkinen & Kilpeläinen, 1999; Heikkinen & Kilpeläinen, 2001; Heikkinen, Aitio, Permi, Folmer & Lappalainen, 1999; Heikkinen, Kangasmäki, Timonen, Kankaanranta, Häkkinen, Lundbom, Vähätalo, Savolainen, 2003; Heikkinen, Mesilaakso & Rahkamaa, 1998; Heikkinen, Permi & Kilpeläinen, 2001; Heikkinen, Rahkamaa & Kilpeläinen, 1997; Heikkinen, Rahkamaa & Kilpeläinen,1998; Heikkinen, Toikka, Karhunen & Kilpeläinen, 2003; Koenig, Brown, Spiller & Lundbom, 1990; Lundbom, Barnett, Bonavita, Patronas, Rajapakse, Tedeschi & DiChiro,1999; Lundbom, Gaily, Vuori, Paetau, Liukkonen, Valanne, Häkkinen & Granström, 2001; Näntö-Salonen, Komu, Lundbom, Heinänen, Alanen, Sipilä & Simell,1999; Permi, Heikkinen, Kilpeläinen & Annila, 1999a; Permi, Heikkinen, Kilpeläinen & Annila, 1999b; Permi, Kilpeläinen & Heikkinen,1999; Permi, Kilpeläinen, Annila & Heikkinen, 2000; Tedeschi, Bertolino, Lundbom, Bonavita, Patronas, Duyn, Verhagen, Chase & DiChiro, 1996; Tedeschi, Litvan, Bonavita, Patronas, Lundbom, DiChiro & Hallet 1997; Varho, Komu, Sonninen, Holopainen, Nyman, Manner, Sillanpää, Aula & Lundbom, 1999) though they haven't specifically studied MRS in FAS/FASD. Neuroradiologist Nina Lundbom is the leading MRS expert in Finland and is the head of the MRS imaging both at the University Central Hospital in Helsinki and at the Helsinki University of Technology. Neuroradiologist Leena Valanne is the leading neuroradiologist in neuropediatrics in Finland and she has a wide experince with MRI studies both in children and adults (Cannon, van Erp, Huttunen, Kaprio, Lönnqvist, Salonen, Valanne, Poutanen & Standertskjöld-Nordenstam, 2000; Cannon, van Erp, Huttunen, Lönnqvist, Salonen, Valanne, Poutanen & Standertskjöld-Nordenstam, 1999; Cannon, van Erp, Huttunen, Lönnqvist, Salonen, Valanne, Poutanen, Standertskjöld-Nordenstam, Gur & Yan, 1998; Cannon, van Erp, Rosso, Huttunen, Lönnqvist, Pirkola, Salonen, Valanne, Poutanen & Standertskjöld-Nordenstam, 2002; Gaily, Appelqvist, Kantola-Sorsa, Liukkonen, Kyyrönen, Sarpola, Huttunen, Valanne & Granström, 1999; Koskinen, Valanne, Ketonen & Pihko, 1995; Lundbom, Gaily, Vuori, Paetau, Liukkonen, Rajapakse, Valanne, Häkkinen & Granström, 2001; Pihko, Louhimo, Valanne & Donner, 1992; Pihko, Tyni, Virkola, Valanne, Sainio, Hovi & Saarinen, 1993; Qvist, Pihko, Fagerudd, Valanne, Lamminranta, Karikoski, Sainio, Rönnholm, Jalanko & Holmberg, 2002; Raininko, Elovaara, Poutiainen, Virta, Valanne, Haltia & Lähdevirta, 1997; Raininko, Elovaara, Virta, Valanne, Haltia & Valle, 1992; Salonen, Valanne, Lamminen, Blomstedt, StandertskjöldNordenstam, Haugen & Wallen, 1995; Santavuori , Valanne, Autti, Haltia, Pihko & Sainio, 1998; Tienari, Salonen, Wikstöm, Valanne & Palo, 1992; Toivanen, Valanne & Tatlisumak , 2002; Valanne, Ketonen & Berg, 1996; Valanne, Ketonen, Majander, Suomalainen & Pihko, 1998; Valanne, Paetau, Suomalainen, Ketonen & Pihko,1996; Valanne, Pihko, Katevuo, Karttunen, Somer & Santavuori, 1994; Virkola, Lappalainen, Valanne & Koskiniemi, 1997). Dr Valanne has also participated in the earlier MRI study of our study group (Autti-Rämö, 2002).

d. RESEARCH DESIGN AND METHODS

Study #1. Neurocognitive profile and longterm outcome of adolescents and young adults diagnosed with FAS or FASD.

Rationale

This study consists of two parts, with the following aims:

(1) To clarify the behavioral, psychosocial and educational status of the subjects. The types and magnitude of secondary disabilities that are associated with FAS/FASD in Finland will be

evaluated. Problems that significantly hamper the performance of the subjects in every-day life, and risk and protective factors that influence the rates of occurrence of secondary disabilities are identified.

