Fetal Alcohol Spectrum Disorders Current Science and Research Trends

Susan M. Smith, Ph.D.
Professor, Nutritional Sciences
University of Wisconsin-Madison
President, Fetal Alcohol Spectrum Disorders Study Group

FETAL ALCOHOL SPECTRUM DISORDERS Study Group

www.fasdsg.org

The FASDSG is a society with over 400 clinicians and scientists performing research on FASD.

The binding interests of our members are:

- the desire to fully understand the etiology of FASD
- Describe the characteristics of FASD at multiple levels
- Devise ways to improve the lives of children, adolescents and adults with FASD

Research Society on Alcoholism

Current Science & Research Trends: An Update

- Current scope of problem
- Diagnostics & Detection
  - Behavior
- Teratogenic Effects
  - Underlying mechanisms of damage
- Prevention, Intervention & Treatment
  - Nutritional Modifiers

Teratogenic Effects of Alcohol

- Impaired brain & nervous system development
  - Cognitive & behavioral abnormalities
- Body growth deficits
- Craniofacial anomalies
- Cardiac malformations
- Other organ malformations
  - Eyes, teeth, ears, limbs, kidney & urinary tract
- Endocrine / hormonal alterations
  - Cortisol, pituitary hormones

Current Challenges in FASD

- Hard numbers on scope of problem: incidence, cost
- Public perceptions of moderate drinking risk
- Improved diagnostics (sensitivity, accuracy)
- Identification & prevention of at-risk pregnancies
  - Interventions that improve prenatal outcomes
- Treatments that improve postnatal outcomes
- Better understanding of mechanism
  - Pinpoint the disrupted activities / systems
  - Leverage into treatments for prevention / remediation

