



# FETAL ALCOHOL FORUM<sup>©</sup>

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May 2009

## INTRODUCTION

Though much attention is paid to alcohol harm throughout life, alcohol damage caused before birth is under-recognised and under-diagnosed.

To increase recognition of Fetal Alcohol Spectrum Disorder (FASD) and to promote collaboration between medical professionals, Lord Mitchell and the National Organisation for Fetal Alcohol Syndrome – UK ([NOFAS-UK](http://www.nofas-uk.org)) brought together Presidents of the Royal Colleges, leading researchers and healthcare professionals to launch the FETAL ALCOHOL FORUM. The inaugural meeting took place in the House of Lords, London, England in January 2009.

In our first issue we are honoured to have original articles contributed by eminent doctors and researchers around the world.

We are privileged to have a contribution from Dr Kenneth Jones who in 1973, with his colleague Dr David Smith, first identified and named Fetal Alcohol Syndrome (FAS) in the United States. We are also pleased to introduce new groundbreaking research by Professor James Reynolds and colleagues, who have developed an FASD eye-tracking diagnostic tool.

Original articles are followed by abstracts/links to recent FASD collaborative studies from the USA, Canada, England, Scotland, Northern Ireland, Finland, Spain, Argentina and China.

The FETAL ALCOHOL FORUM is a bi-annual publication. If you would like to contribute an original article, an overview of fetal alcohol issues in your country, new studies or other information of interest to the international medical community, please go to [contribute](#). We also welcome your [feedback](#).

Please feel free to forward this newsletter to colleagues and others interested in FASD. If you would like to be a part of the FORUM network, click on the [link](#).

NOFAS-UK would like to thank Lord Mitchell for making the FORUM possible, Jo Egerton for research and editorial expertise, Chantel D'souza the FORUM Co-ordinator and Point 6 Designs Ltd for the FORUM logo design.

Susan Fleisher  
Executive Director  
NOFAS-UK



**Tuesday, 13<sup>th</sup> January 2009 the FETAL ALCOHOL FORUM  
House of Lords, London, England.**

**PHOTO:** (Front Row) Dr Ron Gray, National Perinatal Epidemiology Unit, University of Oxford, Susan Fleisher, Director NOFAS-UK, M Attwell, Chair NOFAS-UK, Lord Mitchell, Prof Ian Gilmore, President Royal College of Physicians, Prof Sabaratnam Arulkumaran, Presiednt RCOG, Liz Stephens, President Royal College of Midwifery, (Second Row) Dr Margaret Barrow, Hon Lecturer, Depart of Genetics, University of Leicester, Dr Margaret Boyle, Senior Medical Officer, DHSS, Northern Ireland, Prof Wendy Atkin, Imperial College, Dr Elisabeth Rosser, Consultant Geneticist, Great Ormond Street Hospital, Lady Mitchell, Phyllis Teesdale, Trustee, (Third Row), Dr Kieran O'Malley, Consultant, Adolescent Psychiatrist, Belfast, Sir Ross Cranston, Trustee, Dr Raja Mukherjee, St Georges Hospital Medical School, Richard Lynn, British Paediatric Surveillance Unit, RCPCH, Celia Atkin, Founding Patron, (Fourth Row), Dr Philippa Russell, Chair, Prime Minister's Commission on Carers, National Children's Bureau, Robert Phipps, DHSS, Northern Ireland, Dr Patricia Hamilton, President, RCPCH, Prof Sheila Hollins, Former Pres, Royal College of Psychiatrists, Prof of Psychiatry, St Georges University, George Roycroft, Senior Policy Executive, BMA, author-BMA FASD Guide, Dr Maggie Watts, Chair, Scottish Association of Alcohol and Drug Action Teams, Crispin Acton, Programme Manager, DH Alcohol Policy Team, Peter Atkin, Trustee, Anne-Marie Winstone, Research Midwife, Addenbrooke's Hospital, Cambridge, Prof Barry Carpenter, Fellow, U. of Oxford, RSM.

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**The National Organisation for Fetal Alcohol Syndrome UK**

157 Beaufort Park  
London NW11 6DA  
England

Tel: 020 8458 5951

Fax: 020 8209 3296

Email: [nofas-uk@midlantic.co.uk](mailto:nofas-uk@midlantic.co.uk)

Website: [www.nofas-uk.org](http://www.nofas-uk.org)

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*\*In the interest of brevity, Fetal Alcohol Spectrum Disorder has been abbreviated to FASD*

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## RECOGNITION AND HISTORY OF THE FETAL ALCOHOL SYNDROME

Kenneth Lyons Jones M.D.

Division of Dysmorphology/Teratology, Department of Pediatrics, University of California, San Diego School of Medicine, La Jolla, CA. USA

A similar pattern of altered growth and morphogenesis, referred to as the Fetal Alcohol Syndrome (FAS), was reported in 1973 in eleven unrelated children all of whom were born to chronic alcoholic women who continued to drink heavily throughout pregnancy<sup>1,2</sup>. Soon after those initial reports, evidence became available indicating that an association between heavy maternal alcohol consumption and serious problems in the offspring was not a new observation.

For example, in response to outcries from social critics regarding the extent of alcohol consumption in 18th century London, a select committee of the British House of Commons was established in 1834 to investigate drunkenness, prior to the establishment in that same year of an Alcoholic Licensure Act.<sup>3</sup> Evidence presented to that committee indicated that infants born to alcoholic women sometimes had “a starved, shriveled, and imperfect look” Thereafter, in 1899, Dr. William Sullivan investigated female alcoholics at the Liverpool Prison.<sup>4</sup> He was able to document an increased frequency of early fetal death and early infant mortality in their offspring. Despite these worrisome indications that maternal alcoholism might lead to developmental anomalies in their offspring, no serious evaluation of the problem was undertaken and the medical community generally remained agnostic regarding this issue.

That was in fact the case in February 1973 when Dr. David Smith was asked by Dr. Shirley Anderson, who directed the Pediatric Outpatient Clinic at the King County Hospital, to come down from his office at the University of Washington to evaluate eight children all of whom had been born to alcoholic mothers. As Dr. Smith's Postdoctoral Fellow in Dysmorphology, I accompanied him. Those eight children were there that morning thanks to the intellectual curiosity and perseverance of Dr. Christie Ulleland, a Pediatric Resident at the University of Washington. One night five years earlier Dr. Ulleland was informed by an Obstetric Resident that an alcoholic woman was in labor and that delivery was imminent. She raced to the library to find out everything she could about the effects of alcohol on fetal development and discovered that there was no information. Based on that lack of data, she set out to learn everything she could about the subject. From 1968 to 1969, she was able to ascertain eleven babies who had been born to alcoholic women. Soon thereafter, Dr. Ulleland accepted an opportunity to join a Pediatric Practice in the Seattle area and she turned over the care of those children to Dr. Shirley Anderson.

Dr. Anderson invited eight of those eleven children to the Pediatric Outpatient Clinic at King County Hospital that morning for an evaluation. As we went from one child to the next, it became clear that four of the eight had a very specific pattern of malformation that included microcephaly, short palpebral fissures, and a smooth philtrum. Later that day we searched for children with those same three features in Dr. Smith's unknown file which included hundreds of children with birth defects that he had evaluated over the years but had been unable to



diagnose. Two children were identified with the same three features and when we went back to look at their mother's charts, we discovered that both children had been born to alcoholic women. Over the next week, we identified two additional children, one in Dayton, Ohio where Dr. Smith was a visiting professor and one at the Children's Orthopedic Hospital and Medical Center in Seattle. Soon after what we thought were the initial publications describing the Fetal Alcohol Syndrome we became aware of a study published by Dr. Paul Lemoine of Nantes, France. I wrote Dr. Lemoine and he wrote back saying that he had published a paper in 1968 in which he identified features very similar to what we had described in the Lancet. "However", he wrote, "my French colleagues did not believe me then and they do not believe me to this day".

It is important to recognize that Lemoine's colleagues in France were not the only naysayers. If something as common as alcohol, it was reasoned, had such a profound effect on fetal development, it would have been recognized years before as a human teratogen. Ironically, observations regarding the adverse effects of alcohol on fetal development had previously been made. Unfortunately no one took those observations seriously. It took someone with immense creativity, intelligence and energy, who trained himself to observe trifles on a physical examination, to make others recognize the importance of that observation. That man was David W. Smith.

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Original Article, 13 January 2009

## FASD IN THE UK AND ITS IMPACT ON AFFECTED CHILDREN AND ADULTS

Dr Raja Mukherjee,

Consultant psychiatrist and FASD specialist, Surrey and Borders Partnership NHS Foundation Trust, Bracketts resource centre 116 – 118 Station Rd East, Oxted Surrey RH8 0QA [raja.mukherjee@sabp.nhs.uk](mailto:raja.mukherjee@sabp.nhs.uk)

Fetal Alcohol Spectrum disorders describe a range of conditions in affected fetuses that are caused by the ingestion of Alcohol by a pregnant mother. Whilst the amount and quantity of alcohol required to cause harm as well as the individual variability in risk factors continues to draw headlines, the effects on the children and adults often goes unrecognised. Research has shown how difficult it can be to recognise cases of FASD, especially non dysmorphic ones, however it has been further shown that the presence of facial features does not necessarily relate to severity of difficulties.

In the UK the prevalence of Alcohol consumption in pregnancy has been shown to vary, but most reported figures estimate the rate at around 55-60%. This is in contrast to the 90% who drink regularly in the UK. The identification of pregnancy often occurs with the first missed period. Fortunately for many this will remain within the safe period for a pregnancy as until the maternal fetal connection is made the embryo is not affected by maternal consumption. Subsequent drinking can however have an effect. The brain, unlike the face, continues to develop throughout the entirety of pregnancy. Early (first trimester) development is related mainly to broad structure formation, whilst the third trimester is related to rapid expansion of white matter, gliosis and cell migration. These can also be linked to periods where harm occurs. Work on basic animal models, where other factors can be controlled, have shown that all these mechanisms and more can be affected by alcohol in pregnancy. Alcohol is a very non specific drug in terms of its interaction and increasingly complex mechanisms of action are being established.

For those affected the nature of the problems seen is also unresolved. Whilst internationally much work has been undertaken in terms of correlating psychological deficits, relating this to phenomenological outcomes is yet to be established. The relationship between behaviour, psychological deficits and different psychiatric diagnoses require clarification. Seeing children and adults referred to a national FASD diagnostic and functional assessment clinic (as part of a wider specialist neurodevelopmental clinic) insight and hypotheses can be developed. These require later more detailed scientific observation and study. The findings from the first cohort have been submitted for publication. Whilst the work conducted in the clinic represents a pilot of methodology by applying principles from behavioural phenotype research it does allow differences in presentation to be explored and compared. One clear finding is that the aetiological factors in a human population cannot be easily controlled for in small scale studies. Often these children present with mixed confounders of poly substance abuse and neglect. Despite this however in cases where these confounders do not occur similar patterns appear to be presenting themselves. This requires further clarification and more rigorous testing before firm conclusions about the relationship between alcohol and the various neurodevelopmental and behavioural outcomes can be established.

Further there is a perceived lack of knowledge in both the general public and professionals about FASD. Anecdotal and evidence from direct feedback at conferences would suggest this to be the case, yet what is actually understood and known has yet to be scientifically studied. The ethical difficulties of researching this subject and the perceived distress it may cause requires different types of methodology to be adopted in order to establish these suppositions as fact. This work is hoped to commence in 2009.

FASD was an area often neglected in UK research in the past with almost 20 years of under activity whilst many other parts of the world continued to show concern for the damage alcohol may be causing. The UK now has much to offer to the international literature on this subject through close collaboration and joint approaches.

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## FAS IN SCOTLAND THE START OF A PERSONAL JOURNEY

Dr Maggie Watts

Consultant in Public Health Medicine, NHS Ayrshire & Arran  
Chairperson, Scottish Association of Alcohol and Drug Action Teams

Up till 2003, I had not considered the effects of alcohol on the unborn child during more than a decade of involvement in alcohol misuse. My focus had been on adults and, on occasion, on children whose parents or carers drank. With a public health perspective, I was concerned with a drug that causes a wide array of health, social and criminal problems, being responsible for more than 41,600 acute hospital admissions in Scotland (2007) and 2371 deaths directly related to alcohol (2005) – more than enough of a challenge!

As with other changes in my medical career, my involvement in FAS can be laid at the door of an encounter with an influential clinician – in this case, consultant paediatrician John McClure, who had a longstanding interest in FAS. Over a thirty two year period, John had acquired a caseload of some thirty children with FAS, and more siblings and others with FASD. A retrospective study of these children indicated an incidence of FAS in Ayrshire and Arran of 0.2/1000 live births. This is at the lower end of the reported incidence rates for the US of 0.2-1.5/1000 live births obtained from surveillance programmes, the most similar form of study. With this level of incidence for a consultant with a special interest in the condition, I then wondered whether the rest of Scotland reflected this, bearing in mind the high volume of alcohol consumed in Scotland and the known levels of health damage.

It is very difficult to obtain an accurate picture of conditions such as FAS in Scotland. It does not form a category that is routinely reported. Scottish recording systems are based mainly on deaths – and FAS is not a fatal condition of itself - and hospital admissions – and children with FAS don't tend to need hospital admission as a result of their condition. The other routine recording systems, such as the child health surveillance scheme or the congenital defects register are also selective as to who is recorded and do not cover all areas of Scotland. Since FAS, whilst present at birth, may not be recognised until later in life, there is the potential for considerable under-reporting of its incidence. Data collected centrally indicates numbers in single figures each year (Table 1) and is derived from an answer to a Scottish parliamentary question in 2007. Dawn Primarolo, answering a question on the incidence of FAS in the House of Commons in October 2008, indicated that it was not possible to provide accurate figures on the number of babies born with the condition.

Table 1. Incidence of FAS in Scotland 1996-2005 – number and rate per 1000 births for singleton births

Year	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005 (prov)
Number	4	6	3	1	4	5	4	2	10	0
Rate	0.07	0.1	0.05	0.02	0.08	0.1	0.08	0.04	0.2	0

Despite being unable to find an accurate indication of incidence, I continued to find out about FAS. A survey of local health, social care and education professionals indicated an awareness of the condition, little current practical experience but considerable concern about the potential for missed cases and the overshadowing of alcohol damage by the emphasis during pregnancy on illicit drug use. They also intimated that they did not feel confident in providing support and information for families. This was reinforced when I contacted adoption agencies and was contacted by affected families – they felt that professionals needed more training and information about FAS and FASD in order to be able to support them. They also expressed concern about the length of time taken and delays in the process for obtaining the diagnosis of FAS.

I used this information and discussion with colleagues across Scotland as indicative of a need to inform professionals more about FAS and simple ways in which it could be managed. In July 2005, with the support of the Scottish Association of Alcohol Action Teams and FASAware, we held a one day national conference attended by more than one hundred people on FAS with Dan Dubovsky, from the FASD Center for Excellence, US, as keynote speaker. This day, whilst very useful in bringing the diagnosis to the attention of a wide range of staff, was only of limited value in the absence of a plan to raise awareness of FAS and enhance training and skills. So we needed a plan...

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Original Article, 13 January 2009

## FETAL ALCOHOL SYNDROME – THE GENETICIST’S VIEW

Dr Shane McKee, Clinical Geneticist, Northern Ireland

*Dr Shane McKee is a Clinical Geneticist for the Northern Ireland Regional Genetics Service, based at Belfast City Hospital. The Genetics Service is closely interlinked with other aspects of the National Health Service, and receives referrals from many sources. Most of the caseload involves families with genetic disorders, including familial cancers, but a significant element is the diagnosis and assessment of birth defects and intellectual disability, caused by genetic and environmental factors. Like other regions of the UK and Ireland, Northern Ireland has seen an increase in referrals querying a diagnosis of Fetal Alcohol Syndrome, and a real need exists for information and support for families and health professionals.*

Alcohol ingested during pregnancy is a proven morphological and neurological teratogen – next to nicotine, the most common toxic substance to which fetuses are exposed in utero. Considerable evidence has been amassed which shows that disorders due to fetal alcohol exposure are a significant drain on health service resources, have a significant adverse effect on development and long term prospects, and proportionally disadvantage families from lower income groups. Direct causal links between these problems and alcohol have been established.

Dysmorphologists (doctors, generally clinical geneticists and paediatricians, specialising in the diagnosis of malformation syndromes) have long recognised a specific malformation syndrome associated with alcohol ingestion during pregnancy – the Fetal Alcohol Syndrome (FAS). Typical findings in a child with FAS are:

- Developmental delay / long-term intellectual disability
- Behavioural problems, resembling ADHD & autism, with disruptive behaviour, lack of awareness of personal safety, difficulty concentrating, etc.
- Microcephaly (overall small brain size, due to permanent loss of neurons)
- Short stature and overall growth deficiency
- Specific facial anomalies, such as narrow palpebral fissures, hypertelorism, arched eyebrows, small nose, long smooth philtrum, thin upper lip, micrognathia
- Neonatal jitteriness, hypoglycaemia, intra-uterine growth retardation, temperature instability

The full FAS picture is only seen in a minority of fetuses exposed to alcohol, and it seems that the timing during the pregnancy, as well as the amount, and genetic and nutritional factors in both the mother and fetus may play a role in determining the severity of the effects. A general safe upper limit of alcohol during pregnancy has not been established (contrary to some media reports), although (perhaps obviously) lower levels are associated with fewer problems. The only advice that has been shown to be unambiguous, understood, and applicable for general roll-out to pregnant women is to completely abstain from alcohol during pregnancy.