(2) To describe the neurocognitive test profile of adolescents and young adults with FAS/FASD, and to compare it to that of a contrast group of subjects with ADHD, without FAS/FASD, as well as to a normal control group. Characteristic strengths and weaknesses of the FAS/FASD group are described.

A third, less explicit aim is to study to what extent good health care and schooling provided by society may influence the expression of secondary disabilities of prenatal alcohol damage. The severity of the primary, FASD-related neurocognitive impairments is compared with the severity of the secondary disabilities. We expect to demonstrate that Finnish persons with FASD achieve an internationally relatively good societal adaptation. It is to note that this international comparison will probably only be the subject of a discussion of results rather than put in evidence by direct measurements.

Methodology

Subjects

In the planned study adolescents and young adults diagnosed as FAS or FASD (n=40-60) between 12 and 20 years of age are included in this study. The young adults (aged 18 to 20) are recruited from a prospective follow-up study (Autti-Rämö et al., 1991 ab; 1992 ab; Korkman, 1998; Autti-Rämö, 2000; Korkman, 2003) in which the length and dosing of prenatal alcohol exposure has been verified during pregnancy (Halmesmäki, 1988). The adolescents are recruited from a clinical patient pool at the Hospital for Children and Adolescents, University of Helsinki. From the clinical records it can be seen that during the study years (1983-1993) 5 to 10 children per year have been given the diagnoses of FAS/FASD. Most of these children have been diagnosed during infancy or before school age, and the prenatal alcohol exposure could be verified retrospectively from the mother. Most of the children with FAS have been taken into custody, but children with FASD live either with biological or foster parents or in orphanages. Other substance abuse (cannabis, heroin, amfetamin etc) during pregnancy was very rare in Finland before the late 90s and the study group is thus not expected to include children with mixed prenatal substance exposure. To ensure that diagnostic procedures are similar across different projects involved in the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), consultations by dysmorphologist MD Eugene Hoyme from the Dysmorphology Core are possible. Medical case records, recent photos as well as photos of the subjects at a younger age (when available) are examined. Further, semistructured and structured interviews of the caregivers are conducted by Åse Fagerlund or Ilona Autti-Rämö.

In addition, a *normal control group* (n=30) and a *contrast group* (n=30) consisting of same-aged subjects are assessed. The contrast group is to have a comparable cognitive level as the FAS/FASD group, according to psychometric test findings performed at a younger age (see below). Therefore, the contrast group can be specified only after scrutinizing the medical records of the FAS/FASD group. If the FAS/FASD subjects in the sample have a relatively good cognitive level, the contrast group will consist of subjects with ADHD/ADD. If their cognitive level is generally poor, the contrast persons of choice will be those with general learning disorder (LD). The control group and the contrast group are matched with the FAS/FASD groups with respect to age, gender, geographical region and, if possible, SES. In addition, the contrast group will also be matched on IQ.

The control group is recruited by stratified random sampling from a defined population stratum. The distribution of the FAS/FASD group on geographical region, gender and age and, if possible, social background (SES and/or parental education) is determined. The appropriate number of control subjects will be sought from the appropriate geographical region: Helsinki region, other city/town, rural area, taking areal differences into account (different parts of cities/towns have different social structures). If permission is obtained from the municipalities persons with the appropriate gender and age are identified from the medical records of the school health controls. A second option is to advertise the need for voluntary participation in schools, high-schools and larger employers. The matching will be performed primarily as a one-to-one matching procedure but as completely matching pairs of subjects is rarely achieved the aim is to obtain comparable groups.

The contrast group is recruited from the files of patients at the Helsinki University Hospital, following the study of medical records of the persons with FAS/FASD. First, the geographical region, gender, age and social background (SES and/or parental education if possible), as well as previous IQ data of each FAS/FASD subject is determined. Thereafter, a corresponding contrast group is recruited from the selected diagnostic group as obtained from the case files of the Helsinki University Hospital case files.

Other than having prenatal alcohol exposure, or problems with attention/hyperactivity all participants will be healthy. As Finland has two official languages, an inclusion criterion is that one of them, Finnish or Swedish, is the primary language spoken. Exclusion criteria are as follows: Significant head injury with loss of consciousness more than 30 minutes, significant physical (e.g., uncorrected visual impairment or cerebral palsy) or psychiatric disability (e.g., psychosis) that would preclude participation, and other potential causes of mental deficiency (e.g., congenital hypothyroidism, neurofibromatosis, chromosomal abnormalities). Subjects will also be excluded from the contrast and control groups if prenatal alcohol exposure is known or suspected or information is unavailable. Regarding race only Caucasian persons are participating, since it is the prevalent racial population in Finland.