2009 Binge Drinking Rates

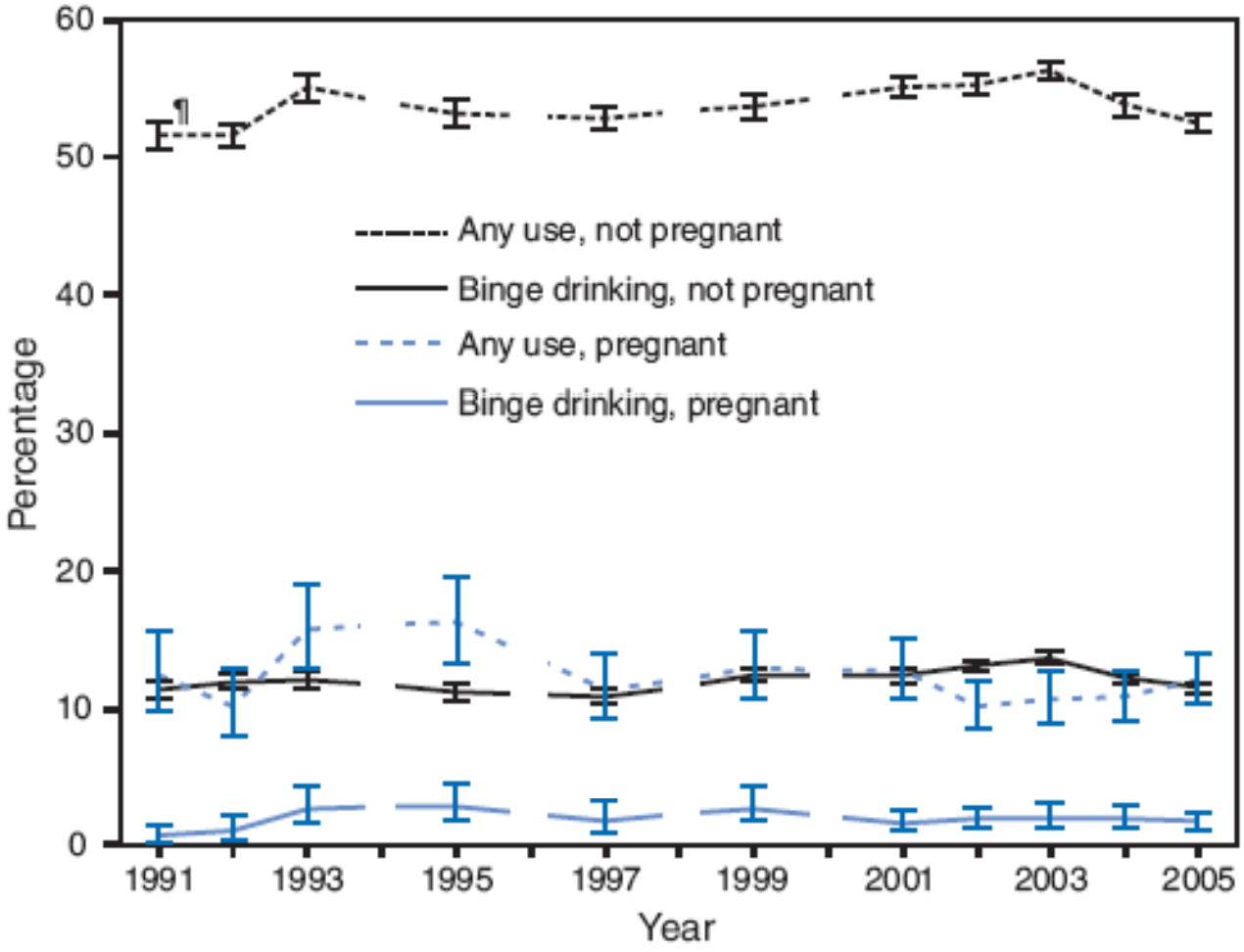
MMWR: Dec 10, 2010; Jan 14, 2011

- BRFSS (Behavioral Risk Factor Surveillance System)
- Binge Drinking: 4 drinks/occasion for women
- National rate: 10.0% of all women
  - 8.1 – 6.5% of women aged 18-44 yrs
  - 3.1 episodes in past 30 days (3.0-3.2)

- Varies widely by State, Income, Ethnicity
  - Wisconsin #1: 22.8% of all adults
  - Risk increases as income and education increase
  - Highest risk in non-Hispanic whites (17.5%)

Binge Drinking is not Decreasing

MMWR, May 22, 2009



Pregnant, any use

Pregnant, binge use

Societal Push-Back on Moderate Drinking Risk

A Drink or Two During Pregnancy? Not So Fast

New Study: OK to Drink While Pregnant? AUTO START: ON | OFF

ABC WORLD NEWS WITH DIANE SAWYER By MIKAELA CONLEY, ABC News Medical Unit
Oct. 6, 2010