Some children have problems that do not meet the criteria for a full diagnosis of FAS, but nevertheless it is felt that their problems derive from alcohol exposure. FAS is therefore one end of a spectrum of “Fetal Alcohol Spectrum Disorders” (FASD). This spectrum incorporates “Alcohol-Related Birth Defects” (ARBD), “Alcohol-Related Neurodevelopmental Disorders” (ARND), and “Partial FAS” (PFAS), although these categories are somewhat loosely-defined, and are not always consistently used in some of the literature.

Because of the difficulties in defining very precise categories along the spectrum, many researchers and diagnosticians use the “four-digit code” (4DC) classification system, which allows data to be captured objectively, and has been shown to be helpful in avoiding some terminological pitfalls. The 4DC has four panels, each representing an aspect of FAS. Each panel is scored from 1 to 4, 1 being “not present”, to 4 being “definitely present”. The four panels are: growth deficiency, facial features of FAS, CNS features of FAS and history of prenatal alcohol exposure. The last panel is often the most difficult to assess, given that history may be very unreliable, but at the end of the process, a child will have a diagnostic code which can be used in clinical follow-up and epidemiological analysis.

Often, a child with suspected FAS is evaluated in a clinic without the biological parents being present; they may be brought along by a foster parent or a social worker. Thus, at best, the history of maternal alcohol ingestion is often second hand, and the story may be influenced by multiple factors. Even when the parents are present, recall of precise amounts of alcohol taken, and their timing, may be vague or impossible to estimate with any accuracy.

There is no specific diagnostic test for FAS, which presents problems if a child is being assessed for adoption or some other services – the diagnosis is purely clinical. This means that it is important for all the information to be available at the time of the diagnostic clinic. There are a number of other genetic conditions which can mimic certain features of FAS. These include Cornelia de Lange syndrome (CDLS), Velocardiofacial Syndrome (VCFS), and

chromosomal microdeletions and duplications (dupdels). It is therefore vital that the people diagnosing FAS have experience in dealing with these other conditions, so that they can be excluded. Indeed, this is why many children are referred to Clinical Geneticists in the UK. Importantly, some of these conditions may be passed from parent to child, and may themselves be associated with learning problems. Low intelligence in mothers may itself be a risk factor for alcohol intake in pregnancy, so teasing out these aspects, and separating as far as possible the “nature” from the “nurture” is vital. The picture may be further complicated by the use of other recreational drugs, including nicotine, which themselves are potentially damaging.

As if that were not enough, young adults with FAS are themselves probably more likely to end up with an alcohol problem, thus potentially handing the problem down for another generation. This “transmission” of FAS is also more likely, because by definition they will carry the genotypes (as yet undetermined) that rendered them more susceptible to alcohol damage in the first place. The extent of this problem remains to be clarified, but it at least underlines the need for services to be provided for these patients when they leave the paediatric system. When a child has been diagnosed with FAS, subsequent siblings (and indeed previous siblings) must be regarded as being at particularly high risk of also being affected. Prevention of recurrence is enormously important – both in general family planning and in resolving alcohol dependence.

The precise incidence of the full Fetal Alcohol Syndrome in the UK is not known, but epidemiological data from across the world, including some studies in regions of the UK suggests an overall level of about 1 per 1000 children. This is of a similar order to the rate for Down syndrome. If the net is widened to include children born with some degree of damage attributable to alcohol exposure, the rate has been conservatively estimated as about 1/100. As such, it dwarfs most other genetic causes of childhood intellectual disability, with a consequent massive effect on the economy and health services, not to mention local communities, which are very often at the sharp end of deprivation.

There are a number of issues that need to be addressed, in terms of prevention and management. These carry resource implications for government, but should not be dodged.

- Consistent government advice must remain that alcohol should NOT be ingested in pregnancy at any level, or at any time (including after the pregnancy when breast-feeding), unless alternative advice can be shown to be safe over the level of a population. Alcoholic beverages should be labelled; media advertising should be used to get the message across
- Proper education and training of health professionals needs to be carried out to ensure that this message reaches all women who are pregnant or considering a pregnancy
- Identification of mothers with an alcohol problem, and intensive support during and after the pregnancy must be a priority. Specific training of antenatal staff should be carried out to help them identify such patients, and a clear referral stream needs to be in place to allow these pregnancies to be managed
- Children with suspected FAS should have ready access to diagnostic services in Clinical Genetics and ongoing management and therapies in Community Paediatrics. More resources need placed in both these areas to allow services to be delivered, and data to be captured

- Biological and adoptive families need additional support to maximise developmental outcomes for these children, and (critically) to lessen the risk of a recurrence

We need to grow up to the serious adverse effect of alcohol exposure on fetuses. Alcohol affordability, even with the current economic downturn, continues to rise; availability is easy; girls are starting to drink at an earlier age, and in greater amounts. No woman actively wants to harm her baby, but for these vulnerable families, the information and the support services are frequently unavailable; health professionals may fail to spot the warning signs, or themselves may be ignorant about the problems. FAS is preventable, so we have a moral duty to prevent it.

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Original Article, 13 January 2009

## **TRANSCONTINENTAL PSYCHIATRIC EXPERIENCE WITH FOETAL ALCOHOL SPECTRUM DISORDERS (FASD)**

Dr. Kieran D. O'Malley  
Child and Adolescent Psychiatrist  
Royal Victoria Hospital/Young Peoples Centre  
Belfast Trust, Belfast, N. Ireland

Introduction: This paper will briefly summarise my clinical experience with children and adolescents with FASD, either the dysmorphological Foetal Alcohol Syndrome (FAS), or the non-dysmorphological Alcohol Related Neurodevelopmental Disorder (ARND), gained over the last nineteen years in Canada, the USA and Ireland.

In the early 1990s I started a clinic for assessment and management of FAS or ARND (Fetal Alcohol Effects as it was known before 1996). The clinic was one of six out-patient child psychiatric clinics in the Child and Family Unit of the Glenrose Hospital, Edmonton with Dr. Alan Carroll as the Chief of Child and Adolescent Psychiatry. The clinic saw patients from a wide geographic area which included Yellowknife, 1,000 miles from Edmonton. I had visited the pioneer FAS clinic in Seattle, run by Dysmorphologist, Dr. Sterling Clarren, and in Saskatoon run by Psychologist, Dr. Jo Nanson. Although the early patients tended to be First Nations by the time the clinic closed five years later at least one third were Caucasian. At one point I did an analysis, subsequently published of thirty three sleep deprived EEGs which were all read by the same paediatric neurologist. The patients all had IQs over 70 and were aged 7 – 19 years of age. Seven were abnormal, all showing Complex Partial Seizure Disorder which responded to carbamazepine. A number of these patients had been referred because of failed response to previous antipsychotic treatment. All the patients presented with a combination of varying levels of consciousness associated with motor episodes often triggered by severe emotions. They, as well, described either auditory or visual hallucinations.

This clinic was a mixture of birth children and adopted or foster children. The birth children commonly grew up in a world of domestic violence and pervasive alcoholism. The clinical challenges of unravelling the psychiatric/behavioural presentation which was a legacy of

organic brain dysfunction from prenatal alcohol exposure from the toxic environmental stressors of early neglect, abandonment or violence was a constant challenge. Nevertheless, it was in the structured adoptive or foster homes that the complex developmental neuropsychiatric sequelae of prenatal alcohol could be seen. The commonest clinical presentation of FAS or ARND (diagnosed FAE at this period) was ADHD, usually the Combined type, with a mixture of physical hyperactivity, impulsivity and inattention. Most patients did not have mental retardation but had a variable mix of specific learning disorders, including mathematics disorder, reading disorder and disorder of written expression.

In the early days of the Edmonton clinic the education system did not recognise FAS or ARND as learning disorders worthy of special education, but a lasting legacy of the clinic is the recognition that both FAS and ARND represent true learning disorder which are not just related to mental retardation.

Clinical medicine is never done in a vacuum, and well respected scientific research from Professor Ann Streissguth in Seattle and Claire Coles in Atlanta among others had already established the patterns of complex learning disorders related to prenatal alcohol exposure.

In the mid 1990s I had moved all my clinical practice to Calgary and now saw psychiatric consultation patients from Alberta, British Columbia and some from Saskatchewan. Developmental neuropsychiatry became my primary clinical interest and patients with FAS, ARND and Autistic Spectrum Disorder became my main focus. During this period it became more clinically apparent that methylphenidate did not seem to be as efficacious for the ADHD of FAS or ARND patients and dextroamphetamine appeared to be a better fit. This was shown in an initial published retrospective study of 30 children and adolescents with FAS or ARND who had ADHD. The other psychiatrists in the study were Dr. Dohner, Montana and Dr. Koplín, South Dakota.

Two other clinical issues stood out during this consultation period.

(i) Many patients had undiagnosed language problems which were in the receptive language area of social cognition and communication and not in the expressive/articulation language area.

(ii) A number of patients presented clinical features consistent with diagnosis of Autistic Spectrum Disorder or Aspergers Disorder (Jo Nanson had already published this observation). I continued this consultation clinic one week a month from 2000 to early 2006.

In 1997 I was fortunate to receive a medical scholarship from the Alberta Medical Association to study at the University of Washington, Seattle, with Professor Ann Streissguth one of the academic research pioneers of FAS. The condition FAS was first named and described by Ken Jones and David Smith in two classical papers in the 1973 Lancet, and Professor Streissguth was the neuropsychologist who analysed the children in the initial papers. I was affiliated with the Department of Psychiatry and Behavioural Sciences and Fetal Alcohol and Drug Unit at the University of Washington from 1997 until early 2006 when I returned to Ireland.

The clinical issues seen and studied during this time that were most striking included:



(i) The risk of suicide in adolescents and young adults with FAS and ARND which appeared related to low frustration tolerance and organically driven impulsivity and not melancholic depression.

(ii) The prevalence of patients with FAS or ARND in juvenile justice systems or adult jails. It was through brain imaging, especially MRI, that the structural damage to the corpus callosum, hippocampus, and cerebellum were being demonstrated in many areas around the world including Seattle. The concept of executive function disorder became a touchstone for understanding irrational, random antisocial acts in patients with FAS or ARND.

(iii) Patients exposed to prenatal alcohol craved alcohol from an early age, had a greater risk of alcohol dependency in adolescence or young adulthood than those with just a family history of alcoholism.

This brings my clinical journey to Ireland. At the moment I am undertaking a clinical analysis of the first fifty children and adolescents with either FAS or ARND seen since returning three years ago.

The clinical presentation of ADHD is less prevalent than in Canada or the USA, but Severe Mood Instability (not unlike rapid cycling bipolar disorder), Conduct Disorder or Aspergers Disorder are more common presentations.

There are immediate striking clinical issues which overwhelm the NHS clinical practice are:

- The high prevalence of prenatal binge drinking exposure,
- The high number of families in which trans-generational FAS or ARND is interwoven into their fabric. Thus creating pervasive disorganised attachment paradigms,
- The presence of early significant trauma which creates a developmental trauma disorder in an already organically vulnerable infant,
- Impulsive suicidal acts which are sometimes successful,
- The number of failed social service placements due to unsuccessful understanding and management of these developmental psychiatric disorders.

Recently deceased Nobel playwright Harold Pinter once wrote "The truth is elusive, but the search is compulsive". The nineteen years of psychiatric experience has clarified time and again the truth that no amount of alcohol is safe during pregnancy. The rest of the clinical work is already with us in many guises and through many generations. I am grateful to be part of this moment and see it as a potential new beginning for these still inadequately appreciated, lifelong conditions which are entirely preventable.

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# A PERSPECTIVE ON NATIONAL FASD RESEARCH AND PRACTICE IN FINLAND

Ilona Autti-Rämö,  
Adj Prof, Pediatric Neurologist

Drinking among women in Finland has increased during the last two decades. Only about 10 per cent of women of childbearing age are currently abstinent. It is alarming how drinking, especially binge drinking, has increased in younger women. Public knowledge of the limits for social and heavy drinking or the risk limits for various disorders/situations is blurred and confusing, for instance, one drink of wine can actually be 125 ml, 175ml or 225 ml of wine.

Several obstetric units have founded special outpatient clinics for pregnant women with alcohol or substance abuse problems. It is being considered, in addition to saving fetuses from being harmed by alcohol or substance abuse, that these specialist clinics could also have a long-term effect on the post-labour life for these women and their families. An ongoing register based study has been set up to analyze the long-term outcome of these women with regards to morbidity, working capacity and mortality. The study will investigate how pregnancy may offer a window of opportunity for these women to change their life.

The consequences of prenatal alcohol exposure is being investigated in three main studies in Finland.

A prospective follow-up on 82 children born to women who abused alcohol in varying severity and duration during pregnancy was initiated in 1982-1984. It showed that the longer the alcohol exposure, the poorer the outcome for the child. It also became evident that the cognitive deficits for Alcohol Related Neurodevelopmental Disorder (ARND) could not always be diagnosed before school age. Nearly all of the children with Fetal Alcohol Syndrome (FAS) were taken into Care, either permanently or temporarily.

A clinical cohort study of 77 children and adolescents with Fetal Alcohol Spectrum Disorder (FASD) has been studied as part of the international CIFASD study. The results of this study emphasise the need for a thorough assessment of major and minor malformations or abnormalities affecting vision, hearing and cognitive development whenever FASD is suspected. It was also confirmed that the dysmorphic feature score alone cannot be used to predict cognitive outcome.

A national study of children with FASD who have been taken into Care revealed that the foster parents and the children in Care are not getting the necessary psycho-social support and the follow-up they need. Their Care is not always well organised.

At a political level there have been two major initiatives. A proposal for warning labels on alcohol bottles about the risks of drinking during pregnancy has had strong support from health care professionals. This proposal was unfortunately rejected by the new government. A more recent proposal is suggesting involuntary care of pregnant women with alcohol or substance abuse problems. This proposal has fuelled a heated debate in both public and professional circles. The final political decision is still under discussion.

Health & Medicine, 6 April 2009

## **FROGS REVEAL CLUES ABOUT THE EFFECTS OF ALCOHOL DURING DEVELOPMENT**

Fetal alcohol spectrum disorder (FASD) and Fetal alcohol syndrome (FAS) cause malformations in babies, including facial defects, short stature, and mental and behavioral abnormalities. The African frog, *Xenopus*, is a valuable tool for understanding early vertebrate development since these embryos are large, easy to work with and very responsive to environmental cues. New research uses this system to address the mechanism underlying the characteristics associated with maternal consumption of alcohol in early pregnancy. Alcohol consumption prevents normal development by inhibiting the production of retinoic acid. Under normal conditions, the levels of retinoic acid made in different areas of the embryo provide cells with necessary information about their proper location and fate. Researchers now show that alcohol steals away the molecules that make retinoic acid and use them for its own process of detoxification, resulting in cellular disorientation during a critical period of development.

The new study, published in *Disease Models & Mechanisms* (DMM), [dmm.biologists.org](http://dmm.biologists.org), provides evidence that the characteristics associated with FASD and FAS come from competition of alcohol for key molecules in a pathway that produce retinoic acid from vitamin A. Retinoic acid is needed for correct positioning of cells in developing embryos and by preventing its normal production, alcohol keeps cells from migrating to their correct positions and maturing properly. The researchers, at the Hebrew University in Israel, found that shutting down a molecule needed to produce retinoic acid, called retinaldehyde dehydrogenase or RALDH2, increased sensitivity of developing embryos to low doses of alcohol. Conversely, more of the molecule RALDH2 protected embryos from the negative effects of alcohol. This provides evidence that alcohol 'hijacks' RALDH2 molecules for its own breakdown process and steals it away from its important role in synthesizing positional and maturation cues during development.

Fetal alcohol spectrum disorder (FASD) and Fetal alcohol syndrome (FAS) cause malformations in babies, including facial defects, short stature, and mental and behavioral abnormalities. The African frog, *Xenopus*, is a valuable tool for understanding early vertebrate development since these embryos are large, easy to work with and very responsive to environmental cues. New research uses this system to address the mechanism underlying the characteristics associated with maternal consumption of alcohol in early pregnancy.

Link to the article,

<http://esciencenews.com/articles/2009/04/06/frogs.reveal.clues.about.effects.alcohol.during.development>

## HAIR ANALYSIS OF FATTY ACID ETHYL ESTERS IN THE DETECTION OF EXCESSIVE DRINKING IN THE CONTEXT OF FETAL ALCOHOL SPECTRUM DISORDERS.

Kulaga V, Pragst F, Fulga N, Koren G.

Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario, Canada.

### Abstract

A serious challenge in diagnosing fetal alcohol spectrum disorder (FASD) is the need to document alcohol use during pregnancy. Maternal/paternal alcohol abuse affects the likelihood of fetal alcohol exposure, and hence the occurrence of FASD. The objective of the current study was to document the use of the fatty acid ethyl ester (FAEE) hair test, a biomarker of excessive alcohol use, in parents at risk of having children with FASD and quantify the prevalence of alcohol use in this population. Hair samples submitted for FAEE testing between October 2005 and May 2007 were evaluated (n = 324). Subjects consisted of the parents of at-risk children. Samples were analyzed using a previously published method. Briefly, samples underwent a liquid-liquid extraction, followed by headspace solid phase microextraction, and were then analyzed by gas chromatography-mass spectrometry using deuterated FAEE as internal standards. Limit of detection and limit of quantification values were between 0.01-0.04 ng/mg and 0.04-0.12 ng/mg, respectively. Positive levels for excessive drinking were ascertained using a cutoff level of 0.5 ng/mg, offering 90% sensitivity and specificity. The rate of positive hair samples for excessive drinking was 33.3% (32.4% among women and 35.4% among men) (n = 324). The majority of samples (62%) had cumulative FAEE levels above a level that excludes strict abstinence (0.2 ng/mg) and many (19%) were highly positive (above 1.0 ng/mg). Of 26 FAEE hair tests for which women were reported to be pregnant, 38% had FAEE hair levels above 0.2 ng/mg and 19% tested positive for excessive drinking, with levels above 0.5 ng/mg; 12% had levels above 1.0 ng/mg. The high rate of positive FAEE results demonstrates that the FAEE hair test corroborates the clinical suspicion of alcohol use in parents of children at risk for FASD. Our results suggest that FAEE hair analysis may be a powerful tool in detecting excessive alcohol use in the perinatal period.