Assessments

Assessments include, first, in-depth interviews and questionnaires administered to the subjects, their caregivers, teacher, or other adult who knows the subject well. The overall aim is to obtain insight into the behavioral, psychosocial and educational outcome of FAS adolescents and young adults. Further, comprehensive neuropsychological assessments are undertaken. The included measures assess the following cognitive domains: general intellectual functioning, attention and executive functions, learning and memory, language, visual-spatial functioning, visual-motor abilities and, academic functioning. Tests conform to the Core Assessment proposed by the CIFASD. Tests included in the Core Battery are the Vineland Adaptive Behavior Scales-Revised (Sparrow, Balla & Cicchetti, 1984), the Youth Self Report checklist (Achenbach, 1991), Leiter International Performance Scale-Revised (Stoelting, 2001), Cambridge Neuropsychological Test Automated Battery (Sahakian & Owen, 1992), Delis-Kaplan Executive Function System (Delis, Kaplan, & Kramer, 2001), Beery Developmental Test of Visual Motor (Beery, 1989) and, the Grooved Pegboard Test (Trites, 1989). In addition, a number of other tests are administered (as described below). Assessments are done by Åse Fagerlund and one or two research assistants (graduate students) supervised by the key investigators.

Interviews and questionnaires

Life History Interview (LHI). The LHI by Streissguth et al. (1996) was developed to focus on secondary disabilities and risk and protective factors that characterize clients with FAS/FASD. The

LHI is a comprehensive structured evaluation of ten major areas of possible long-term functional covariates or consequences characteristic of clients diagnosed with FAS/FASD:

(1) household and family environment
(2) independent living and financial management
(3) present educational and
(4) vocational status
(5) physical abuse, sexual abuse and domestic violence
(6) physical, social and sexual development
(7) behavior management and mental health issues
(8) alcohol and drug use
(9) legal status and criminal justice involvement
(10) companionship and parenting (will be used where relevant)

The LHI has proven to be a useful instrument being used with several hundred diagnosed FAS/FASD clients in the United States. It is administered to caretakers or other informant that knows the client well at the same time as the neuropsychological tests are administered to the subject. The administration time is about 70 minutes. Comparable data from both a control group and a contrast group (ADHD/ADD or LD) are collected as well.

Vineland Adaptive Behavior Scales-Revised (VABS-R). The VABS-R (Sparrow, Balla & Cicchetti, 1984) measures adaptive behavior in 4 domains: communication, socialization, daily living, and motor behavior. It will be used to give a quantitative picture of adaptive skills and impairments in young individuals with FAS/FASD. In Finland, the VABS has been used for clinical purposes but no normed data is available. Therefore, comparison of data between control, contrast and subject groups is undertaken as well as comparison with U.S. norms. VABS-R is one of the measures recommended for use by the CIFASD to enable cross-cultural comparison. As the VABS-R is developed for persons under 19 years of age results for subjects older than 18 years of age will be used with caution or excluded from analysis. Four variables representing the four domains and the composite score will be analyzed. The VABS-R is completed by caretakers or other informant that knows the client well at the same time as the neuropsychological tests are administered to the subject.

Fetal Alcohol Behavior Scale (FABS). FABS (Streissguth, Bookstein, Barr & Press, 1996) is a screening tool consisting of 36 items constructed to reflect the behavioral phenotype of typical fetal alcohol behaviors. Research by Streissguth et al. (1996) and Streissguth, Bookstein, Barr, Press & Sampson (1998) indicate that an average person with FAS/FAE is characterized by three times as many of the items as an average person without fetal alcohol damage. The FABS score has adequate test-retest reliability and is uncorrelated with age, sex, race, and IQ. Items cluster under two general headings: difficulty modulating incoming stimuli and poor cause-and-effect reasoning. The FABS can be used with clients from childhood to adulthood and has maximum usefulness from age 2 up to age 35 (Streissguth, Bookstein, Barr, Press & Sampson, 1998). Thus, it is suitable for use with the present study group. FABS is translated into Finnish and has been used for clinical purposes as an outcome measure in neuropsychological intervention with FAS children (unpublished data). Finnish norms are not available. The FABS is completed by caretakers or other informant that knows the client well as well as by teachers (and if relevant, employers).

Questionnaire for evaluating performance and behavior related to attention and executive functions (The Finnish Questionnaire). A Finnish questionnaire for evaluating performance and behavior related to attention and executive functions is currently under development (Klenberg, Sutinen, Häyrinen, Korkman & Heiskari, in preparation). Expected publication year is 2004. At present (spring 2003) the instrument is pilot tested by Psykologien Kustannus, the main test publisher in Finland. The questionnaire was developed with the aim of obtaining data on the practical consequences of dysexecutive problems. It is expected to be on the market for Finnish psychologists by January 2004. The questionnaire is completed by teachers and parents.

Domains that are evaluated are: 1) Impulse control, 2) Motor hyperactivity, 3) Distractibility, 4) Focused attention, 5) Sustained attention, 6) Flexibility in shifting attention, 7) Power of initiative, and 8) Regulation of own activity. Each domain consists of around 10 items depicting a behavior. Each item is rated on a three-point scale (not a problem - sometimes a problem – often a problem). The questionnaire is in this study completed by caretakers or other informant that knows the individual well. In addition, also teachers (and if relevant, employers) complete the questionnaire.