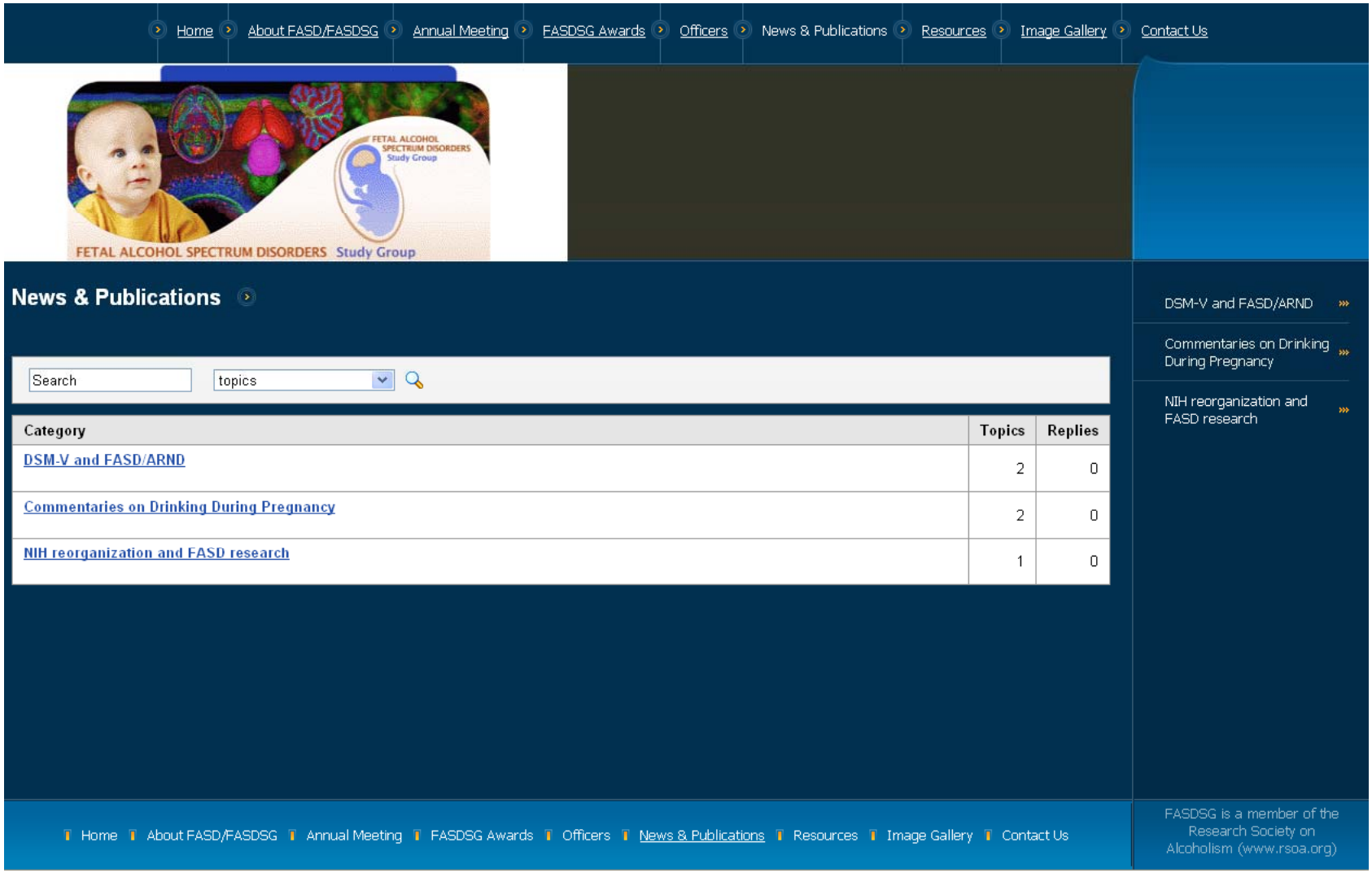
Low–moderate prenatal alcohol exposure and risk to child behavioural development: a prospective cohort study

M Robinson, WH Oddy, NJ McLean, P Jacoby, CE Pennell, NH de Klerk, SR Zubrick, FJ Stanley, JP Newnham
BJOG An International Journal of Obstetrics and Gynaecology 2010;117:1139–1152.