Link to the article,

<http://www.ncbi.nlm.nih.gov/pubmed/19258930>

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## OCULOMOTOR CONTROL IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS ASSESSED USING A MOBILE EYE-TRACKING LABORATORY

C. R. Green <sup>1</sup>, A. M. Mihic <sup>1</sup>, D. C. Brien <sup>1</sup>, I. T. Armstrong <sup>1,2</sup>, S. M. Nikkel <sup>3</sup>, B. C. Stade <sup>4</sup>, C. Rasmussen <sup>5</sup>, D. P. Munoz <sup>1,2,6,7</sup> and J. N. Reynolds <sup>1,8</sup>

<sup>1</sup> The Center for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada

<sup>2</sup> Department of Physiology, Queen's University, Kingston, Ontario, Canada

<sup>3</sup> Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

<sup>4</sup> Department of Paediatrics, St Michael's Hospital, Toronto, Ontario, Canada

<sup>5</sup> Department of Paediatrics, University of Alberta, Edmonton, Alberta, Canada

<sup>6</sup> Department of Psychology, Queen's University, Kingston, Ontario, Canada

<sup>7</sup> Department of Medicine, Queen's University, Kingston, Ontario, Canada

<sup>8</sup> Department of Pharmacology & Toxicology, Queen's University, Kingston, Ontario, Canada

Correspondence to Dr J. N. Reynolds, <sup>8</sup>Department of Pharmacology and Toxicology as above.

E-mail: [jnr@queensu.ca](mailto:jnr@queensu.ca)

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### KEYWORDS

executive function • fetal alcohol syndrome • saccadic eye movements

### ABSTRACT

Prenatal exposure to alcohol can result in a spectrum of adverse developmental outcomes, collectively termed fetal alcohol spectrum disorders (FASDs). This study evaluated deficits in sensory, motor and cognitive processing in children with FASD that can be identified using eye movement testing. Our study group was composed of 89 children aged 8–15 years with a diagnosis within the FASD spectrum [i.e. fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), and alcohol-related neurodevelopmental disorder (ARND)], and 92 controls. Subjects looked either towards (prosaccade) or away from (antisaccade) a peripheral target that appeared on a computer monitor, and eye movements were recorded with a mobile, video-based eye tracker. We hypothesized that: (i) differences in the magnitude of deficits in eye movement control exist across the three diagnostic subgroups; and (ii) children with FASD display a developmental delay in oculomotor control. Children with FASD had increased saccadic reaction times (SRTs), increased intra-subject variability in SRTs, and increased direction errors in both the prosaccade and antisaccade tasks. Although development was associated with improvements across tasks, children with FASD failed to achieve age-matched control levels of performance at any of the ages tested. Moreover, children with ARND had faster SRTs and made fewer direction errors in the antisaccade task than children with pFAS or FAS, although all subgroups were different from controls. Our results demonstrate that eye tracking can be used as an objective measure of brain injury in FASD, revealing behavioral deficits in all three diagnostic subgroups independent of facial dysmorphism.

Link to the article,

<http://www3.interscience.wiley.com/journal/122242961/abstract>

Read full article, [Go to end of this document](#)

American Journal of Obstetrics and Gynecology, Volume 200, Issue 3, March 2009

## **ALCOHOL USE BEFORE AND DURING PREGNANCY IN WESTERN WASHINGTON, 1989-2004: IMPLICATIONS FOR THE PREVENTION OF FETAL ALCOHOL SPECTRUM DISORDERS**

Presented at the 133rd Annual Meeting and Exposition of the American Public Health Association, Philadelphia, PA, Dec. 10-14, 2005.

Therese M. Grant, PhDa, Janet E. Huggins, PhDa, Paul D. Sampson, PhDab, Cara C. Ernst, MAa, Helen M. Barr, MA, MSa, Ann P. Streissguth, PhDa

Received 5 April 2008; received in revised form 23 July 2008; accepted 26 September 2008. published online 25 November 2008.

**Objective** - We examined trends in rates of self-reported pregnancy alcohol use among women in western Washington.

**Study Design** - Between 1989 and 2004, we conducted 3 studies in western Washington State on problems that are associated with maternal prenatal alcohol or drug abuse (n = 12,526). To determine study eligibility, we screened hospitalized postpartum women for alcohol and drug use in the month before and during pregnancy. We examined trends in alcohol use rates and identified characteristics that were associated with any drinking and binge drinking ( $\geq 5$  drinks on any occasion).

**Results** - We found a substantial decrease in pregnancy alcohol use between 1989 and 2004 (from 30-12%) across almost all demographic categories. Binge drinking in the month before pregnancy increased significantly among all race categories, except Native American.

**Conclusion** - Increased prepregnancy binge drinking rates may estimate alcohol use during very early gestation and warrant clinical attention because of the potential for fetal alcohol spectrum disorders.

Link to the article,

[http://www.ajog.org/article/S0002-9378\(08\)01096-X/Abstract](http://www.ajog.org/article/S0002-9378(08)01096-X/Abstract)

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PubMed, Can J Clin Pharmacol 2009 Winter

## **COSTS OF FETAL ALCOHOL SPECTRUM DISORDER IN ALBERTA, CANADA.**

Thanh NX, Jonsson E.

## Abstract

**BACKGROUND:** Although many programs targeting fetal alcohol spectrum disorder (FASD) are implemented, the province of Alberta is still lacking information on costs of FASD.

**OBJECTIVES:** To estimate the costs of FASD in Alberta based on available US and Canadian research on costs of FASD, and Alberta data.

**METHODS:** Two types of costs were estimated. The annual long-term economic cost of FASD, which referred to a projected amount of money incurred by lives of the cohort of children born with FASD each year, was estimated by multiplying the lifetime cost of caring for each child born with FASD with the number of children born with FASD each year. The annual short-term economic cost of FASD, which referred to the amount of money incurred by people who are presently living with FASD, was estimated by using a FASD cost calculator online at <http://www.online-clinic.com>. Both were societal costs adjusted to 2008 Canadian dollars.

**RESULTS:** The annual long-term economic cost from the disorders rose from \$130 to \$400 million each year for the Alberta economy. The annual short-term economic cost for FASD in Alberta was from \$48 to \$143 million, and the daily cost for FASD in Alberta was from \$105 to \$316 thousand.

**CONCLUSION:** These numbers suggest a need for a provincial FASD prevention strategy. The costs of FASD can be used to evaluate the benefits of prevention programs to society.

Link to the article,

<http://www.ncbi.nlm.nih.gov/pubmed/19151424>

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PEDIATRICS Vol. 123 No. 2, February 2009

## **BINGE PATTERN OF ALCOHOL CONSUMPTION DURING PREGNANCY AND CHILDHOOD MENTAL HEALTH OUTCOMES: LONGITUDINAL POPULATION-BASED STUDY**

Kapil Sayal, PhDa, Jon Heron, PhDb, Jean Golding, DSc, Rosa Alati, PhDd, George Davey Smith, DScb, Ron Gray, MPHe and Alan Emond, MDc

a Section of Developmental Psychiatry, University of Nottingham, Nottingham, United Kingdom

b Departments of Social Medicine

c Community-Based Medicine, University of Bristol, Bristol, United Kingdom

d School of Population Health, University of Queensland, Herston, Australia

e National Perinatal Epidemiology Unit, University of Oxford, Oxford, United Kingdom

## Abstract

**OBJECTIVE.** Patterns of alcohol consumption during pregnancy such as episodes of binge drinking may be as important as average levels of consumption in conferring risk for later childhood mental health and learning problems. However, it can be difficult to distinguish risk resulting from episodic or regular background levels of drinking. This large study investigates whether patterns of alcohol consumption are independently associated with child mental health and cognitive outcomes, whether there are gender differences in risk, and whether occasional episodes of higher levels of drinking carry any risk in the absence of regular daily drinking during pregnancy.

**METHODS.** This prospective, population-based study used data from the Avon Longitudinal Study of Parents and Children. We investigated the relationships between a binge pattern of alcohol use (consumption of 4 drinks in a day) in the second and third trimesters of pregnancy and childhood mental health problems at 47 and 81 months of age (n = 6355 and 5599, respectively). In a subgroup, we also investigated these relationships with child IQ at 49 months of age (n = 924).

**RESULTS.** After controlling for a range of prenatal and postnatal factors, any episodes of consuming 4 drinks in a day were independently associated with higher risks for mental health problems (especially hyperactivity/inattention) in girls at the age of 47 months and in both genders at 81 months. There was no association with IQ scores at 49 months after adjustment for confounders. The consumption of 4 drinks in a day continued to carry risk for mental health problems (especially hyperactivity/inattention) in the absence of regular daily drinking.

**CONCLUSIONS.** The consumption of 4 drinks in a day on an occasional basis during pregnancy may increase risk for child mental health problems in the absence of moderate daily levels of drinking. The main risks seem to relate to hyperactivity and inattention problems.

Read Full Article,

<http://pediatrics.aappublications.org/cgi/reprint/123/2/e289>

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Hum. Reprod. Advance Access, Published online on December 17, 2008

## **ETHANOL EXPOSURE INDUCES DIFFERENTIAL MICRORNA AND TARGET GENE EXPRESSION AND TERATOGENIC EFFECTS WHICH CAN BE SUPPRESSED BY FOLIC ACID SUPPLEMENTATION**

Lin-Lin Wang<sup>1,2</sup>, Zhaofeng Zhang<sup>1</sup>, Qiong Li<sup>1</sup>, Ruiyue Yang<sup>1</sup>, Xinrong Pei<sup>1</sup>, Yajun Xu<sup>1</sup>, Junbo Wang<sup>1</sup>, Shu-Feng Zhou<sup>2,3</sup> and Yong Li<sup>1,3</sup>

1 Department of Nutrition and Food Hygiene, School of Public Health, Peking University, Beijing 100191, P. R. China 2 Division of Chinese Medicine, School of Health Sciences, WHO Collaborating Center for Traditional Medicine, RMIT University, Bundoora, VIC 3083, Australia



3 Correspondence address. Tel: +86-10-82801177/+61-3-9925-7794; Fax: +86-10-82801177/+61-3-9925-7178; E-mail: liyong@bjmu.edu.cn/shufeng.zhou@rmit.edu.au

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**BACKGROUND:** microRNAs (miRNAs) play an important role in development and are associated with birth defects. Data are scant on the role of miRNAs in birth defects arising from exposure to environmental factors such as alcohol.

**METHODS:** In this study, we determined the expression levels of 509 mature miRNAs in fetal mouse brains with or without prenatal ethanol exposure using a miRNA microarray technique, verified by northern blot and PCR. Mouse embryos in culture were used to examine the effect of ethanol treatment on expression of the putative target genes of miR-10a (Hoxa1 and other Hox members) at mRNA and protein level. Open field and Morris water maze tests were also performed at post-natal day 35.

**RESULTS:** Ethanol treatment induced major fetal teratogenesis in mice and caused mental retardation in their offspring, namely lower locomotor activity ( $P < 0.01$ ) and impaired task acquisition. Of the screened miRNAs, miR-10a, miR-10b, miR-9, miR-145, miR-30a-3p and miR-152 were up-regulated (fold change  $>1.5$ ) in fetal brains with prenatal ethanol exposure, whereas miR-200a, miR-496, miR-296, miR-30e-5p, miR-362, miR-339, miR-29c and miR-154 were down-regulated (fold change  $<0.67$ ). Both miR-10a and miR-10b were significantly up-regulated ( $P < 0.01$ ) in brain after prenatal ethanol exposure. Ethanol treatment also caused major obstruction in the development of cultured embryos, with down-regulated Hoxa1. Co-incubation with folic acid blocked ethanol-induced teratogenesis, with up-regulated Hoxa1 and down-regulated miR-10a ( $P < 0.01$ ).

**CONCLUSIONS:** The study provided new insights into the role of miRNAs and their target genes in the pathogenesis of fetal alcohol syndrome.

Link to the article,

<http://humrep.oxfordjournals.org/cgi/content/Abstract/den439v1/>

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Alcoholism: Clinical and Experimental Research; Volume 32 Issue 12, December 2008

## **NEUROPSYCHOLOGICAL STUDY OF FASD IN A SAMPLE OF AMERICAN INDIAN CHILDREN: PROCESSING SIMPLE VERSUS COMPLEX INFORMATION**

Alfredo S. Aragón, Wendy O. Kalberg, David Buckley, Lindsey M. Barela-Scott, Barbara G. Tabachnick, and Philip A. May

From the University of New Mexico (ASA, WOK, DB, LMB-S, BGT, PAM), Albuquerque, New Mexico

## ABSTRACT

**Background:** Although a large body of literature exists on cognitive functioning in alcohol-exposed children, it is unclear if there is a signature neuropsychological profile in children with Fetal Alcohol Spectrum Disorders (FASD). This study assesses cognitive functioning in children with FASD from several American Indian reservations in the Northern Plains States, and it applies a hierarchical model of simple versus complex information processing to further examine cognitive function. We hypothesized that complex tests would discriminate between children with FASD and culturally similar controls, while children with FASD would perform similar to controls on relatively simple tests.

**Methods:** Our sample includes 32 control children and 24 children with a form of FASD [fetal alcohol syndrome (FAS) = 10, partial fetal alcohol syndrome (PFAS) = 14]. The test battery measures general cognitive ability, verbal fluency, executive functioning, memory, and fine-motor skills.

**Results:** Many of the neuropsychological tests produced results consistent with a hierarchical model of simple versus complex processing. The complexity of the tests was determined "a priori" based on the number of cognitive processes involved in them. Multidimensional scaling was used to statistically analyze the accuracy of classifying the neurocognitive tests into a simple versus complex dichotomy. Hierarchical logistic regression models were then used to define the contribution made by complex versus simple tests in predicting the significant differences between children with FASD and controls. Complex test items discriminated better than simple test items. The tests that conformed well to the model were the Verbal Fluency, Progressive Planning Test (PPT), the Lhermitte memory tasks, and the Grooved Pegboard Test (GPT). The FASD-grouped children, when compared with controls, demonstrated impaired performance on letter fluency, while their performance was similar on category fluency. On the more complex PPT trials (problems 5 to 8), as well as the Lhermitte logical tasks, the FASD group performed the worst.

**Conclusions:** The differential performance between children with FASD and controls was evident across various neuropsychological measures. The children with FASD performed significantly more poorly on the complex tasks than did the controls. The identification of a neurobehavioral profile in children with prenatal alcohol exposure will help clinicians identify and diagnose children with FASD

Link to the article,

<http://www3.interscience.wiley.com/journal/121428143/Abstract>

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PubMed, Neurotoxicology, November 2008

**THE PROTECTIVE EFFECT OF NEURONAL NITRIC OXIDE SYNTHASE (NOS) AGAINST ALCOHOL TOXICITY DEPENDS UPON THE NO-CGMP-PKG PATHWAY AND NF-KAPPAB.**

Bonthius DJ, Bonthius NE, Li S, Karacay B.

Department of Pediatrics, College of Medicine, University of Iowa, Iowa City, IA, USA. daniel-bonthius@uiowa.edu

## Abstract

Fetal alcohol syndrome (FAS) stems from maternal alcohol abuse during pregnancy and is an important cause of mental retardation and hyperactivity in children. In the developing brain, alcohol can kill neurons, leading to microencephaly. However, due to their genetic makeup, some individuals are less vulnerable than others to alcohol's neurotoxic effects. Animal studies have demonstrated that one particular gene, neuronal nitric oxide synthase (nNOS), protects developing neurons in vivo against alcohol-induced death. We utilized pharmacologic techniques to demonstrate that nNOS protects neurons against alcohol toxicity by activating the NO-cGMP-PKG signaling pathway. Cerebellar granule cell cultures derived from mice carrying a null mutation for nNOS (nNOS<sup>-/-</sup> mice) were substantially more vulnerable than cultures from wild-type mice to alcohol-induced cell death. However, activation of the pathway at sites downstream of nNOS protected the cultures against alcohol toxicity. Conversely, blockade of the pathway rendered wild-type cultures vulnerable to alcohol-induced death. We further identified NF-kappaB as the downstream effector through which nNOS and the NO-cGMP-PKG pathway signal their neuroprotective effects. Tumor necrosis factor-alpha (TNF-alpha), which activates NF-kappaB, ameliorated alcohol-induced cell death in nNOS<sup>-/-</sup> and wild-type cultures, while an NF-kappaB inhibitor (NFi) blocked the protective effects of TNF-alpha and worsened alcohol-induced cell death. Furthermore, NFi blocked the protective effects of NO-cGMP-PKG pathway activators, demonstrating that NF-kappaB is downstream of the NO-cGMP-PKG pathway. As wild-type neurons matured in culture, they became resistant to alcohol toxicity. However, this maturation-dependent alcohol resistance did not occur in nNOS<sup>-/-</sup> mice and could be reversed in wild-type mice with NFi, demonstrating that nitric oxide and NF-kappaB are crucial for the development of alcohol resistance with age. Thus, nNOS protects developing neurons against alcohol toxicity by activating the NO-cGMP-PKG-NF-kappaB pathway and is crucial for the acquisition of maturation-dependent alcohol resistance.