Youth Self Report checklist (YSR). The YSR checklist developed by Achenbach (1991) is used to obtain the views of the adolescents' own perception of their psychoemotional competencies and problems. It provides an overview of the subjective well-being and possible self-reported signs of psychopathology in an individual. All subscales are administered. The scale was developed for youths who have at least fifth-grade reading skills, but can be administered orally to those who have poor reading skills. The results are expressed as two competence scales (Activities and Social) and three summary scales (Internalizing, Externalizing, and Total) scores. Finnish and Swedish versions of the YSR are in clinical use in Finland.

Previous test results. Previous test results will be collected from the patient files:
(a) WISC-R (Wechsler, 1984) has been administered to all subjects when they were in school-age;
(b) Subtests from NEPSY (or earlier versions named NEPS and NEPSU; Korkman, 1980; Korkman, 1988, 1988) have been administered as well. Since the examinations of subjects have been done for clinical purposes, the subtests administered vary between subjects. The subtests that have been administered in the majority of cases are selected and recorded.

In addition to the formal data collection, data are collected from the files concerning the home environment and caregiver of the FAS/FASD participants during the childhood years. Among other things all evidence of changes of primary caregiver is noted as well as the number of times the child was taken in custodial care, age at placement in foster home, the length of time a biological father has been a significant support to the child, and, when the biological mother has been the primary caregiver, any indication of the severity of her alcohol abuse. Further, the special therapies (e.g. speech and language therapy, medical treatment of ADHD) and special education obtained by the FAS/FASD participant is recorded when evident in the files. The participant and adult informant will also be asked about these data in structured interviews.

Developmental external risk and protective factors are evaluated based on the obtained data concerning home environment throughout earlier development. It is assumed that an optimal developmental (early placement in a foster home, or biological parents -- mother and/or father -- who were able to provide a warm and secure home environment) will act as a protective factor so that they influence the outcome variables in a positive direction. Another modifying factor may be the amount of special therapies and/or education provided to the individuals with neurocognitive and learning impairments.

Neuropsychological Test Battery

Leiter International Performance Scale-Revised (LIPS-R). The LIPS-R (Stoelting, 2001) was developed and standardized in the Unites States for individuals 2 – 20 years of age. It provides an assessment of nonverbal cognitive ability (the Visualization and Reasoning Domain battery; VR) as well as an assessment of attention and memory (the Attention and Memory Battery; AM). The complete battery ranges from 10 to 20 subtests depending on age. The VR Battery requires about 40 minutes to administer and the AM Battery, about 35 minutes. The LIPS-R is correlated with other frequently used measures of ability, including the WISC-III (.85). It also includes "growth" scores that can be used to assess progress in children with developmental disability and to chart relatively small difference in cognitive performance over time or between groups.

The LIPS-R has several characteristics that make it appropriate for the Collaborative Study. It is completely nonverbal and does not require verbalization from either examiner or child. The child is not required to read or write any material. For this reason, the same form can be used in different countries and in different cultural groups. The norms are based on a United States population. In this study, the Swedish version of the manual is used.

Cambridge Neuropsychological Test Automated Battery (CANTAB). CANTAB is a computerized behavioral battery originally developed for assessment of cognitive deficits in humans with neurodegenerative diseases or brain damage (Sahakian & Owen, 1992). It consists of 13 interrelated computerized tests of memory, attention and executive functions and allows for a decomposition of complex clinical tasks into their cognitive components. CANTAB has been validated in neurosurgical patients and patients with basal ganglia disorders, Alzheimer's disease, depression, and schizophrenia (Dorion et al., 2002; Dorin, Duyme, Zanca, Dubois & Beau, 2001; Elliott, Robbins, McKenna & Sahakian, 1998; Fray & Robbins, 1996) but has also recently been used for measuring executive functions in childhood (Hughes & Graham, 2002).

CANTAB uses non-verbal stimuli and a touch screen for recording responses, which allows testing with limited verbal requirements and provides accurate measurement of reaction time. Testing is conducted on an Advantech PPC 120 computer with a 12-inch touch-sensitive screen. All participants are seated 60 cm away from the screen to discourage resting a hand on the computer and are administered the same subtests in the same order. CANTAB testing takes 30-45 minutes. The test includes the following subtests: Motor Screening, Big-Little Circle, Pattern Recognition Memory, Spatial Recognition Memory, Delayed Matching to Sample, Paired Associates Learning, Spatial Span, Intra-Extra Dimensional Shift and, Stockings of Cambridge. The nonverbal nature of the CANTAB subtests makes them largely language independent and culture free. CANTAB forms part of the core battery of the consortium and will serve as a tool for cross-cultural comparisons.

Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001*).* D-KEFS is an individually administered series of tests used to assess key components of executive functions, both verbally and spatially. It is a standardized test used to assess higher-level cognitive functions in both children and adults and was normed on individuals ranging in age from 8 to 89 years old. There are nine tests within D-KEFS: Sorting, Trail Making, Verbal Fluency, Design Fluency, Color-Word Interference, Tower, 20 Questions, Word context, and Proverb. In the present study Verbal Fluency and the Design fluency will be used. These subtests correspond to subtests administered earlier to many of the FAS/FASD test persons and may provide an idea of development in this area. The NEPSY. A Developmental Neuropsychological Assessment (Korkman, Kirk & Kemp, 1998) is a neuropsychological instrument that is widely used in Finland. The subtests in NEPSY that correspond to the above are the Verbal Fluency and Design Fluency subtests.