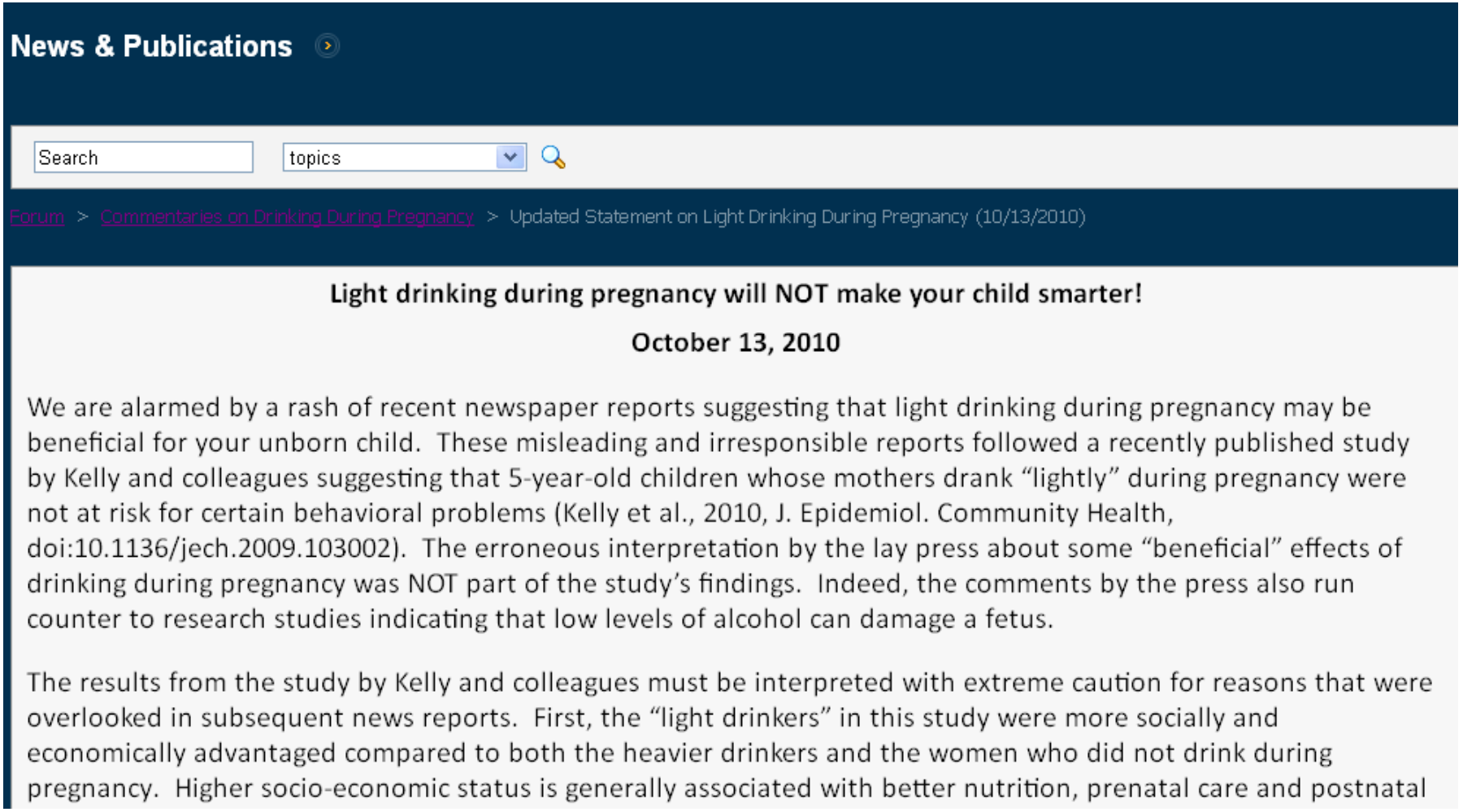
Light drinking during pregnancy: still no increased risk for socioemotional difficulties or cognitive deficits at 5 years of age?

Yvonne J Kelly, Amanda Sacker, Ron Gray, John Kelly, Dieter Wolke, Jenny Head, Maria A Quigley
J Epidemiol Community Health (2010). doi:10.1136/jech.2009.103002

A resource for your use: FASDSG.org



FASD Study Group
Light-Drinking Policy Statement



News & Publications

Search topics

Forum > Commentaries on Drinking During Pregnancy > Updated Statement on Light Drinking During Pregnancy (10/13/2010)

Light drinking during pregnancy will NOT make your child smarter!

October 13, 2010

We are alarmed by a rash of recent newspaper reports suggesting that light drinking during pregnancy may be beneficial for your unborn child. These misleading and irresponsible reports followed a recently published study by Kelly and colleagues suggesting that 5-year-old children whose mothers drank "lightly" during pregnancy were not at risk for certain behavioral problems (Kelly et al., 2010, J. Epidemiol. Community Health, doi:10.1136/jech.2009.103002). The erroneous interpretation by the lay press about some "beneficial" effects of drinking during pregnancy was NOT part of the study's findings. Indeed, the comments by the press also run counter to research studies indicating that low levels of alcohol can damage a fetus.