Link to the article,

<http://www.ncbi.nlm.nih.gov/pubmed/18824032>

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Nature Medicine; November 2008 Volume 14, No 11

## INTERVENTIONS MIGHT OFFER A PREGNANT PAUSE IN ADDICTION

Erika Check Hayden  
San Francisco

### Abstract

Over the past decade, researchers have been developing strategies for blocking alcohol's damage. Among the most promising has been the use of a nutrient called choline, found in

foods such as eggs, nuts and liver and recently recognized as essential to normal brain development.

Neuroscientist Jennifer Thomas at San Diego State University in California has found that if given at the same time as alcohol to pregnant rats, choline lessens the learning deficits of their offspring (Neurotoxicol. Teratol. 22, 703–711; 2000). More intriguingly, if given to baby rats during the brain development stage that corresponds to that seen in human infants and young children, choline still ameliorates hyperactivity and spatial learning deficits (Behav. Neurosci. 121, 120–130; 2007). Thomas is not sure how choline works to ameliorate these deficits; the nutrient is a precursor to numerous molecules, including neurotransmitters, cell membrane components and signaling factors. But knowing the mechanism may not be essential, as choline is a nutrient, not a drug, and may therefore be less risky.

Moreover, the fact that choline might help after birth is seen as a huge plus, as many pregnant women don't disclose their drinking, making it unlikely that they can be treated during pregnancy.

Still, Thomas has already begun a study to look at the effects of supplementing pregnant women's diets with choline. Scientists have high hopes for the strategy: "It's one of the most promising approaches," says Kenneth Warren, acting director of the US National Institute on Alcohol Abuse and Alcoholism in Bethesda, Maryland. Warren, Thomas and others stress that women should, of course, try not to drink at all during pregnancy. But if they cannot, Thomas hopes her work may one day spare their children from this drug's devastating effects.

Read Full Article,

<http://www.nature.com/nm/journal/v14/n11/full/nm1108-1168.html>

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Can J Clin Pharmacol Vol 15(3); October 24, 2008

## **GENDER AND ATTENTION DEFICITS IN CHILDREN DIAGNOSED WITH A FETAL ALCOHOL SPECTRUM DISORDER**

Original Research

Lisa E Herman, Michelle C Acosta, Pi-Nian Chang

**Background** - A portion of children are born with Fetal Alcohol Spectrum Disorders (FASD). Most present with significant difficulties in attention, with attention-deficit/hyperactivity disorder (ADHD) being the most common psychiatric co-morbidity.

**Objectives** - The current study will describe behavioral and executive functioning (EF) deficits in attention in a group of children with FASD. Effects of gender and ADHD diagnosis will be explored.

**Methods** - Existing data from the University of Minnesota's Pediatric Psychology clinic was

utilized. Of 191 children with FASD in the database, 36 children (ages 6-16) had complete scores on measures of behavioral and EF attention deficits. Multivariate Analyses of Variance (MANOVA) were used to examine the impact of gender and ADHD diagnosis on behavioral checklist scores and on a variety of EF measures.

**Results** - FASD males were significantly more likely to be diagnosed with ADHD (68%) than FASD females (29%). No impact of gender or diagnosis was found for behavioral measures of attention, but an interaction of gender and diagnosis emerged for EF. Females with ADHD evidenced deficits in EF compared to females without ADHD. However, males with ADHD performed better on measures of EF than their non-ADHD counterparts.

**Conclusion** - An ADHD diagnosis in FASD children needs to be reconsidered, especially for males.

Read Full Article,

[http://www.cjcp.ca/pdf/FAR8003\\_Herman\\_e411-e419.pdf](http://www.cjcp.ca/pdf/FAR8003_Herman_e411-e419.pdf)

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Journal of Child Psychology and Psychiatry; Published Online: 23 October 2008

## **EXECUTIVE FUNCTION DEFICITS IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS (FASD) MEASURED USING THE CAMBRIDGE NEUROPSYCHOLOGICAL TESTS AUTOMATED BATTERY (CANTAB)**

C.R. Green 1 , A.M. Mihic 1 , S.M. Nikkel 6 , B.C. Stade 7 , C. Rasmussen 8 , D.P. Munoz 1,3,4,5 , and J.N. Reynolds 1,2

1 The Centre for Neuroscience Studies and Departments of 2Pharmacology & Toxicology, 3 Physiology, 4 Psychology and 5 Medicine, Queen's University, Kingston, Ontario, Canada; 6 Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada; 7 Department of Paediatrics, St. Michael's Hospital, Toronto, Ontario, Canada; 8 Department of Paediatrics, University of Alberta, Edmonton, Alberta, Canada

Correspondence to James N. Reynolds, Department of Pharmacology and Toxicology, Queen's University, Kingston, Ontario, K7L 3N6, Canada; Tel: (613) 533-6946; Fax: (613) 533-6412; Email: jnr@queensu.ca

Conflict of interest statement: No conflicts declared.

### **ABSTRACT**

**Background:** Chronic prenatal alcohol exposure causes a spectrum of deleterious effects in offspring, collectively termed fetal alcohol spectrum disorders (FASD), and deficits in executive function are prevalent in FASD. The goal of this research was to test the hypothesis that children with FASD exhibit performance deficits in tasks that assess attention, planning and spatial working memory.

**Methods:** Subjects (8–15 years male and female children) with a diagnosis of fetal alcohol syndrome (FAS), partial FAS (pFAS), or alcohol-related neurodevelopmental disorder (ARND), and age- and sex-matched controls, completed four tasks selected from the Cambridge

Neuropsychological Tests Automated Battery (CANTAB®).

Results: Compared with age-matched control children ( $n = 92$ ), subjects with FASD ( $n = 89$ ) exhibited longer reaction and decision times (effect size range; Cohen's  $d = .51$  to  $.73$ ), suggesting deficits in attention. Children with FASD demonstrated deficits in planning and spatial working memory that became more pronounced when task difficulty increased. The largest effect size in this study population (Cohen's  $d = 1.1$ ) occurred in the spatial working memory task. Only one outcome measure revealed differences across the diagnostic subgroups, although all groups were different from control.

Conclusion: This study demonstrates that deficits in multiple executive function domains, including set shifting, planning and strategy use, attention and spatial working memory, can be assessed in children with FASD using an easy to administer, brief battery of computer-based neuropsychological tasks. The tasks appear to be equally sensitive for brain injury resulting from prenatal exposure to alcohol, regardless of the presence of facial dysmorphism.

Link to the article,

<http://www3.interscience.wiley.com/journal/121478698/Abstract>

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Child and Adolescent Mental Health; Published Online: 1 October 2008

## FETAL ALCOHOL SPECTRUM DISORDERS: AN OVERVIEW OF INTERVENTIONS FOR AFFECTED INDIVIDUALS

Amali N. Chandrasena<sup>1</sup>, Raja A. S. Mukherjee<sup>2</sup> & Jeremy Turk<sup>1</sup>

<sup>1</sup> Academic Child & Adolescent Mental Health, Clinical Developmental Sciences, St George's University of London, Cranmer Terrace, London, SW17 0RE, UK

<sup>2</sup> Surrey and Borders Partnership NHS Trust, Bracketts Resource Centre, 116-118 Station Road East, Oxted, RH8 0QA, UK. E-mail: [rmukherj@sgul.ac.uk](mailto:rmukherj@sgul.ac.uk)

Expression of competing interest: RM is a medical advisory to the NOFAS UK international advisory panel and Parents for Children. He has also received lecture fees for presenting on the subject of FASD from various groups including BAAF, Parents for Children, NOFAS UK FAS Aware UK and Janssen Cilag.

### ABSTRACT

Whilst much has been written about understanding the diagnostic and underlying pathological processes related to prenatal alcohol exposure, far less has been directed at the management of affected individuals. We undertake a review of the literature focusing on a range of interventions including psychological, social, educational, pharmacological as well recent advances and directions. This paper is designed to give an overview on the management of this complex disorder.

Link to the article,

<http://www3.interscience.wiley.com/journal/121428022/Abstract>

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## FETAL ALCOHOL SYNDROME: A PROSPECTIVE NATIONAL SURVEILLANCE STUDY

Elizabeth J Elliott 1\*, Janet M Payne 2, Anne Morris 3, Eric Haan 4 and Carol A Bower 2

1 University of Sydney and Children's Hospital at Westmead, Australia

2 Telethon Institute for Child Health Research Perth WA, Australia

3 University of Sydney, Australia

4 Women's and Children's Hospital Adelaide, Australia

\* To whom correspondence should be addressed. E-mail: elizabe2@chw.edu.au.

Accepted 8 August 2007

### Abstract

**Objective:** To describe the epidemiology of cases of fetal alcohol syndrome (FAS) seen by Australian paediatricians.

**Method:** Active, national case-finding using the Australian Paediatric Surveillance Unit. Monthly reporting of incident cases aged <15 years by paediatricians between January 2001 and December 2004.

**Results:** Over 1150 paediatricians submitted reports each month to the APSU. Of 169 reported cases, 92 fulfilled the study criteria for FAS. There was a significant increase in the number of children reported each year from 2001 to 2004. Of 92 children, 53.3% were male, 35.7% were preterm (<37w gestation), and 64.6% were of low birth weight (<2.5kg). Most (94.4%) had 'high risk' exposure to alcohol in utero and 78.3% were exposed to one or more additional drugs. The median age at diagnosis was 3.3 years (range newborn to 11.9 years): 6.5% were diagnosed at birth and 63% by 5 years of age. Of the 92 cases, 56% had growth deficiency, 53.2% had microcephaly, 85.9% had evidence of central nervous system dysfunction; 24% had additional birth defects; 5.4% had sensorineural deafness and 4.3% had visual impairment. . Of children with FAS, 65% were Indigenous; 51% had a sibling with FAS; and only 40.2% lived with a biological parent.

**Conclusion:** Our data are the only prospective national data available on FAS throughout the world. These findings highlight the severity, complexity and impact of FAS; the need for effective strategies for prevention; and the need for education to facilitate earlier diagnosis, referral and reporting of cases. Words: 246

Link to the article,

<http://adc.bmj.com/cgi/content/abstract/adc.2007.120220v1>

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# SACCADIC EYE MOVEMENTS AND EXECUTIVE FUNCTION IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDERS (FASD): RESULTS FROM A MULTI-CENTERED STUDY

Author: Green, COURTNEY

Series/Report no.: Canadian theses

## Abstract:

A serious consequence of maternal consumption of alcohol during pregnancy is the fetal alcohol syndrome (FAS): characterized by growth deficiency (both pre- and post-natal), craniofacial dysmorphology and central nervous system (CNS) dysfunction. However, in the absence of the characteristic facial features, and without confirmed history of alcohol exposure, clinical diagnosis remains a significant challenge. Recently, the term fetal alcohol spectrum disorders (FASD) has been adopted to encompass all diagnoses relating to a history of prenatal alcohol exposure.

The purpose of this study was to test the following three general hypotheses: Children with FASD

- 1) demonstrate specific deficits in oculomotor control that can be measured using saccadic eye movement tasks,
- 2) display specific deficiencies in multiple domains of executive function that can be determined using standardized neuropsychological tasks, and
- 3) reveal deficits in oculomotor control that correlate with deficiencies in executive function as measured using standardized neuropsychological tasks.

A preliminary study revealed significant deficits in saccadic eye movement tasks and provided the foundation for a large, multi-centered study assessing oculomotor control and neuropsychological function in children with FASD. A mobile laboratory was created, which facilitated recruitment of 92 control subjects and 89 subjects with FASD. We found significant evidence for oculomotor deficits across multiple outcome measures following the saccadic eye movement experiments, especially for oculomotor tasks that probe aspects of executive function. Additionally, children with FASD exhibited performance deficits in neuropsychological tasks that assess planning, attention, spatial working memory and strategy; cognitive skills also included within the domain of executive function. Finally, significant correlations between these two objective measures were found for children with FASD, which were not evident in the control sample. These findings are consistent with significant frontal lobe dysfunction. This is an exciting area of research that may hold promise in developing effective screening tools that can assist in the diagnosis of individuals with a history of prenatal alcohol exposure.

Read Full article,

[https://qspace.library.queensu.ca/dspace/bitstream/1974/1389/1/Green\\_Courtney\\_R\\_200808\\_PhD.pdf](https://qspace.library.queensu.ca/dspace/bitstream/1974/1389/1/Green_Courtney_R_200808_PhD.pdf)

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# CHRONIC ETHANOL EXPOSURE INDUCES ALTERATIONS IN THE NUCLEOCYTOPLASMIC TRANSPORT IN GROWING ASTROCYTES

[ORIGINAL ARTICLE]

Marín, María Pilar<sup>\*,1</sup>; Tomas, Mónica<sup>†,1</sup>; Esteban-Pretel, Guillermo<sup>\*</sup>; Megías, Luis<sup>‡</sup>; López-Iglesias, Carmen<sup>§</sup>; Egea, Gustavo<sup>¶</sup>; Renau-Piqueras, Jaime<sup>\*</sup>

<sup>\*</sup>Section of Biología y Patología Celular, Centro de Investigación, Hospital 'La Fe', Valencia, Spain

<sup>†</sup>Department of Biología Celular e Histología, Faculty of Medicina, University of Murcia, Murcia, Spain

<sup>‡</sup>Department of Anatomía y Embriología Humana, Faculty of de Medicina, University of Granada, Granada, Spain

<sup>§</sup>Servicios Científico-Técnicos, Parque Científico, University of Barcelona, Barcelona, Spain

<sup>¶</sup>Department of Biología Celular i Anatomía Patològica, Faculty of Medicina, IDIBAPS, University of Barcelona, Barcelona, Spain

Address correspondence and reprint requests to Jaime Renau-Piqueras, Section of Biología y Patología Celular, Centro de Investigación, Hospital Universitario 'La Fe', Avda. Campanar 21, Valencia E-46009, Spain. E-mail: renau\_jai@gva.es

<sup>1</sup>Both these authors contributed equally to this study.

Abbreviations used: 3H-Met, L-[methyl-3H]methionine; Exp1/CRM1, exportin1; FAS, fetal alcohol syndrome; Imp $\alpha$ 2, importin or karyopherin  $\alpha$ 2; Imp $\beta$ 3, importin or karyopherin  $\beta$ 3; NE, nuclear envelope; NPC, nuclear pore complex; PBS, phosphate-buffered saline; RanBP, Ran-binding protein.

Received November 27, 2007; revised manuscript received May 12, 2008; accepted May 27, 2008.

## Abstract

Nucleocytoplasmic transport is a crucial process for cell function. We assessed the general effect of chronic alcohol exposure on this transport in growing astrocytes for the first time. Import and export of proteins to the nucleus were examined by pulse-chase experiments using 3H-methionine, and we showed that ethanol induces a delay in both processes. Furthermore, we took an approach to evaluate the mechanisms involved in this effect. Whereas alcohol did not affect the amount and the distribution of several representative proteins that participate in nuclear import, such as RanBP1, RanGAP1 and the importins  $\alpha$ 2 and  $\beta$ 3, it decreased the amount of Exp1/CRM1, which is a general export receptor involved in the nuclear export. In addition, the density and distribution of nuclear pore complexes, which contribute to nucleocytoplasmic transport, were also affected by ethanol. These effects can be related with changes found in the content of several proteins associated with the nuclear envelope and the nuclear pore complex structure such as lamins A/C, and nucleoporins p62 and RanBP2, respectively. These results suggest that ethanol could interfere with some of the important processes regulated by nucleocytoplasmic transport in astrocytes and support the idea that one of the main ethanol targets is intracellular transport.

Link to the article,

<http://pt.wkhealth.com/pt/re/jneu/Abstract.00005064-200808040-00039.htm;jsessionid=JJ4b9p5QNpnBHYfQdL7nqcNhhJnmTtM2RjdI6FPCLyVn5zf0p0kL!-1694466489!181195629!8091!-1>

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Journal of Child and Adolescent Psychopharmacology, August 2008

## **MEDICATION EFFECTS ON SYMPTOMS OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER IN CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER**

Jenna Doig, B.H.Sc. (Hon.)

Medical Student, Faculty of Medicine, University of Toronto, Toronto, Canada.

John D. McLennan, M.D., Ph.D., F.R.C.P.C.

Departments of Community Health Sciences, Psychiatry, and Pediatrics, University of Calgary, Calgary, Canada.

W. Ben Gibbard, M.D., M.Sc., F.R.C.P.C.

Department of Pediatrics, University of Calgary, Calgary, Canada.

### **Abstract**

Attention-deficit/hyperactivity disorder (ADHD) may be the most common mental health disorder in children with fetal alcohol spectrum disorders (FASD). Despite this, little information is available regarding the effectiveness of ADHD treatment in this population. This study, conducted within a clinical service, aimed to assess the impact of medication on symptoms of ADHD in children with FASD by determining (a) the extent of change in ADHD symptoms with medication, and (b) whether differences in improvement are seen between symptom domains. Data were extracted from the medical records of 27 children with FASD who had been referred to an ADHD medication service at the Alberta Children's Hospital in Canada. Participants were primarily male and ranged in age from 5 years 6 months to 14 years 5 months. Teacher MTA-SNAP-IV scores were the primary outcome measure. Baseline, best, and change scores across three symptom domains (inattention, hyperactivity/impulsivity, and opposition/defiance) were determined. A total of 41 medication trials was conducted. More children obtained normalized best scores for hyperactivity/impulsivity ( $n = 18$ ) and opposition/defiance ( $n = 19$ ) than for inattention ( $n = 9$ ) across medication trials. These findings suggest that inattention may be less responsive to ADHD medication. Replication in larger samples with a placebo-controlled design is required.