Beery Developmental Test of Visual Motor Integration (VMI). The VMI assesses visual-motor integration by requiring the child to copy 24 geometric figures and is one of the measures recommended for use by the CIFASD (Beery, 1989). This test is constructed to measure the level of visual-motor development. Each design is harder than the last and testing is continued until three consecutive figures are failed. There are two supplemental tests: the VMI Visual Perception and the VMI Motor Coordination tests. These tests use the same stimulus forms and thus are comparable to the main test. Normative U.S. data are available for ages 3-18. Results for subjects older than 18 years of age are in this study used with caution or excluded from analysis. Administration time is approximately eight minutes.

Grooved Pegboard Test. The Grooved Pegboard Test is also recommended for use by the CIFASD to enable cross-cultural comparison and consists of a pegboard with 25 grooved slots (Trites, 1989). The subject is required to place a grooved peg into each of the slots first with the right hand and then the left hand. The time to complete the task with each hand is recorded. Normative data are available for children ages five to 16. Thus, results for subjects older than 16 years of age are used with caution or excluded from analysis. Administration time is approximately 8 minutes.

Wechsler Intelligence Scale for Children-Third Edition (WISC-III) or Wechsler Intelligence Scale for Adults-Third Edition (WAIS-III) Vocabulary and Comprehension. In our earlier comprehensive neuropsychological assessments of children and adolescents exposed to prenatal alcohol language skills have been among the most affected domains of neurocognitive development (Korkman et al., 1998; Korkman et al., 2002). A few verbal tests are therefore necessary additions to the nonverbal, cross-cultural core battery. One of the most robust tests of verbal performance level is the Wechsler Scales subtest Vocabulary (Wechsler, 1991; Wechlser, 1997). This subtest has a correlation with Verbal IQ (VIQ) of .78 in the Finnish norm data for the WISC-III (Wechsler, 1999). A second subtest of choice is the Comprehension subtest which has the second highest correlation with VIQ of .77. Together these two subtests will give an estimate of VIQ.

NEPSY subtests of verbal capacities. In Finland there are no standardized neuropsychological tests for the adolescents range. In practice, the most widely used neuropsychological instrument for patients aged 12 to 22 is the NEPSY. A Developmental Neuropsychological Assessment (Korkman, Kirk & Kemp, 1997; 1998). The test is standardized only up to age 12 years 11 months, however, preliminary norm data exist for adolescents aged 13 years 0 months to 14 years 11 months (see Korkman, Kettunen & Autti-Rämö, 2002). Three of the more complex language-based subtests are administered. For these subtests the results from the control group is used as a norm reference. In the validation study undertaken in conjunction with the standardization of the NEPSY in the United States (Korkman, Kirk & Kemp, 1998) these subtests were those that discriminated FAS children most strongly from carefully matched control subjects. Similar results were obtained in the recent study on Finnish adolescents exposed to prenatal alcohol (Korkman, Kettunen & Autti-Rämö, 2002). The subtests are shown to have sufficient variation (no ceiling effect) at the 12-year-level to be sensitive in a normal population of 12-year-olds. Developmental curves tend to show only marginal increase in neuropsychological tests after age 5 to 10 years (Korkman, Kemp & Kirk, 2001). Individuals with FAS/FASD are not expected to perform above that level. Moreover, NEPSY subtests have been administered to the present FAS/FASD test persons on previous clinical assessments. The following subtests are included:

Auditory Attention and Response Set. This is a test of selective attention to verbal stimuli. It also puts demands on mental set and control and thus on executive functions. The test person listens to a long array of words, presented on audiotape. On the first part of the subtest, the Auditory Attention task, the test person takes a red token from a pile of tokens of various colours whenever the word “red” is said, and drops it into a box. On the second part, the Response Set task, the test person drops a yellow token in the box whenever the word “red” is said, a red token whenever the word “yellow” is said, and a blue token whenever the word “blue” is said.

Memory for Names. This subtest is a name learning task. Eight line drawings of children's faces are presented. Each drawing is named and the test person repeats the name. After that the test person is shown the drawings and is asked to recall the names. Correct responses are provided when necessary. This procedure is repeated twice. Half an hour after the immediate recognition task the drawings are shown again and the test person is asked to name them (delayed recognition). The names of the Finnish, North American and Swedish standardized test versions are specific to the culture of each country.

List Learning. This subtest is a verbal learning task similar to the California Verbal Learning Test (Delis, Kramer, Kaplan & Ober, 2000). The test person is read a list of 15 unconnected words and repeats as many he/she remembers. The procedure is repeated four more times, after which a new (interference) list is taught once and recalled. The test person is, thereafter, asked to recall the first list once more, and again half an hour later.

Lukilasse. To measure academic achievement it is necessary to use tests with norms in accordance with the education system in the country in question. In Finland one such test called *Lukilasse* (Häyrinen, Serenius-Sirve, Korkman, 1999) has recently been developed and standardized. Lukilasse includes measurements of performance on reading speed, reading comprehension, spelling and arithmetics.