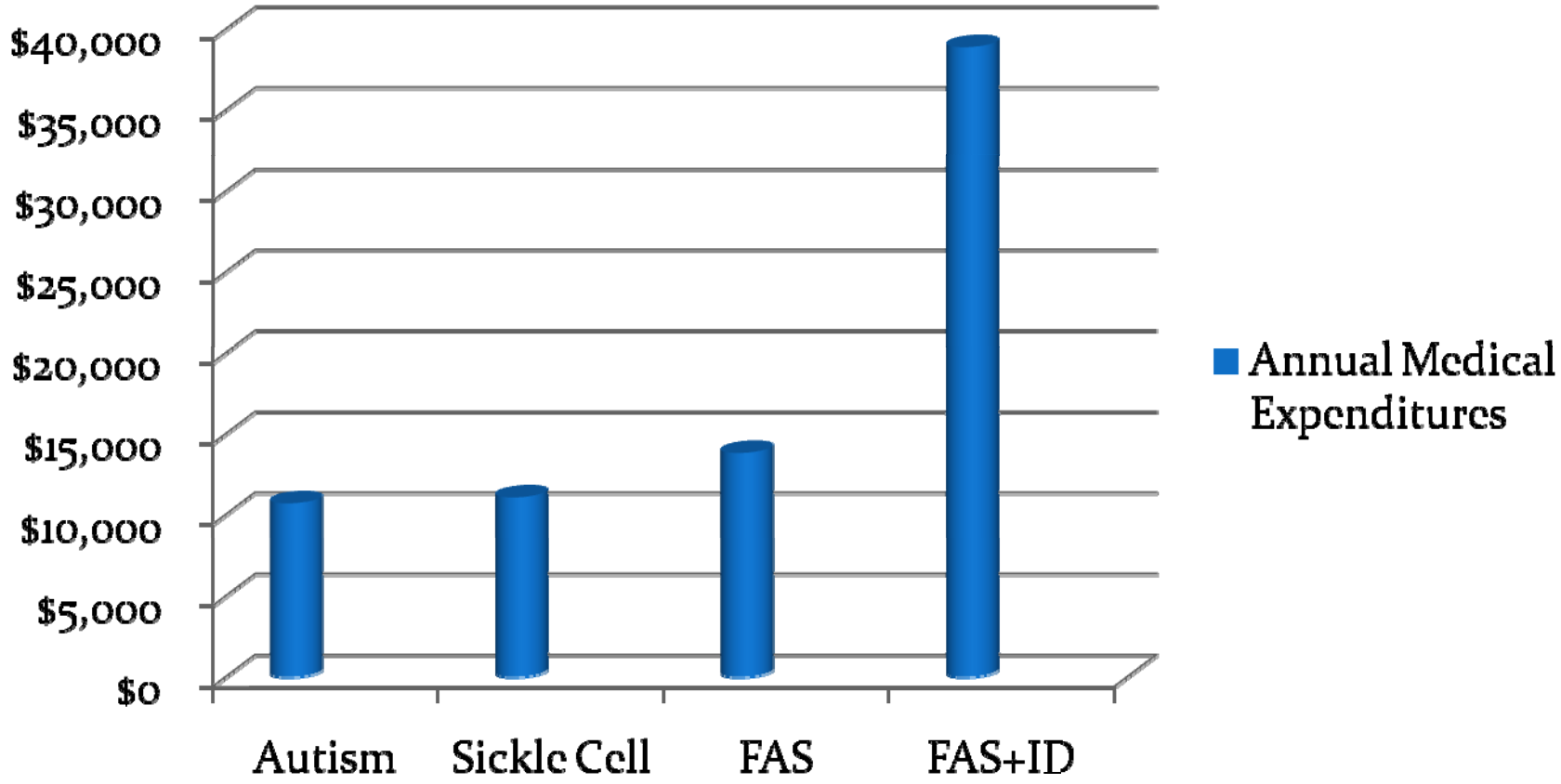
The results from the study by Kelly and colleagues must be interpreted with extreme caution for reasons that were overlooked in subsequent news reports. First, the "light drinkers" in this study were more socially and economically advantaged compared to both the heavier drinkers and the women who did not drink during pregnancy. Higher socio-economic status is generally associated with better nutrition, prenatal care and postnatal

Cost Estimates for FAS & FASD

- Current values are underestimates
- Often omit non-medical cost drivers:
  - Child welfare costs/payments, law enforcement costs, pain & suffering, loss of potential income, housing
- Popova et al. Alc Alcohol 2011
  - Canada: $16,259 - $22,473/yr; $1.12M lifetime
  - US: $1.6M - $2.5M lifetime
- Amendah et al. Neurotox Teratol 2011
  - Medicaid pediatric enrollees, 2003-2005

Medical Expenditures for FAS Children (U.S.)

Amendah et al. Neurotox Teratol 2011



Diagnostics & Detection

Recent approaches to selectively identify those with prenatal alcohol exposure.