Link to the article,

<http://www.liebertonline.com/doi/abs/10.1089/cap.2007.0121>

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## **AUTOMATED DIAGNOSIS OF FETAL ALCOHOL SYNDROME USING 3D FACIAL IMAGE ANALYSIS**

S Fang, J McLaughlin, J Fang, J Huang, I Autti-Rämö, Å Fagerlund, SW Jacobson, LK Robinson, HE Hoyme, SN Mattson, E Riley, F Zhou, R Ward, ES Moore, T Foroud and Collaborative Initiative on Fetal Alcohol Spectrum Disorders\*

Shiaofen Fang, Jason McLaughlin, Jiandong Fang, Jeffrey Huang, Department of Computer Science, Purdue University, Indianapolis, IN, USA

Ilona Autti-Rämö, Department of Child Neurology, HUCH Hospital for Children and Adolescents, Helsinki, Finland and Finnish Office for Health Technology Assessment

### **ABSTRACT**

Authors – Fang S, McLaughlin J, Fang J, Huang J, Autti-Rämö I, Fagerlund Å, Jacobson SW, Robinson LK, Hoyme HE, Mattson SN, Riley E, Zhou F, Ward R, Moore ES, Foroud T, and the Collaborative Initiative on Fetal Alcohol Spectrum Disorders.

Objectives – Use three-dimensional (3D) facial laser scanned images from children with fetal alcohol syndrome (FAS) and controls to develop an automated diagnosis technique that can reliably and accurately identify individuals prenatally exposed to alcohol.

Methods – A detailed dysmorphology evaluation, history of prenatal alcohol exposure, and 3D facial laser scans were obtained from 149 individuals (86 FAS; 63 Control) recruited from two study sites (Cape Town, South Africa and Helsinki, Finland). Computer graphics, machine learning, and pattern recognition techniques were used to automatically identify a set of facial features that best discriminated individuals with FAS from controls in each sample.

Results – An automated feature detection and analysis technique was developed and applied to the two study populations. A unique set of facial regions and features were identified for each population that accurately discriminated FAS and control faces without any human intervention.

Conclusion – Our results demonstrate that computer algorithms can be used to automatically detect facial features that can discriminate FAS and control faces.

Link to the article,

<http://www3.interscience.wiley.com/journal/120755909/Abstract>

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Am J Physiol Regul Integr Comp Physiol; First published May 28, 2008

## **ACID-SENSITIVE CHANNEL INHIBITION PREVENTS FETAL ALCOHOL SPECTRUM DISORDERS CEREBELLAR PURKINJE**

## CELL LOSS

Jayanth Ramadoss,<sup>1</sup> Emilie R. Lunde,<sup>1</sup> Nengtai Ouyang,<sup>1</sup> Wei-Jung A. Chen,<sup>2</sup> and Timothy A. Cudd<sup>1</sup>

<sup>1</sup>Department of Veterinary Physiology and Pharmacology and Michael E. DeBakey Institute, College of Veterinary Medicine and Biomedical Sciences and <sup>2</sup>Department of Neuroscience and Experimental Therapeutics, Texas A&M Health Science Center, College Station, Texas

Submitted 28 March 2008 ; accepted in final form 22 May 2008

### Abstract

Ethanol is now considered the most common human teratogen. Educational campaigns have not reduced the incidence of ethanol-mediated teratogenesis, leading to a growing interest in the development of therapeutic prevention or mitigation strategies. On the basis of the observation that maternal ethanol consumption reduces maternal and fetal pH, we hypothesized that a pH-sensitive pathway involving the TWIK-related acid-sensitive potassium channels (TASKs) is implicated in ethanol-induced injury to the fetal cerebellum, one of the most sensitive targets of prenatal ethanol exposure. Pregnant ewes were intravenously infused with ethanol (258 ± 10 mg/dl peak blood ethanol concentration) or saline in a "3 days/wk binge" pattern throughout the third trimester. Quantitative stereological analysis demonstrated that ethanol resulted in a 45% reduction in the total number of fetal cerebellar Purkinje cells, the cell type most sensitive to developmental ethanol exposure. Extracellular pH manipulation to create the same degree and pattern of pH fall caused by ethanol (manipulations large enough to inhibit TASK 1 channels), resulted in a 24% decrease in Purkinje cell number. We determined immunohistochemically that TASK 1 channels are expressed in Purkinje cells and that the TASK 3 isoform is expressed in granule cells of the ovine fetal cerebellum. Pharmacological blockade of both TASK 1 and TASK 3 channels simultaneous with ethanol effectively prevented any reduction in fetal cerebellar Purkinje cell number. These results demonstrate for the first time functional significance of fetal cerebellar two-pore domain pH-sensitive channels and establishes them as a potential therapeutic target for prevention of ethanol teratogenesis.

Read Full Article,

<http://ajpregu.physiology.org/cgi/reprint/295/2/R596>

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American Journal of Obstetrics and Gynecology: Volume 198(4), April 2008

## MEASUREMENT OF DIRECT ETHANOL METABOLITES SUGGESTS HIGHER RATE OF ALCOHOL USE AMONG PREGNANT WOMEN THAN FOUND WITH THE AUDIT-A PILOT STUDY IN A POPULATION-BASED SAMPLE OF SWEDISH WOMEN

Wurst, Friedrich Martin MD, PhD<sup>a,b</sup>; Kelso, Erika MD<sup>c</sup>; Weinmann, Wolfgang PhD<sup>d</sup>; Pragst, Fritz PhD<sup>e</sup>; Yegles, Michel PhD<sup>f</sup>; Sundström Poromaa, Inger MD, PhD<sup>c,\*</sup>

a Psychiatric University Clinic, Basel, Switzerland

b Department of Psychiatry and Psychotherapy II/Addiction Medicine, Christian-Doppler Clinic, Paracelsus Medical University, Salzburg, Austria

c Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden

d Department of Forensic Toxicology, Institute of Legal Medicine, University Hospital, Freiburg, Germany

e Institute of Legal Medicine, Humboldt-University, Berlin, Germany

f Department of Toxicology, Laboratoire National de Santé, Université du Luxembourg, Luxembourg.

\* Reprints: Inger Sundström Poromaa, Department of Women's and Children's Health, Uppsala University, 751 85 Uppsala, Sweden. inger.sundstrom@kbh.uu.se.

Received April 11, 2007; revised Aug. 1, 2007; accepted Oct. 12, 2007.

This study was supported by grants from Systembolagets forskningsfond, Sweden.

Presented at the 11th Congress of the European Society for Biomedical Research on Alcoholism, Berlin, Germany, Sept. 23-26, 2007.

## Abstract

**Objectives:** The objective of the study was to investigate whether biomarkers of alcohol consumption would provide additional information to the use of a validated alcohol questionnaire in pregnant women.

**Study Design:** One hundred three pregnant women were included in the study. The women completed the Alcohol Use Disorders Identification Test (AUDIT) questionnaire, and a urine and hair sample was collected. The urine samples were used for determination of ethyl glucuronide (EtG) and ethyl sulfate and the hair samples for EtG and fatty acid ethyl esters (FAEE).

**Results:** Twenty-six women (25.2%) were identified as possible alcohol consumers by the combined use of AUDIT and direct ethanol metabolites. Seven subjects had EtG or FAEE levels in hair highly suspicious of heavy drinking, but only 1 of these were positive according to the AUDIT questionnaire

**Conclusion:** The combined use of the AUDIT questionnaire and direct ethanol metabolites appear to identify more potential alcohol consumers among pregnant women than does the sole use of the AUDIT questionnaire.

Link to the article,

<http://pt.wkhealth.com/pt/re/ajog/Abstract.00000447-200804000-00020.htm;jsessionid=JT2S JL21PBhnn30dgpv1S5kBZL0L4ghk4kJL32LB1WmnRp2Szy5D!285259918!181195628!8091!-1>

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Journal of Neuroscience Research; Volume 86 Issue 5, April 2008

## GLUTATHIONE CONTENT AS A POTENTIAL MEDIATOR OF THE VULNERABILITY OF CULTURED FETAL CORTICAL NEURONS TO ETHANOL-INDUCED APOPTOSIS

Shivani Kaushal Maffi 1 \*, Mary Latha Rathinam 2, Priscilla P. Cherian 2, William Pate 1, Rhoda Hamby-Mason 2, Steven Schenker 2, George I. Henderson 2

1Department of Medicine, Division of Infectious Diseases, University of Texas Health Science Center, San Antonio, Texas

2Department of Medicine, Division of Gastroenterology and Nutrition, University of Texas Health Science Center, San Antonio, Texas

email: Shivani Kaushal Maffi (maffi@uthscsa.edu)

\*Correspondence to Shivani Kaushal Maffi, Department of Medicine, Division of Infectious Diseases, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229

The first two authors contributed equally to this work.

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ERC-UTHSCSA

## ABSTRACT

Ethanol ingestion during pregnancy elicits damage to the developing brain, some of which appears to result from enhanced apoptotic death of neurons. A consistent characteristic of this phenomenon is a highly differing sensitivity to ethanol within specific neuron populations. One possible explanation for this selective vulnerability could be cellular variations in glutathione (GSH) homeostasis. Prior studies have illustrated that ethanol elicits apoptotic death of neurons in the developing brain, that oxidative stress may be an underlying mechanism, and that GSH can be neuroprotective. In the present study, both multiphoton microscopy and flow cytometry demonstrate a striking heterogeneity in GSH content within cortical neuron populations. Ethanol differentially elicits apoptotic death and oxidative stress in these neurons. When neuron GSH content is reduced by treatment with butathione sulfoxamine, the ethanol-mediated enhancement of reactive oxygen species is exacerbated. Sorting of cells into high- and low-GSH populations further exemplifies ethanol-mediated oxidative stress whereby apoptotic indices are preferentially elevated in the low-GSH population. Western blot analysis of the low-GSH subpopulations shows higher ethanol-mediated expression of active caspase 3 and 24-kDa PARP-1 fragments compared with the high-GSH subpopulation. In addition, neuronal content of 4-hydroxynonenal adducts is higher in low-GSH neurons in response to ethanol. These studies suggest that GSH content is an important predictor of neuronal sensitivity to ethanol-mediated oxidative stress and subsequent cell death. The data support the proposition that the differences in proapoptotic responses to ethanol within specific neuron populations reflect a heterogeneity of neuron GSH content. © 2007 Wiley-Liss, Inc.

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Journal of Neuroendocrinology; Volume 20 Issue 4, April 2008

## PRENATAL ALCOHOL EXPOSURE: FOETAL PROGRAMMING, THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS AND SEX DIFFERENCES IN OUTCOME

J. Weinberg, J. H. Sliwowska, N. Lan and K. G. C. Hellemans

Department of Cellular and Physiological Sciences, The University of British Columbia, Vancouver, Canada.

Correspondence to Joanne Weinberg, Department of Cellular and Physiological Sciences, The University of British Columbia, 2350 Health Sciences Mall, Vancouver, BC, V6T 1Z3, Canada (e-mail: [jweinberg@exchange.ubc.ca](mailto:jweinberg@exchange.ubc.ca)).

## ABSTRACT

Prenatal exposure to alcohol has adverse effects on offspring neuroendocrine and behavioural functions. Alcohol readily crosses the placenta, thus directly affecting developing foetal endocrine organs. In addition, alcohol-induced changes in maternal endocrine function can disrupt the normal hormonal interactions between the pregnant female and foetal systems, altering the normal hormone balance and, indirectly, affecting the development of foetal metabolic, physiological and endocrine functions. The present review focuses on the adverse effects of prenatal alcohol exposure on offspring neuroendocrine function, with particular emphasis on the hypothalamic-pituitary-adrenal (HPA) axis, a key player in the stress response. The HPA axis is highly susceptible to programming during foetal and neonatal development. Here, we review data demonstrating that alcohol exposure *in utero* programmes the foetal HPA axis such that HPA tone is increased throughout life. Importantly, we show that, although alterations in HPA responsiveness and regulation are robust phenomena, occurring in both male and female offspring, sexually dimorphic effects of alcohol are frequently observed. We present updated findings on possible mechanisms underlying differential effects of alcohol on male and female offspring, with special emphasis on effects at different levels of the HPA axis, and on modulatory influences of the hypothalamic-pituitary-gonadal hormones and serotonin. Finally, possible mechanisms underlying foetal programming of the HPA axis, and the long-term implications of increased exposure to endogenous glucocorticoids for offspring vulnerability to illnesses or disorders later in life are discussed.

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Journal - Brain Imaging and Behavior, Volume 2, Number 1, March 2008

## OCCIPITAL-TEMPORAL REDUCTION AND SUSTAINED VISUAL ATTENTION DEFICIT IN PRENATAL ALCOHOL EXPOSED ADULTS

Zhihao Li<sup>1</sup>, Claire D. Coles<sup>2, 3</sup>, Mary Ellen Lynch<sup>2</sup>, Xiangyang Ma<sup>1</sup>, Scott Peltier<sup>1</sup> and Xiaoping Hu<sup>1</sup>

(1) Biomedical Imaging Technology Center, Department of Biomedical Engineering, Emory University & Georgia Institute of Technology, Atlanta, GA 30322, USA

(2) Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA 30322, USA

(3) Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 1256 Briarcliff Rd., Third Floor, Atlanta, GA 30306, USA

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### Abstract

Visual attention problems have been reported in association with prenatal alcohol exposure (PAE). With related behavioral data documented in literature, further investigation of this PAE effect would benefit from integrating functional and anatomical imaging data to ascertain its neurobiological basis. The current study investigated the possible functional and anatomical bases for the PAE-related visual sustained attention deficit. Functional magnetic resonance imaging (fMRI) data were collected while the subjects performed a sustained visual attention task. High resolution, three dimensional anatomical images were also collected for morphometric evaluation. In the alcohol-affected subjects, we observed a significant white and gray matter volume reduction in the occipital-temporal area. Meanwhile, their fMRI activations in the same region resided more superiorly than that of the controls resulting in reduced activation in the ventral occipital-temporal area. The location of this PAE functional abnormality approximately matches that of the significant structural reduction. In addition to the well documented corpus callosum abnormalities observed in PAE subjects, the present results reveal a teratogenic effect on the occipital-temporal area. Furthermore, as the occipital-temporal area plays an important role in visual attention, the current observation suggests a neurobiological underpinning for the PAE related deficit in sustained visual attention.

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Journal of Neuroscience Research; Volume 86 Issue 2, February 2008

## **NEOCORTICAL PLASTICITY DEFICITS IN FETAL ALCOHOL SPECTRUM DISORDERS: LESSONS FROM BARREL AND VISUAL CORTEX**

Alexandre E. Medina \*, Thomas E. Krahe

Department of Anatomy and Neurobiology, Virginia Commonwealth University School of Medicine, Richmond, Virginia

email: Alexandre E. Medina (amedina@vcu.edu)

\*Correspondence to Alexandre E. Medina, Department of Anatomy and Neurobiology, Box 0709, Virginia Commonwealth University Medical Center, 1101 East Marshall Street, Room 12-044, Richmond, VA 23298-0709

Funded by: NIH (NIAAA); Grant Number: AA-13023 (to A.E.M.)

### **ABSTRACT**

Fetal Alcohol Spectrum Disorder (FASD) is characterized by a constellation of behavioral and physiological abnormalities, including learning and sensory deficits. There is growing evidence that abnormalities of neuronal plasticity underlie these deficits. However, the cellular and molecular mechanisms by which prenatal alcohol exposure disrupts neuronal plasticity remain elusive. Recently, studies with the barrel and the visual cortex as models to study the effects of early alcohol exposure on neuronal plasticity shed light on this subject. In this Mini-Review, we discuss the effects of ethanol exposure during development on neuronal plasticity and suggest



environmental and pharmacological approaches to ameliorate these problems. © 2007 Wiley-Liss, Inc.

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Neurobiology of Disease; Volume 29, Issue 1, January 2008

## AMELIORATING EFFECTS OF PREADOLESCENT ANIRACETAM TREATMENT ON PRENATAL ETHANOL-INDUCED IMPAIRMENT IN AMPA RECEPTOR ACTIVITY

Nayana Wijayawardhane, Brian C. Shonesya, Thirumalini Vaithianathana, b, Noemi Pandiellaa, Julia Vaglenovaa, Charles R. Breesea, c, Alexander Dityateva, d and Vishnu Suppiramaniama, ,

aDepartment of Pharmacal Sciences, 401 Walker Building, Harrison School of Pharmacy, Auburn University, Auburn, AL 36849, USA

bDepartment of Pharmacology, University of Tennessee Health Science Center, Memphis, TN 38163, USA

cDepartment of Pharmaceutical, Social and Administrative Sciences, University of Appalachia College of Pharmacy, PO Box 700, Oakwood, VA 24631, USA

dCenter for Molecular Neurobiology, University Medical Center Hamburg-Eppendorf, Hamburg 20246, Germany

### Abstract

Ethanol-induced damage in the developing hippocampus may result in cognitive deficits such as those observed in fetal alcohol spectrum disorder (FASD). Cognitive deficits in FASD are partially mediated by alterations in glutamatergic synaptic transmission. Recently, we reported that synaptic transmission mediated by alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA) is impaired following fetal ethanol exposure. This finding led us to develop a rational approach for the treatment of alcohol-related cognitive deficits using aniracetam, an allosteric AMPAR modulator. In the present study, 28 to 34-day-old rats exposed to ethanol in utero were treated with aniracetam, and subsequently exhibited persistent improvement in mEPSC amplitude, frequency, and decay time. Furthermore, these animals expressed positive changes in synaptic single channel properties, suggesting that aniracetam ameliorates prenatal ethanol-induced deficits through modifications at the single channel level. Specifically, single channel open probability, conductance, mean open and closed times, and the number and burst duration were positively affected. Our findings emphasize the utility of compounds which slow the rate of deactivation and desensitization of AMPARs such as aniracetam.