Procedures

A letter with general information about the study will first be sent to the selected subjects in all groups. If subjects and their caregivers consider participating in the study, they will be contacted (phone or letter) by one of the researchers. During their first visit to the clinic, the procedures and content of the study will be carefully explained to the subjects and their parents. If they agree to participate forms of informed consent will be given and signed before any testing begins. All testings will take place at the Folkhälsan Research Institute in central Helsinki on 2 different visits with a duration of approximately two hours each. The subjects will be tested individually by a psychologist (Åse Fagerlund) or a graduate student under supervision of the key investigators. During one of the testing sessions parents are interviewed with the Life History Interview (conducted by Åse Fagerlund or graduate student). Parents also fill in the requested questionnaires. Permission for contacting teachers will be asked and, if granted, teachers will get the appropriate forms (FABS and the Finnish questionnaire) sent to them by mail.

Data is kept in hard copy form in a locked archive cupboard in a room assigned for the study at Folkhälsan. On the record forms each individual name is given a number. The data will be entered in a software statistics file (SPSS) by using the code number only. The permission to submit part of the data (test results) to the consortium, with no means of identifying individual subjects, is applied for from the relevant Ethical Committee.

Statistical analyses and expected results

The results of the questionnaires are used to describe the behavioral, psychosocial, educational and vocational status of the subjects. Problems that significantly hamper the performance of the subjects in present every-day life will be specified as well as the types and magnitude of secondary disabilities. The findings will be compared to that of the control and the contrast groups.

Statistical calculations include ANOVA of the results on VABS-R and base rates (percentages) of questionnaire findings of secondary disabilities, executive functions problems, and psychopathological indices. Comparison of the FAS/FASD group and the contrast group with respect to these base rates are undertaken using cross tabulation or other nonparametric statistics and, when applicable (sufficiently normally distributed parameters) ANOVA.

It is expected that the FAS/FASD individuals will have relatively more secondary disabilities and executive functions problems as evaluated by the questionnaires LHI and the Finnish executive functions scale. Similarly, the VABS-R will discriminate the groups.

The neurocognitive test results of, first, general psychometric intelligence (estimated VIQ; LIPS-R), and, second, separate neurocognitive abilities (sum scores based on test intercorrelations) forming group test profiles of the FAS/FASD, the control group and the contrast group are compared. Characteristic patterns are described.

To compare the test profiles multivariate analyses of variance will be undertaken when applicable (comparable error variances in groups). When error variances are not comparable a repeated measures ANOVA will be undertaken for the same purpose. This method of analysis has been called profile analysis because it permits entering numerous (max. 20) subtests as dependent variables in the same ANOVA (Tabachnick & Fidell, 1996). An alpha level of .05 will be employed. Post-hoc analyses, power analyses and effect size analyses (e.g. eta squared) will be undertaken in connection with the ANOVA's.

Based on earlier results it is expected that language and attention tests as well as tests purported to measure executive functions will discriminate most strongly between the FAS/FASD group and the control group. Visuomotor tests, tests of nonverbal reasoning and of nonverbal memory will be discriminate less strongly. In all, the test profiles pf the FAS/FASD group will show widespread and diffuse impairments.

The results of the questionnaires examining secondary disabilities are also related to the neurocognitive test results. We seek to establish to what extent secondary disabilities (total score on FABS, and on YRS; are explained by neurocognitive status (cognitive ability evaluated by LIPS-R) as well as specific neurocognitive variables (executive functions tasks, attention tasks, verbal tasks) using hierachical, fixed-order (theory-driven) multiple regression analysis. The aim is to see to what extent primary neurocognitive impairments explain the secondary disabilities.

It is hypothesized that both cognitive level as evaluated at a younger age and present dysexecutive problems will explain the difficulties of the subjects to achieve a good mental health and educational and vocational status as young adults. It is hypothesized that, compared to the contrast group the FAS/FASD will have more secondary disabilities than would be expected on the basis of the general psychometric intelligence. These secondary disabilities will be mainly due to dysexecutive problems.

Based on all these results characteristic strengths and weaknesses may be identified that may serve as markers for identifying subjects affected by alcohol but without the typical facial appearance.

Further, the influence of protective/risk factors: childhood home environment, therapies and special education is evaluated. Variables formed of these measurements are entered into the obtained hierarchical multiple regression model. An alpha-level of .05 is maintained.

Finally, the possibilities of comparable, cross-cultural studies by comparing the regression coefficients ratio with those obtained in other countries will be explored. A comparison of the relationship between primary and secondary abilities in the FAS/FASD group with corresponding figures obtained in other countries could give insight into the extent to which the societal context may exert a modifying influence on the consequences of fetal alcohol exposure.

Study #2. Magnetic Resonance Spectroscopy (MRS) findings and Structural Brain Imaging (MRI) of 12- to 20-year-olds diagnosed as having FAS or FASD.

Rationale

This study includes two parts, undertaken with MRS and with MRI. The main aim of this study is to study the brain pathology underlying characteristic impairments of FAS/FASD subjects, and to compare both MRS and MRI findings with neuropsychological findings.