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PNAS January 8, 2008 vol. 105 no. 1

## AN ALCOHOL BINDING SITE ON THE NEURAL CELL ADHESION MOLECULE L1

Enrique Arevalo<sup>\*,†</sup>, Sivananthaperumal Shanmugasundararaj<sup>\*,†</sup>, Michael F. Wilkemeyer<sup>‡</sup>, Xiaowei Dou<sup>‡</sup>, Suzhen Chen<sup>‡</sup>, Michael E. Charness<sup>‡,§</sup>, and Keith W. Miller<sup>\*,†</sup>

+Author Affiliations

\*Department of Anesthesia and Critical Care, Massachusetts General Hospital, Boston, MA 02114;

†Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115; and

‡Veterans Affairs Boston Healthcare System and Department of Neurology, Harvard Medical School, West Roxbury, MA 02132

Edited by Solomon H. Snyder, Johns Hopkins University School of Medicine, Baltimore, MD, and approved November 15, 2007 (received for review August 18, 2007)

### Abstract

Prenatal ethanol exposure causes fetal alcohol spectrum disorders (FASD) in part by disrupting the neural cell adhesion molecule L1. L1 gene mutations cause neuropathological abnormalities similar to those of FASD. Ethanol and 1-butanol inhibit L1-mediated cell–cell adhesion (L1 adhesion), whereas 1-octanol antagonizes this action. To test the hypothesis that there are alcohol binding sites on L1, we used 3-azibutanol and 3-azioctanol, the photoactivatable analogs of 1-butanol and 1-octanol, to photolabel the purified Ig1–4 domain of human L1 (hL1 Ig1–4). 3-Azibutanol (11 mM), like ethanol, inhibited L1 adhesion in NIH/3T3 cells stably transfected with hL1, whereas subanesthetic concentrations of 3-azioctanol (14  $\mu$ M) antagonized ethanol inhibition of L1 adhesion. 3-Azibutanol (100–1,000  $\mu$ M) and 3-azioctanol (10–100  $\mu$ M) photoincorporated into Tyr-418 on Ig4 and into two adjacent regions in the N terminus, Glu-33 and Glu-24 to Glu-27. A homology model of hL1 Ig1–4 (residues 33–422), based on the structure of the Ig1–4 domains of axonin-1, suggests that Glu-33 and Tyr-418 hydrogen-bond at the interface of Ig1 and Ig4 to stabilize a horseshoe conformation of L1 that favors homophilic binding. Furthermore, this alcohol binding pocket lies within 7 Å of Leu-120 and Gly-121, residues in which missense mutations cause neurological disorders similar to FASD. These data suggest that ethanol or selected mutations produce neuropathological abnormalities by disrupting the domain interface between Ig1 and Ig4. Characterization of alcohol agonist and antagonist binding sites on L1 will aid in understanding the molecular basis for FASD and might accelerate the development of ethanol antagonists.

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# DIETARY ZINC SUPPLEMENTATION DURING PREGNANCY PREVENTS SPATIAL AND OBJECT RECOGNITION MEMORY IMPAIRMENTS CAUSED BY EARLY PRENATAL ETHANOL EXPOSURE

Brooke L. Summers<sup>a, b</sup>, Catherine M.A. Henry<sup>d</sup>, Allan M. Rofec and Peter Coyle<sup>a, c</sup>,

<sup>a</sup>Hanson Institute, Institute of Medical and Veterinary Science, Adelaide, SA 5000, Australia

<sup>b</sup>School of Molecular and Biomedical Science, Department of Physiology, University of Adelaide, Adelaide, SA 5000, Australia

<sup>c</sup>Veterinary Services Division, Institute of Medical and Veterinary Science, Adelaide, SA 5000, Australia

<sup>d</sup>Faculty of Medicine, University of New South Wales, Sydney, NSW 2052, Australia

## Abstract

Alcohol-induced zinc (Zn) deficiency is one of the mechanisms proposed as a cause of ethanol teratogenicity. Subcutaneous Zn treatment with ethanol in early pregnancy has been shown to prevent birth abnormalities and memory impairments in mice. This study examined whether dietary Zn supplementation throughout pregnancy can prevent cognitive impairments caused by early ethanol exposure. Pregnant C57BL/6J mice were fed either a control (35 µg Zn/g) or Zn-supplemented (200 µg Zn/g) diet throughout pregnancy. On gestational day (GD) 8, mice received two intraperitoneal injections (4 h apart) of either saline or 25% ethanol (0.015 mL/g). All offspring were screened for physical and behavioural defects (e.g. growth, visual, exploratory, anxiety, motor deficits). Twenty-four phenotypically-normal offspring were randomly selected from each of the four treatment groups (saline ± Zn-supplementation, ethanol ± Zn-supplementation) and tested at 60 d of age using a cross-maze escape task for spatial learning and memory impairments, and an object recognition task. While no differences were observed between treatments for spatial learning, offspring exposed to ethanol demonstrated spatial memory impairments at both 12 and 28 d after learning an escape task, with less correct trials and increased escape latency scores compared with saline-treated mice. Furthermore, these mice also exhibited impairments in object recognition memory. In comparison, ethanol-exposed offspring from dams fed a Zn-supplemented diet throughout pregnancy did not display spatial memory or object recognition deficits, performing at the same level as saline-treated offspring. Therefore, dietary Zn-supplementation during pregnancy prevents spatial and object recognition memory impairments caused by ethanol exposure during early pregnancy.

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## FETAL LEARNING ABOUT ETHANOL AND LATER ETHANOL RESPONSIVENESS: EVIDENCE AGAINST "SAFE" AMOUNTS OF PRENATAL EXPOSURE

Paula Abate\*,<sup>1</sup>, Mariana Pueta\*<sup>1,2</sup>, Norman E. Spear and Juan C. Molina\*<sup>1,2</sup>,

\* Instituto de Investigación Médica Mercedes y Martín Ferreyra C.P. 5016, Córdoba, Argentina; Facultad de Psicología, Universidad Nacional de Córdoba, C.P. 5000, Córdoba, Argentina; CEBICEM, Facultad de Ciencia, Exactas, Físicas y Naturales, Universidad Nacional de Córdoba, C.P. 5000, Córdoba, Argentina; and Department of Psychology, Center for Developmental Psychobiology, Binghamton University, Binghamton, New York 13902

Near-term fetuses of different mammalian species, including humans, exhibit functional sensory and learning capabilities. The neurobiological literature indicates that the unborn organism processes sensory stimuli present in the amniotic fluid, retains this information for considerable amounts of time, and is also capable of associating such stimuli with biologically relevant events. This research has stimulated studies aimed at the analysis of fetal and neonatal learning about ethanol, a topic that constitutes the core of the present review. Ethanol has characteristic sensory (olfactory, taste, and trigeminal) attributes and can exert pharmacologic reinforcing effects. The studies under examination support the hypothesis that low to moderate levels of maternal ethanol intoxication during late pregnancy set the opportunity for fetal learning about ethanol. These levels of prenatal ethanol exposure do not generate evident morphologic or neurobehavioral alterations in the offspring, but they exert a significant impact upon later ethanol-seeking and intake behaviors. Supported by preclinical and clinical findings, this review contributes to strengthening the case for the ability of prenatal ethanol exposure to have effects on the postnatal organism.

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Antioxidants & Redox Signaling, 2008

## NRF2-MEDIATED TRANSCRIPTIONAL INDUCTION OF ANTIOXIDANT RESPONSE IN MOUSE EMBRYOS EXPOSED TO ETHANOL IN VIVO: IMPLICATIONS FOR THE PREVENTION OF FETAL ALCOHOL SPECTRUM DISORDERS

Jian Dong

Bowles Center for Alcohol Studies and Department of Cell and Developmental Biology University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Kathleen K. Sulik

Bowles Center for Alcohol Studies and Department of Cell and Developmental Biology University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Shao-yu Chen

Bowles Center for Alcohol Studies and Department of Cell and Developmental Biology University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

## Abstract

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor that is important in protection against oxidative stress. This study was designed to determine the role of Nrf2 signaling in transcriptional activation of detoxifying and antioxidant genes in an in vivo mouse fetal alcohol syndrome model. Maternal ethanol treatment was found to increase both Nrf2 protein levels and Nrf2-ARE binding in mouse embryos. It also resulted in a moderate increase in the mRNA expression of Nrf2 downstream target detoxifying and antioxidant genes as well as an increase in the expression of antioxidant proteins. Pretreatment with the Nrf2 inducer, 3H-1,2 dithiole-3-thione (D3T), significantly increased Nrf2 protein levels and Nrf2-ARE binding, and strongly induced the mRNA expression of Nrf2 downstream target genes. It also increased the expression of antioxidant proteins and the activities of the antioxidant enzymes. Additionally, D3T pretreatment resulted in a significant decrease in ethanol-induced reactive oxygen species generation and apoptosis in mouse embryos. These results demonstrate that Nrf2 signaling is involved in the induction of antioxidant response in ethanol-exposed embryos. In addition, the potency of D3T in inducing antioxidants as well as in diminishing ethanol-induced apoptosis suggests that further exploration of the antiteratogenic effect of this compound will be fruitful.

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### The National Organisation for Fetal Alcohol Syndrome UK

157 Beaufort Park  
London NW11 6DA  
England

Tel: 020 8458 5951

Fax: 020 8209 3296

Email: [nofas-uk@midlantic.co.uk](mailto:nofas-uk@midlantic.co.uk)

Website: [www.nofas-uk.org](http://www.nofas-uk.org)

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## COGNITIVE NEUROSCIENCE

# Oculomotor control in children with fetal alcohol spectrum disorders assessed using a mobile eye-tracking laboratory

C. R. Green,<sup>1</sup> A. M. Mihic,<sup>1</sup> D. C. Brien,<sup>1</sup> I. T. Armstrong,<sup>1,2</sup> S. M. Nikkel,<sup>3</sup> B. C. Stade,<sup>4</sup> C. Rasmussen,<sup>5</sup> D. P. Munoz<sup>1,2,6,7</sup> and J. N. Reynolds<sup>1,8</sup>

<sup>1</sup>The Center for Neuroscience Studies, Queen's University, Kingston, Ontario, Canada

<sup>2</sup>Department of Physiology, Queen's University, Kingston, Ontario, Canada

<sup>3</sup>Department of Genetics, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada

<sup>4</sup>Department of Paediatrics, St Michael's Hospital, Toronto, Ontario, Canada

<sup>5</sup>Department of Paediatrics, University of Alberta, Edmonton, Alberta, Canada

<sup>6</sup>Department of Psychology, Queen's University, Kingston, Ontario, Canada

<sup>7</sup>Department of Medicine, Queen's University, Kingston, Ontario, Canada

<sup>8</sup>Department of Pharmacology & Toxicology, Queen's University, Kingston, Ontario, Canada

**Keywords:** executive function, fetal alcohol syndrome, saccadic eye movements

## Abstract

Prenatal exposure to alcohol can result in a spectrum of adverse developmental outcomes, collectively termed fetal alcohol spectrum disorders (FASDs). This study evaluated deficits in sensory, motor and cognitive processing in children with FASD that can be identified using eye movement testing. Our study group was composed of 89 children aged 8–15 years with a diagnosis within the FASD spectrum [i.e. fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), and alcohol-related neurodevelopmental disorder (ARND)], and 92 controls. Subjects looked either towards (prosaccade) or away from (antisaccade) a peripheral target that appeared on a computer monitor, and eye movements were recorded with a mobile, video-based eye tracker. We hypothesized that: (i) differences in the magnitude of deficits in eye movement control exist across the three diagnostic subgroups; and (ii) children with FASD display a developmental delay in oculomotor control. Children with FASD had increased saccadic reaction times (SRTs), increased intra-subject variability in SRTs, and increased direction errors in both the prosaccade and antisaccade tasks. Although development was associated with improvements across tasks, children with FASD failed to achieve age-matched control levels of performance at any of the ages tested. Moreover, children with ARND had faster SRTs and made fewer direction errors in the antisaccade task than children with pFAS or FAS, although all subgroups were different from controls. Our results demonstrate that eye tracking can be used as an objective measure of brain injury in FASD, revealing behavioral deficits in all three diagnostic subgroups independent of facial dysmorphism.

## Introduction

Adverse outcomes occurring in offspring as a consequence of prenatal exposure to alcohol have been documented (McGee & Riley, 2006; Kodituwakku, 2007). Fetal alcohol spectrum disorder (FASD) is the umbrella term used to represent the full range of teratogenic effects attributed to gestational alcohol exposure, including fetal alcohol syndrome (FAS) (Koren *et al.*, 2003). An FAS diagnosis requires the presence of prenatal and postnatal growth restriction, craniofacial dysmorphism, and central nervous system dysfunction (Clarren & Smith, 1978; Chudley *et al.*, 2005). In the absence of one or more of these features, individuals may receive a diagnosis of partial FAS (pFAS) or alcohol-related neurodevelopmental disorder (ARND).

Individuals with FASD may present with a range of impairments in executive function (Lezak, 1995; Funahashi, 2001), which include deficits in spatial working memory, planning, response inhibition, abstract thinking, and the ability to shift attention (Rasmussen, 2005; Kodituwakku, 2007). Impairments in executive function and social skills reported by parents and teachers demonstrate that pervasive deficits impact on behaviors across multiple settings (Schonfeld *et al.*, 2006).

Measurement of eye movement control is a powerful tool for assessing executive function (Munoz & Everling, 2004). An extensive literature based on neurophysiological, anatomical, imaging and lesion studies has contributed to our understanding of the neural circuits controlling saccadic eye movements (Heide & Kompf, 1998; Pierrot-Deseilligny *et al.*, 2004; Leigh & Zee, 2006; Sweeney *et al.*, 2007), and paradigms have been used extensively in basic and clinical research (Munoz *et al.*, 2007; Ramat *et al.*, 2007).

*Correspondence:* Dr J. N. Reynolds, <sup>8</sup>Department of Pharmacology and Toxicology as above.

E-mail: jnr@queensu.ca

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In this study, subjects were required to look either towards (prosaccade) or away from (antisaccade) a peripheral target that appeared on a computer monitor. Prosaccades can be triggered automatically by visual inputs to the saccade-generating circuit from the visual and posterior parietal cortices (Munoz & Everling, 2004). Antisaccades require additional steps of processing: suppression of the automatic prosaccade and initiation of the voluntary antisaccade. Successful antisaccade performance relies on circuitry that includes higher brain centers such as the frontal cortex and basal ganglia (Munoz & Everling, 2004). Deficits in parietal and frontal cortices and basal ganglia have been previously reported in FASD (McGee & Riley, 2006), making saccade tasks an appropriate tool for assessing executive function.

In a previous report (Green *et al.*, 2007c), we described eye movement abnormalities in a small cohort of children with FASD. However, the sample size was too small to allow determination of the effects of delayed development or diagnosis within the FASD spectrum on oculomotor control. To address these important questions, we developed a mobile laboratory that facilitated eye movement testing in different communities across Canada. We hypothesized that children with FASD display a developmental delay in eye movement control, such that younger children exhibit greater deficits than older children. Moreover, we predicted that differences in the magnitude of deficits in oculomotor control exist among the diagnostic subgroups, such that the children with FAS demonstrate the most profound deficits. Preliminary versions of these data have been presented in abstract form (Green *et al.*, 2007a,b).

## Materials and methods

### Participants

All experimental procedures were reviewed and approved by the Human Research Ethics Boards of Queen's University, the Children's Hospital of Eastern Ontario (Ottawa subjects), and the University of Alberta (Edmonton subjects). Children with FASD were recruited from eight different communities across Ontario and one community in Alberta. A total of 189 subjects were recruited into the study: 92 (40 males, 52 females;  $11.2 \pm 0.2$  years of age; range, 8–15 years) were control children (non-FASD), and 97 were grouped as having FASD. Of the 97 subjects included in the FASD group, 89 (44 males, 45 females;  $10.7 \pm 0.2$  years of age; range, 8–15 years) had a diagnosis within the FASD spectrum (FAS, pFAS, and ARND), and eight were suspected and/or exposed, but had yet to receive a definitive diagnosis. The children with FASD were previously assessed at local diagnostic clinics in accordance with the Canadian Diagnostic guidelines (Chudley *et al.*, 2005). Datasets from one control subject and one subject with FASD were lost because of equipment problems. All data included in the analysis for the FASD group were obtained from the 88 children who had received a diagnosis within the spectrum and 91 controls. For the purpose of analysis based on age, children were placed in one of three separate age bins: 8–10 years, 11–12 years, and 13–15 years.

Of the 89 children with FASD, 60 were medicated for behavioral symptoms related to their co-morbidities (Table 1). On the test day, primary care-givers were asked to withhold the stimulant medication until the testing was completed. Of the 38 children taking stimulant medications, eight were tested on medication. For the remaining 30 children, the last daily dose of stimulant medication was administered a minimum of 12 h prior to testing.

All control subjects had no known neurological, psychiatric or visual disorders, other than requiring corrective lenses. Primary care-

TABLE 1. Demographic data for subjects

Category	Control ( <i>n</i> = 92)	FASD ( <i>n</i> = 89)
Age $\pm$ SD (years)	$11.2 \pm 0.2$	$10.7 \pm 0.2$
Male : female	40 : 52	44 : 45
Parent/care-giver level of education $\pm$ SD (years)	$16.5 \pm 0.3$	$14.4 \pm 0.3^*$
Medication, <i>n</i> (%)		
Stimulant	0 (0)	38 (43)
Antipsychotic	0 (0)	29 (33)
Antidepressant	0 (0)	10 (11)
Anticonvulsant	0 (0)	3 (3)
Other <sup>†</sup>	12 (13)	20 (22)
Co-morbidity (10% of subjects with FASD, <i>n</i> (%))		
Sleeping disorders	10 (11)	55 (62)
ADHD/ADD	0 (0)	53 (60)
Oppositional defiant disorder	0 (0)	19 (21)
Anxiety	0 (0)	15 (17)
Asthma	12 (13)	10 (11)
Depression	1 (1)	10 (11)
Ratio of adults/children (home) $\pm$ SD	$0.88 \pm 0.04$	$0.76 \pm 0.06^*$
Living with biological parents, <i>n</i> (%)	87 (95)	15 (17)
Parent or care-giver employed, <i>n</i> (%)	79 (86)	65 (73)

ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; FASD, fetal alcohol spectrum disorder; SD, standard deviation. \* $P < 0.05$ .

<sup>†</sup>Antihistamine, anti-asthma, oral contraceptives, melanin.

givers were informed of the nature of the study, and provided written consent on behalf of the participants. All subjects completed one 1-h eye movement session. Each subject received \$10 and a small gift for participating in the study.

### Saccade task

All participants performed a blocked design saccade task (Fig. 1), consisting of two blocks of prosaccade and two blocks of antisaccade trials, each consisting of 80 trials (320 trials in total). Subjects received

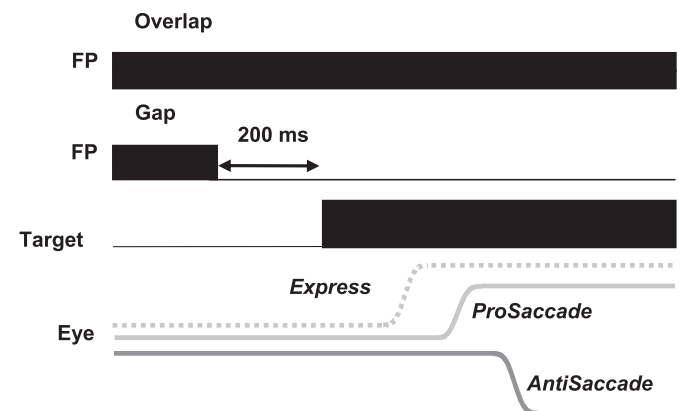


FIG. 1. In the prosaccade task, the subject was instructed to look from the central fixation point (FP) towards the eccentric target. In the antisaccade task, the subject was instructed to look away from the eccentric target to the opposite side. In both tasks, the state of fixation was manipulated such that, in the overlap condition, the FP remained illuminated while the target appeared, and in the gap condition, the FP was extinguished for a period of 200 ms before the target appeared. In both conditions, the saccadic reaction time was measured from the time of target appearance to the initiation of the first saccade.

breaks when needed, and refreshments were provided upon completion of the task. Participants were seated comfortably in a darkened room, facing the center of a laptop screen located 46 cm away. Task presentation on the laptop screen was produced using E-PRIME software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). A red spot with a luminosity of  $\sim 12.5$  cd/m<sup>2</sup>, and  $x = 0.57$  and  $y = 0.32$  coordinates in CIE space (relative to the background lumination of  $\sim 1.0$  cd/m<sup>2</sup>, and  $x = 0.34$  and  $y = 0.34$  coordinates in CIE space) was positioned at the center of the screen, and served as the initial fixation point (FP). Red target spots were positioned on the screen at 15° to the right or left of the central FP. The screen was diffusely illuminated between trials, to avoid dark adaptation. Each trial began with a 250-ms period of darkness. The FP appeared for 1000 ms, and then one of two conditions occurred (Fig. 1). In the gap condition, the FP was extinguished and, after a period of 200 ms, the target appeared in the right or left visual field. In the overlap condition, the FP remained illuminated while the target appeared.

In the block of prosaccade trials, participants were instructed to look towards the target as soon as it appeared. In the block of antisaccade trials, participants were instructed to look away from the target to the opposite side. After the target had been illuminated for 1000 ms, all visual stimuli disappeared. The background illumination then reappeared, indicating the end of that trial. Target location (right or left) and fixation condition (gap or overlap) were pseudo-randomly interleaved throughout each block of trials. Subjects were asked to repeat and demonstrate the instructions to the experimenter, to ensure that they understood the task before the onset of data collection.

#### Recording and analysis of eye movement

The video-based infrared eye tracker (ISCAN Inc., Burlington, MA, USA) was adapted for use as a mobile laboratory, and transported to each test center. Eye position was measured using a head-mounted camera that was connected to a data acquisition computer. The video-based infrared eye tracker tracked the pupil movement, and measures of eye position and pupil size were extracted at a sampling rate of 240 Hz. Only the left eye position was digitized. Saccades were detected off-line at three standard deviations above the background, and must have lasted for longer than five sample points (MATLAB, custom software, The Mathworks, Inc., Natick, MA, USA).

Saccadic reaction time (SRT) was defined as the time from target appearance to initiation of the first saccade that exceeded 30°/s. Saccades were scored as correct if the first movement after target appearance was  $> 5^\circ$  in amplitude and in the correct direction (i.e. towards the target for prosaccades, and away from the target for antisaccades). Saccades were scored as incorrect if the first saccade after the appearance of the target was in the wrong direction relative to the instruction (i.e. away from the target in the prosaccade, and towards the target in the antisaccade). All saccade marks and direction errors were verified off-line. The mean SRT in the prosaccade and antisaccade task was computed from all correct trials with reaction latencies between 90 and 1000 ms, to eliminate short-latency anticipatory saccades (Munoz *et al.*, 1998). In addition, we measured express saccades (latency: 90–140 ms), which are the shortest-latency visually triggered saccades (Fischer *et al.*, 1993; Dorris *et al.*, 1997); this express epoch was confirmed for the mobile laboratory. There was some variability in the experimental conditions across multiple test sites. Most notable was the amount of ambient light in which the test sessions were conducted, and we attempted to control for this variability by covering external light sources (i.e. windows) with curtains or sheets. However, target luminosity changed very little regardless of these differences in background ambient light. We also

maintained similar set-up protocols to ensure that equipment and experimenter/subject space was consistent for each test site.

The following parameters were computed for each condition (gap, overlap): the mean SRT for correct trials, the coefficient of variation (CV) of SRT for correct trials [(CV = standard deviation/mean)  $\times$  100], the percentage of express saccades, and the percentage of direction errors.

#### Inclusion/exclusion criteria

In order to determine inclusion and exclusion criteria, SRT histograms were prepared for each subject for each experimental task (prosaccade, antisaccade) and condition (gap, overlap). On the basis of these figures, subjects were placed in bins according to their performance. For example, selection A included all subjects who could perform saccades under each task and condition, and selection E included those subjects who could only perform prosaccades. This approach provided a way of excluding subjects who could not perform certain tasks or situations where only a minimum number of trials were completed under a given condition. Univariate data analyses were conducted for each outcome measure for each task (prosaccade and antisaccade) in each condition (overlap and gap), including only the datasets from those subjects who were successful in performing the given task in the specified condition. Subsequently, analysis including both tasks and both conditions demonstrated that the statistical comparisons obtained from the complete dataset were not different from the individual univariate analyses. Therefore, statistically significant outcome measures from the complete dataset constituted a true representation of the study population.

#### Data analysis

The two experimental tasks (prosaccade and antisaccade) contained one within-subject factor [fixation state (gap vs. overlap)] and three between-group factors [clinical group (FASD vs. control), age (bins: 8–10 years, 11–12 years, and 13–15 years), and sex]. As attention deficit hyperactivity disorder (ADHD) results in deficits in performance of eye movement tasks (Munoz *et al.*, 2003), and ADHD was a frequently reported co-morbidity in the FASD group in this study, we included co-morbid ADHD as a covariable in the data analysis. Moreover, the impacts of medication use and parent/care-giver level of education on the performance of eye movement tasks were also tested for in the analysis. Thus, the data were first tested using multiple analysis of covariance (MANCOVA, SPSS v. 16, SPSS, Inc., Chicago, IL, USA), to examine how the dependent measures (SRT, CV, express saccades, and direction errors) were affected by the fixed factor of clinical group (control vs. FASD), and by the covariables of age, sex, co-morbid ADHD, medication use, and parental level of education. Subsequently, all dependent measures (SRT, CV, express saccades, and direction errors) were analysed using ANOVA with  $\alpha$  set at 0.05. Difference scores (i.e. anti-effect and gap-effect) were analysed with two-tailed, unpaired Student's *t*-tests corrected with Welch's approximation when the assumption for homogeneity of variance was not met. The effect of diagnosis (ARND, pFAS, and FAS) was also determined by matching each subject in the FASD group (as closely as possible) to a control subject by age and sex. FASD and control subjects, once subdivided, were analysed by univariate analyses to test for differences between the diagnostic groups, and a Newman-Keuls *post hoc* test for multiple comparisons was conducted to contrast the pairs. Effect sizes were calculated from the means and standard deviations obtained for the major outcome measures (Cohen, 1988).



We focus on descriptions of the relevant statistical parameters for comparisons and interactions that occurred between the control and FASD groups.

## Results

Consistent with previous studies (Munoz *et al.*, 1998; Dafoe *et al.*, 2007), the MANCOVA revealed significant main effects of task [prosaccade vs. antisaccade,  $F_{4,169} = 40.8$ ,  $P < 0.01$ , effect size ( $\eta^2$ ) = 0.49, power = 1] and fixation condition (gap vs. overlap,  $F_{4,169} = 11.0$ ,  $P < 0.01$ ,  $\eta^2 = 0.21$ , power = 1). There were significant interactions between task and clinical group ( $F_{4,169} = 7.8$ ,  $P < 0.01$ ,  $\eta^2 = 0.16$ , power = 1), task and age ( $F_{4,169} = 16.2$ ,  $P < 0.01$ ,  $\eta^2 = 0.28$ , power = 1), task and fixation state ( $F_{4,169} = 5.0$ ,  $P < 0.01$ ,  $\eta^2 = 0.11$ , power = 0.96), and fixation state and age ( $F_{4,169} = 4.4$ ,  $P < 0.01$ ,  $\eta^2 = 0.21$ , power = 1). The MANCOVA analysis did not reveal any effect of co-morbid ADHD, medication use or parental level of education on any of the dependent measures. We further tested the potential influence of the covariables by performing a multivariate stepwise regression analysis, which revealed a small effect of co-morbid ADHD (< 5% of the variance) for SRT, but not for any other dependent measure. As there was no significant interaction between group and fixation state, the data for the overlap and gap conditions were combined for analyses of the effect of the diagnostic subgroups.

### Saccadic reaction time

Figure 2 depicts the cumulative distribution of SRT for correct responses (positive values) and direction errors (negative values) in all

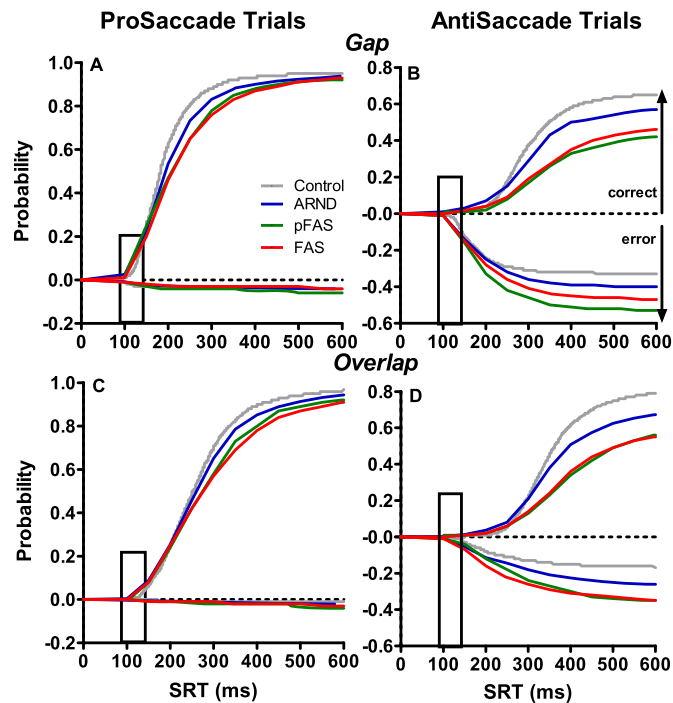


FIG. 2. Cumulative distribution of saccadic reaction times (SRTs) for correct responses (positive values on the ordinate) and direction errors (negative values on the ordinate) for prosaccade (A and C) and antisaccade (B and D) trials in the gap (A and B) and overlap (C and D) conditions. ARND, alcohol-related neurodevelopmental disorder data; pFAS, partial fetal alcohol syndrome data; FAS, fetal alcohol syndrome data. The open box highlights the express saccade epoch (90–140 ms).

experimental conditions for control children and those diagnosed with ARND, pFAS, or FAS. Children with FASD had longer SRTs than controls ( $F_{1,165} = 18.6$ ,  $P < 0.001$ ). The anti-effect (anti-SRT – pro-SRT) provides a measure of the difference in reaction times for antisaccades and prosaccades, thus illustrating differences in the voluntary and automatic mechanisms. The anti-effect for children with FASD was not significantly different from that of control children in the overlap or gap conditions ( $P > 0.05$ ). The mean anti-effects were  $100 \pm 7$  ms and  $119 \pm 7$  ms for children with FASD, and  $94 \pm 5$  ms and  $109 \pm 4$  ms for controls, in the overlap and gap conditions, respectively.

The gap-effect (overlap SRT – gap SRT) provides a measure of the difference between fixation conditions, and serves to illustrate whether there are deficits in the processes of disengagement from fixation. The mean gap-effects for prosaccades were  $71 \pm 4$  ms for children with FASD and  $75 \pm 3$  ms for control subjects, and there was no significant difference between groups ( $P > 0.05$ ). Similarly, the gap-effect for antisaccades was also not significantly different between the two groups ( $P > 0.05$ ), and the means were  $51 \pm 7$  ms and  $60 \pm 2$  ms for FASD and control subjects, respectively.

After pairing of each child within the diagnostic subgroup with the appropriate control, unpaired *t*-tests were conducted. In the prosaccade task, complete datasets were obtained from 42 children with ARND, 18 with pFAS, and 25 with FAS; in the antisaccade task, there were 41 children with ARND, 18 with pFAS, and 24 with FAS. In comparison to their matched controls, children with ARND had longer prosaccade SRTs ( $t_{80} = 2.6$ ,  $P < 0.05$ ), but were not different for antisaccade SRTs ( $P > 0.05$ ), although the scores approached significance ( $P = 0.06$ ). Children with pFAS were not significantly different from their matched controls with respect to prosaccade SRTs ( $P > 0.05$ ), but did have longer antisaccade SRTs ( $t_{36} = 3.1$ ,  $P < 0.01$ ). As compared to their matched controls, children with FAS demonstrated longer prosaccade SRTs ( $t_{61} = 3.1$ ,  $P < 0.01$ ) and antisaccade SRTs ( $t_{45} = 3.6$ ,  $P < 0.01$ ).

We were also interested in determining whether there were significant differences between children with ARND, pFAS and FAS across the different outcome measures. There were no significant differences among the diagnostic subgroups for prosaccade SRTs (Fig. 3A). However, there was a significant difference for antisaccade SRT ( $F_{2,79} = 5.7$ ,  $P < 0.01$ ), such that children with pFAS and FAS had longer SRTs than children with ARND ( $P < 0.05$ ) (Fig. 3D).

### CV SRT

The CV expresses the intra-subject variability in SRT. Children with FASD demonstrated greater variability than controls ( $F_{1,165} = 32.0$ ,  $P < 0.001$ ). This difference in SRT variability among children in the FASD group is probably due to increased heterogeneity in task performance resulting from differing degrees of brain injury and subsequent dysfunction following prenatal alcohol exposure.

In comparison to their matched control groups, children with ARND or pFAS were not different for prosaccade CV ( $P > 0.05$ ; Fig. 3B). In contrast, children with ARND ( $t_{79} = 3.7$ ,  $P < 0.01$ ) and pFAS ( $t_{36} = 3.3$ ,  $P < 0.01$ ) were different from their matched control groups for antisaccade CV (Fig. 3E). As compared to their matched controls, children with FAS demonstrated greater prosaccade CV ( $t_{46} = 3.2$ ,  $P < 0.01$ ) and antisaccade CV ( $t_{45} = 3.7$ ,  $P < 0.01$ ) (Fig. 3B and E).

Among the diagnostic subgroups, there were no significant differences in CV for prosaccades or antisaccades (Fig. 3B and E) ( $P > 0.05$ ).