Methodology - MRS (Study #2a)

Subjects

The subjects for the MRS study are recruited from the older patients to analyse characteristic features of FAS/FASD (n=20; see Study #1 for closer information on patient recruitment). Ten age-matched normally performing young adults are recruited for controls. Subjects are excluded from the study if they have any metal implants, or are pregnant.

Procedures

The MRS study is performed by a 1.5 Tesla Siemens Sonata MR-Imager with a 3D-spectroscopy program at the University Central Hospital, Helsinki. The 3D program allows acquisition of spectral information from 800ml of brain during a 17 min acquisition time. The main volumes of interest (VOI) to test our hypothesis on the relation between glial and grey matter structures are frontal and parietal lobes and basal ganglia. According to our previous study the most frequent abnormal structural finding observed visually in MRI was hypoplasia of vermis and thus another VOI will be cerebellum. The metabolic functional brain imaging requires the children to stay motionless in the magnet camera for approximately 45 to 60 minutes, the acquisition time being 17 min for each VOI. Successful investigations require careful preparation of the subjects and ability to stay motionless for a longer period than needed for normal MRI. Therefore, only the older adolescents/young adults in the study are recruited for the MRS. An imaging series to allow segmentation, i.e. determination of the volumes of GM, WM and CSF of the brain is also collected (10min).

Statistical analysis and interpretation of results - MRS

The hypothesis is that the MRS reveals metabolic changes in the white matter and in the grey matter and give information on the status of the glial cell and the neural cell populations components. The spectra in VOI are analysed with a the Siemens system software using a lineship fitting procedure which will provide numerical results for Cho, Cr and NAAA resonance integrals peak areas. Statistical comparisons between groups and correlational analysis are performed to seek relationships between neurobiological parameters and neuropsychological test results.

Methodology - MRI (Study #2b)

Subjects

All adolescents and young adults (age range 12-20) with FAS/FASD entering the study are assessed with MRI; patient recruitment is described in the corresponding section in Study #1. However, subjects are excluded from the study if they have any metal implants, or are pregnant.

Procedures

The MRIs are purchased from a private neuroradiologic clinic Teslamed. Anatomical MR images are obtained using a Siemens Vision Symphony 1.5 T scanner. The structural scan consists of a 3-dimensional magnetization prepared rapid gradient echo (3-D MPRAGE) T1-weighted MRI scan (TR, 11.08 ms; TE, 4.3 ms; flip angle 88). The slice thickness being 1.2 to 1.5 mm. Imaging parameters can be altered as a result of image inspection by the Imaging Core investigators (ref core imaging protocol). The time interval for data acquisition is 30 minutes, the longest period for one data acquisition being 5 minutes. According to our previous experience with FAS children it is possible to conduct the study in this age range without anesthesia.

Assessments

Images are evaluated visually by an experienced neuroradiologist (Leena Valanne) who has participated in the earlier structural imaging study of FAS/FASD children with the research group. The detailed visual analysis is important in order to evaluate whether MRI of the brain can be a useful tool in clinical practice when the FAS/FASD diagnosis is being considered. More detailed analyses of the imaging data are analysed as part of the CIFASD consortium under the supervision of Dr Elizabeth Sowell, UCLA (see the imaging protocol for details on the analysis).

Statistical analysis and interpretation - MRI

Studies published this far have shown a large variation in structural abnormalities after prenatal alcohol exposure. The consortium provides the possibility to gather a larger amount of imaging data (both structural and volumetric) to identify the areas that are most vulnerable. It also provides the possibility to perform correlational analysis between structural data and neuropsychological findings. As drinking habits differ between various countries and cultures it may also be possible to identify whether the pattern of drinking is linked to special brain pathology.

e. HUMAN SUBJECTS

Protection of Human Subjects

1. Risks to subjects

Human Subjects Involvement and Characteristics

Participants for this proposed study are adolescents and young adults with FAS/FASD as well as a contrast group of ADHD/ADD and normally developing controls. Adolescents will range in age from 12-20 years of age and approximately 120 children will be included. Groups will be similar in terms of age, gender, race, and socioeconomic status. Other than having prenatal alcohol exposure, or problems with attention/hyperactivity all participants will be healthy. As Finland has two official languages, another inclusion criterion is that one of them, Finnish or Swedish, is the primary language spoken. The exclusion criteria are as follows: Significant head injury with loss of consciousness more than 30 minutes, significant physical (e.g., uncorrected visual impairment or cerebral palsy) or psychiatric disability (e.g., psychosis) that would preclude participation, and other potential causes of mental deficiency (e.g., congenital hypothyroidism, neurofibromatosis, chromosomal abnormalities). In addition, subjects will be excluded from the brain imaging parts of the study (Study #2) if they have any metal implants, or are pregnant. Subjects will be excluded from the contrast and control groups if prenatal alcohol exposure is known or suspected or information is unavailable. Adolescents and young adults are the main focus of this research because it has proven to be a period when difficulties originating from fetal alcohol syndrome culminate. Furthermore, intellectual disability is common in the majority of individuals with FAS/FASD and thus their inclusion is necessary.