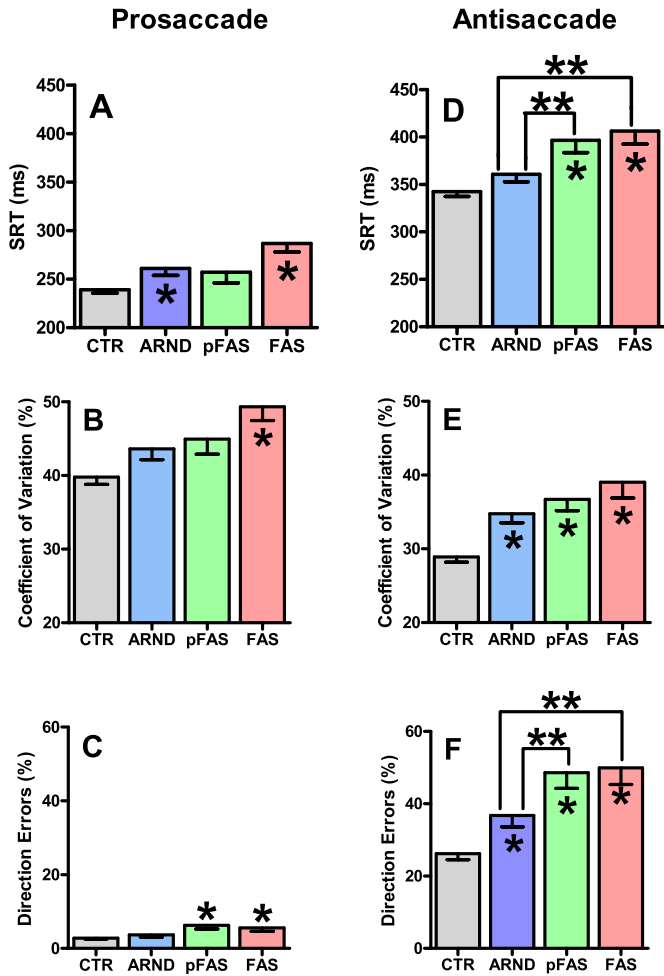


FIG. 3. Quantification of parameters for the prosaccade (A–C) and antisaccade (D–F) tasks. (A and D) Mean saccadic reaction times (SRTs) for correct responses. (B and E) Coefficient of variation in SRT [(standard deviation of SRT/mean SRT) × 100%]. (C and F) Percentage of direction errors. CTR, control data (subgroups combined); ARND, alcohol-related neurodevelopmental disorder data; pFAS, partial fetal alcohol syndrome data; FAS, fetal alcohol syndrome data. \* $P = 0.05$  as compared with matched-control subjects; \*\* $P < 0.05$  for ARND difference from pFAS and FAS.

**Express saccades**

In contrast to our previous findings (Green *et al.*, 2007c), where children with FASD generated significantly fewer express saccades, there was no effect of either clinical group (control vs. FASD) or diagnostic subgroup (ARND, pFAS, FAS) on the proportion of express saccades ( $P > 0.05$ ) (data not shown).

**Direction errors**

Children with FASD made more direction errors than controls ( $F_{1,165} = 30.5$ ,  $P < 0.001$ ). In comparison to their matched control group, children with ARND were not different for direction errors in the prosaccade task, although the difference approached significance ( $P = 0.055$ ). As compared with their respective control groups, children with pFAS ( $t_{36} = 3.7$ ,  $P < 0.01$ ) or FAS ( $t_{46} = 2.0$ ,  $P < 0.05$ ) made more direction errors in the prosaccade task (Fig. 3C). In the antisaccade task, children with ARND ( $t_{79} = 3.8$ ,  $P < 0.01$ ), pFAS ( $t_{36} = 2.7$ ,  $P < 0.05$ ) or FAS ( $t_{45} = 4.0$ ,  $P < 0.01$ ) all

made more direction errors than their matched control groups (Fig. 3F).

Among the diagnostic subgroups, there were no significant differences in the percentage of direction errors for prosaccades (Fig. 3C) ( $P > 0.05$ ). In contrast, there was a significant difference between the diagnostic subgroups for errors in the antisaccade task ( $F_{2,79} = 3.9$ ,  $P < 0.05$ ), such that children with ARND made fewer direction errors than the children with pFAS or FAS (Fig. 3F).

**Age**

To examine the effect of age, children in the two experimental groups (controls and FASD) were distributed into different age bins: 8–10 years, 11–12 years, and 13–15 years. The ANOVA revealed a significant effect of age for SRT ( $F_{2,165} = 11.2$ ,  $P < 0.001$ ), CV ( $F_{2,165} = 9.6$ ,  $P < 0.001$ ), and direction errors ( $F_{2,165} = 13.5$ ,  $P < 0.001$ ), but not for express saccades ( $F_{2,165} = 0.4$ ,  $P = 0.6$ ). Consistent with previous studies (Munoz *et al.*, 1998), performance in these tasks improved across the range of ages tested for children with FASD and controls, as observed for antisaccade SRT and percentage of direction errors in the gap and overlap conditions (Fig. 4). The same observations were made for antisaccade CV, as well as prosaccade SRT, CV, and percentage of direction errors (not shown). However, there was no interaction between age and group, which suggests that deficits in oculomotor control in children with FASD cannot be explained by developmental delay alone, as they failed to achieve age-matched control levels of performance.

**Effect size**

The effect size was calculated for the dependent measures (SRT, CV, express saccades, and direction errors) for both prosaccade and

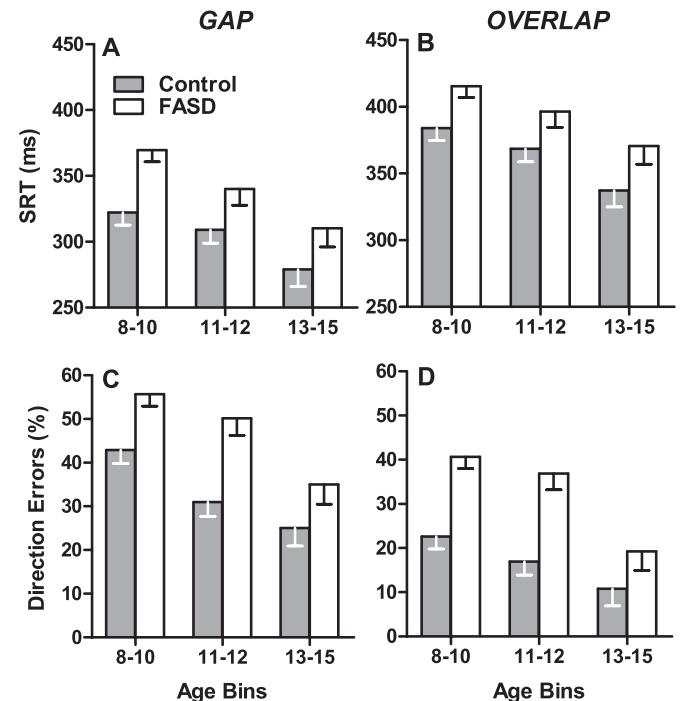


FIG. 4. Mean saccadic reaction times (SRTs) (A and B) and direction errors (C and D) vs. age for the antisaccade task in the gap (A and C) and overlap (B and D) conditions. Shaded bars, control data; open bars, fetal alcohol spectrum disorders (FASD) data.

TABLE 2. Effect size for eye movement outcome measures

Task	Cohen's <i>d</i>	Effect-size ( <i>r</i> )
Prosaccade SRT	-0.64	-0.31
Prosaccade coefficient of variation	-0.59	-0.28
Prosaccade express saccades	0.07	0.04
Prosaccade direction errors	-0.60	-0.29
Antisaccade SRT	-0.69	-0.33
Antisaccade coefficient of variation	-0.99	-0.44
Antisaccade direction errors	-0.92	-0.42

SRT, saccadic reaction time.

antisaccade tasks (Table 2). With the exception of express saccades, these outcome measures demonstrated moderate to large effect sizes (0.5–0.99), indicating a significant degree of non-overlap in the performance of the two groups.

## Discussion

In this study, subjects were required to look either towards (prosaccade) or away from (antisaccade) a peripheral target that appeared on a computer monitor. The former probes the ability of subjects to generate automatic visually triggered saccades, and the latter tests the ability to suppress the automatic saccade and generate a voluntary response in the opposite direction. Children with FASD exhibited increased saccadic reaction times, increased intra-subject variability, and increased direction errors. We also demonstrated that the greatest magnitude of difference in performance across the diagnostic subgroups occurred for antisaccade tasks, which reflects deficits in executive function (Munoz & Everling, 2004). Moreover, children with FASD never achieved a level of performance equivalent to that of the age-matched control group, which suggests that deficits in eye movement control may persist into adulthood (Chudley *et al.*, 2007). We discuss these findings as they relate to the current understanding of oculomotor control and diagnostic subgroups of FASD.

### Oculomotor circuitry

The oculomotor system has been well characterized (Heide & Kompf, 1998; Munoz & Everling, 2004; Pierrot-Deseilligny *et al.*, 2004; Sweeney *et al.*, 2007). The main cortical areas involved in saccade generation are the parietal eye field located in the posterior parietal cortex (PPC), the frontal eye fields (FEFs), the dorsolateral prefrontal cortex (dlPFC), and the supplementary eye fields (SEFs) in the frontal lobe (Munoz & Everling, 2004), all of which project directly to the intermediate layers of the superior colliculus (SCi) to control saccade production. Oculomotor areas of the frontal cortex also send projections to the SCi via the direct, indirect and hyperdirect pathways through the basal ganglia (Hikosaka *et al.*, 2000; Nambu *et al.*, 2002; Munoz & Everling, 2004; Munoz *et al.*, 2007). The basal ganglia are generally associated with cognitive and motor function, and play a key role in oculomotor control (Hikosaka *et al.*, 2000). The caudate nucleus is related to oculomotor behaviors that are necessary for predicting environmental changes (Hikosaka *et al.*, 1989; Cameron *et al.*, 2007). Decreased activity in this component of the basal ganglia may impede performance even in simple oculomotor tasks such as the prosaccade and antisaccade tasks.

Parietal eye field lesions produce increased prosaccade latencies, with little effect on volitional saccades in monkeys (Lynch & McLaren, 1989); unilateral lesions to the PPC increase prosaccade

latency in both the gap and overlap conditions in humans (Pierrot-Deseilligny *et al.*, 1987, 1991b). Patients with lesions to the FEF demonstrate profound difficulties in initiating antisaccades, leading to elevated SRTs (Rivaud *et al.*, 1994; Gaymard *et al.*, 1999), suggesting its critical role in the initiation of intentional voluntary saccades. Lesions to the dlPFC lead to an increase in direction errors (i.e. automatic prosaccades) in the antisaccade paradigm, whereas prosaccades are relatively unaffected (Guitton *et al.*, 1985; Pierrot-Deseilligny *et al.*, 1991a). The SEF is important for saccade sequences by combining or coordinating voluntary saccades, and may be important for generation of successful antisaccades (Schlag-Rey *et al.*, 1997; Gaymard *et al.*, 1998).

The results from our study demonstrate two areas of deficient oculomotor control in children with FASD: (i) saccade initiation leading to increased SRTs; and (ii) saccade suppression resulting in increased direction errors in the antisaccade task. These deficits are consistent with damage to basal ganglia and parietal and frontal cortices. Structural magnetic resonance imaging (MRI) studies have demonstrated a number of abnormalities following prenatal alcohol exposure: (i) a disproportionate reduction in the parietal lobe (Archibald *et al.*, 2001); (ii) a relative increase in gray matter and decrease in white matter in the perisylvian cortex of the parietal lobes (Sowell *et al.*, 2001); (iii) reduced brain growth in the frontal lobes, including the orbitofrontal cortex (Riley *et al.*, 2004); and (iv) decreased basal ganglia volumes, with specific reductions in the caudate nucleus (Mattson *et al.*, 1996). Decreased caudate activity has also been shown using the blood oxygenation level-dependent signal from functional MRI studies in subjects with FASD following tasks that require inhibitory control (Fryer *et al.*, 2007). Taken together, these findings indicate that prenatal alcohol exposure has prolonged effects on brain development long after the *in utero* insult. These results are consistent with the known deficits in executive function associated with FASD (Rasmussen, 2005), and implicate the basal ganglia and parietal and frontal cortices as areas of particular sensitivity to prenatal ethanol exposure.

To summarize, PPC damage probably contributes to the increased SRTs observed for prosaccades in children with FASD, whereas damage to frontal structures (FEF, SEF, and dlPFC) and basal ganglia lead to increased SRTs for antisaccades and reduced ability to suppress automatic saccades. Downstream structures such as the SCi are probably affected only indirectly via aberrant projections from the frontal or parietal cortices or basal ganglia. On the basis of the normal prosaccade metrics in FASD (Green *et al.*, 2007c) and the normal gap-effect (this study), it appears that the SCi and brainstem saccade-generating circuits remain structurally intact (Leigh & Zee, 2006), and the functional abnormalities are due to atypical connections arising from upstream structures. We attribute the increased direction errors observed in the prosaccade task to difficulties in focused attention in children with FASD. Future functional imaging studies using the same oculomotor tasks will confirm or refute the extent of involvement of these structures, and provide more definitive answers.

In contrast to our previous report (Green *et al.*, 2007c), children with FASD did not execute fewer express saccades than controls. This observation was not attributed to sudden performance improvement by the children with FASD; rather, it was due to the control subjects, who generated fewer express saccades under the experimental conditions used in the mobile laboratory. In our previous study, complete darkness was achieved during experimental testing; however, during target presentation, the same conditions were not possible using the mobile laboratory, and the presence of ambient luminance probably underlies this result. These observations warrant further investigation.

### Developmental delay and FASD subgroups

This large-scale study allowed us to address questions related to the effects of age and diagnostic subgroup on oculomotor behavior in children with FASD. There was no age by group interaction in performance of the oculomotor tasks. Although there was an improvement with age, subjects with FASD failed to achieve age-matched control levels of task performance at any of the ages tested. This suggests that the deficits in oculomotor control cannot be explained by developmental delay alone; they are probably attributable to brain injury that persists well into adulthood (Chudley *et al.*, 2007), involving dysfunction of the frontal–striatal circuitry.

We postulated that eye movement testing would reveal differences in the magnitude of deficits among the diagnostic subgroups (i.e. FAS, pFAS, and ARND). For instance, we expected that children with FAS, who are considered to be at the more severe end of the spectrum, would exhibit the greatest magnitude of deficits in eye movement control. This postulate was supported by the data obtained for the antisaccade task, which revealed that children with ARND had shorter SRTs, and made fewer direction errors, than children with pFAS or FAS. On a number of neuropsychological tests that probe aspects of executive function, published studies of children prenatally exposed to alcohol have reported no performance differences between dysmorphic and non-dysmorphic children (Mattson *et al.*, 1999; Schonfeld *et al.*, 2006). Alcohol-exposed individuals with and without facial features exhibited statistically significant increases in cortical thickness, demonstrating that the facial phenotype was not a prerequisite for brain dysmorphology (Sowell *et al.*, 2007). In a functional MRI study, response inhibition in children and adults with heavy prenatal alcohol exposure showed no significant differences in the regions of interest between individuals with and without an FAS diagnosis, although both groups were significantly different from control subjects (Fryer *et al.*, 2007). Notably, children with ARND are most difficult to diagnose in a clinical situation, as they lack the facial dysmorphology (Chudley *et al.*, 2005). Although we found differences between the diagnostic subgroups in the antisaccade task, all subgroups were different from their age-matched controls, even the children with ARND (Fig. 3). Thus, measuring deficits in eye movement control may have significant potential for screening individuals at risk for FASD.

### Study limitations

The majority of children in the FASD group (83%) were living in foster or adoptive homes, and in the majority of cases (74%) the primary care-giver was employed at the time of testing. Information on medical and family histories, including drug and alcohol abuse by first-generation relatives, was collected for each participant in the study. However, for a large proportion of the children in the FASD group (those in foster or adoptive homes), information on maternal and paternal drug and alcohol abuse was not available, which prevents us from examining the impact of family history on the performance of eye movement tasks in our study group. A positive family history of alcohol abuse has been found to influence some, but not all, parameters of eye movement tasks (Blekher *et al.*, 2002) and to contribute to an increase in the number of impulsive errors in executive function tasks (Saunders *et al.*, 2008). Thus, the inability to examine this potential confound is a limitation of the current study. Co-morbidities, in particular ADHD, occur with high frequency in children with FASD (Table 1). However, in the current study we found that co-morbid ADHD could not account for the deficits in performance of eye movement tasks found for the FASD group. Interest-

ingly, there was a small but statistically significant contribution of co-morbid ADHD on SRT, which suggests that co-morbid disorders may contribute to differing patterns of behavioral deficits in eye movement control in children with FASD. We are currently conducting a separate study to more thoroughly investigate the potential contribution of co-morbid disorders such as ADHD to the deficits in eye movement behaviors observed in children with FASD.

### Conclusion

Saccadic eye movement tasks show promise for assessing the brain injury resulting from prenatal exposure to alcohol. Children between the ages of 8 and 15 years demonstrated profound deficits across many outcome measures for both prosaccade and antisaccade tasks, suggesting dysfunction in frontal and parietal cortices and the basal ganglia. Thus, eye movement experiments, and particularly the antisaccade task, provide objective measures of executive dysfunction in children with FASD and may provide a more sensitive measure of overall cognitive function. This is an important point, as it has been shown that performance across tasks of executive function were lower in FASD than would be otherwise predicted by IQ alone, supporting the need for novel tools that can provide sensitive and specific assessments of brain injury (Niccols, 2007). With the advent of eye tracker systems equipped for use in MRI, it will be possible to identify the specific cortical and subcortical regions underlying these deficits.

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### Abbreviations

ADHD, attention deficit hyperactivity disorder; ARND, alcohol-related neurodevelopmental disorder; CV, coefficient of variation; dlPFC, dorsolateral prefrontal cortex; FAS, fetal alcohol syndrome; FASD, fetal alcohol spectrum disorder; FEF, frontal eye field; FP, fixation point; MRI, magnetic resonance imaging; pFAS, partial fetal alcohol syndrome; PPC, posterior parietal cortex; SCi, intermediate layers of the superior colliculus; SEF, supplementary eye field; SRT, saccadic reaction time.

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