Source of Materials

Data collected for the proposed studies will be in the form of test results, questionnaires, and interviews, as well as records from brain imaging assessments (MRS and MRI). All data will be obtained specifically for research purposes. Hospital records including the patients' medical history will be used with permission from parents/caregivers and hospital's ethical committee.

Potential Risks

There are no potential social, economic, or legal risks to the subjects and only minimal psychological and physical risks. It is possible that the subjects will experience frustration because of poor performance on the neuropsychological tests. This risk will be managed by utilizing reasonable criteria for discontinuation for all tasks. On tasks that are administered via computer, there is a small risk of eyestrain or headache from staring at the computer screen. This risk will be managed by limiting the amount of time on any one task wherever possible. In addition, the child's comfort level will be monitored throughout the testing, and testing will be discontinued if necessary. Further, there are no known adverse effects from exposure to magnetic fields (MRS and MRI). However, there is a certain discomfort related to the need of staying motionless during the imagings. The imager makes a loud, banging noise while it is taking pictures. Some subjects undergoing this procedure may become anxious. If at any time during the testing the subject feels anxious, the testing will be stopped.

2. Adequacy of protection against risks

Recruitment and Informed Consent

Adolescents and young adults diagnosed as FAS/FASD (n=40-60) between 12 and 20 years of age are included in this study. The young adults (aged 18 to 20) are recruited from a prospective follow-up study in which the length and dosing of prenatal alcohol has been verified during pregnancy. The adolescent children are recruited from a clinical patient pool from the Hospital for Children and Adolescents, University of Helsinki. In addition, a *normal control group* (n=30) and a *contrast group* (n=30) consisting of same-aged subjects are assessed. The control group is recruited by stratified random sampling from a defined population stratum. The distribution of the FAS/FASD group on geographical region, gender and age and, if possible, social background (SES or parental education) is determined. The appropriate number of control subjects will be sought from the appropriate geographical region: Helsinki region, other city/town, rural area, taking areal differences into account (different parts of cities/towns have different social structures). If permission is obtained from the municipalities persons with the appropriate gender and age are identified from the medical records of the school health controls. A second option is to advertise the need for voluntary participation in schools, high-schools and larger employers. The matching will be performed primarily as a one-to-one matching procedure but as completely matching pairs of subjects is rarely achieved the aim is to obtain comparable groups. The contrast group is recruited from the files of patients at the Helsinki University Hospital, following the study of medical records of the persons with FAD/FASD. First, the geographical region, gender, age and social background (SES and/or maternal education), as well as previous IQ data of each FAS/FASD subject is determined. Thereafter, a corresponding contrast group is recruited from the selected diagnostic group as obtained from the case files of the Helsinki University Hospital case files.

Informed consent will be obtained from parents or legal guardians of all participants. Following IRB approval, one of the researchers will review an informed consent document with each parent and subject and any questions will be answered. The informed consent document will include a description of the study and any potential risks (as described above) or benefits. In addition, assent will be obtained from all subjects themselves.

Protection Against Risk

The minimal psychological risk of frustration during the neuropsychological testing will be managed by utilizing reasonable criteria for discontinuation for all tasks. For the risk of eyestrain, the risk will be managed by limiting the amount of time on any one task wherever possible. In addition, the child's comfort level will be monitored throughout the testing, and testing will be discontinued if necessary. Regarding the brain imaging part of the study there are no known adverse effects from exposure to magnetic fields (MRS and MRI). Potential risks will be minimized through a careful interview of exclusion criteria before any testing begins (e.g. if the subject has any metal objects in his/her body or is pregnant). If subjects for any reason become anxious during the brain imaging sessions the imaging will be stopped.

3. Potential benefits for the proposed research to the subjects and others

All participants and their parents/caregivers will get a summary of the test results from the comprehensive neuropsychological testing. In addition, on request, and only with written permission of the legal guardian, test results will be provided to the health care providers or teachers in order to improve care of the child. The results from the MRS and MRI studies may not directly benefit the participants.

4. Importance of the knowledge to be gained

The knowledge to be gained from the proposed research centers around improving our understanding of the effects of heavy prenatal alcohol exposure on brain function in adolescents and young adults. Although all individual participants may not benefit directly, the knowledge gained from this research may help to identify a profile of strengths and weaknesses in individuals with heavy prenatal alcohol exposure and subsequently improve treatments available for this population. Thus, the importance of the research far outweighs the minimal risk it involves.

Inclusion of Women

Participants in the proposed series of studies will be both male and females. Five of the six key personnel are female.

Inclusion of Minorities

Participants in the proposed series of studies are male and female adolescents and young adults. No racial or ethnic group will be excluded, but the population in Finland is almost exclusively Caucasian and, hence, subjects will likely consist only of Caucasians.

Inclusion of Children

Participants in the proposed series of studies are male and female adolescents and young adults in the age range of 12 to 20 years.

Data and Safety Monitoring Plan

Not applicable.

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Statistical Analysis

Statistician – To be appointed