Collaborative Initiative on FASD (CIFASD): A new research resource

- Created in 2003 & sponsored by NIAAA
- Creates a common terminology for FASD data
- Creates a central repository for FASD data
- Includes 16 different centers
  - US (San Diego, New Mexico, Northern Plains, UCLA, Atlanta, Indy, etc.), Cape Town, Helsinki, Moscow, Ukraine
- Creates a large data cohort for research & study
- Goal: develop diagnostics, interventions, treatments

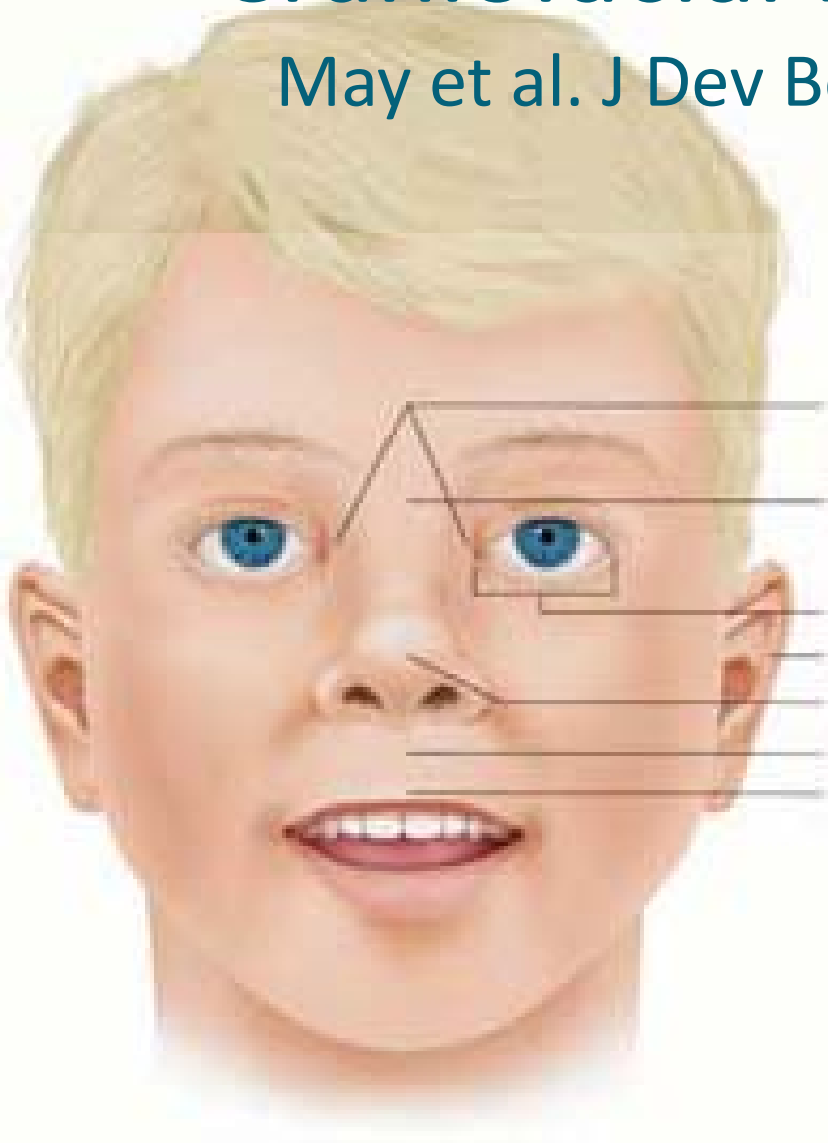
CIFASD

Mattson et al. 2010 Alcohol 44:635

- Children ages 7-21, both sexes, all ethnic/racial groups
- Four groups: Controls (nonexposed), FASD (PAE ± FAS diagnosis), low IQ (54-88, nonexposed), ADHD (DSM-IV, nonexposed)
- Exposure: >4 drink/occasion at least weekly or >13 drinks/wk
- Standardized neurobehavioral test battery
  - Intellect, attention, executive function, memory, visual-motor, interhemispheric transfer, symptomatology
- Brain imaging (fMRI, MRI); 3D facial imaging
- DNA collection, demographics

Craniofacial Dysmorphology

May et al. J Dev Behav Ped 2010 31:304



Epicanthal folds, epicanthal & pupillary distance

Flat nasal bridge **p=0.001**

Small palpebral fissures **p<0.001**

Upturned nose

Smooth philtrum **p<0.001**

Thin upper lip **p<0.001**

Fifth Finger Clinodactyly **p<0.001**

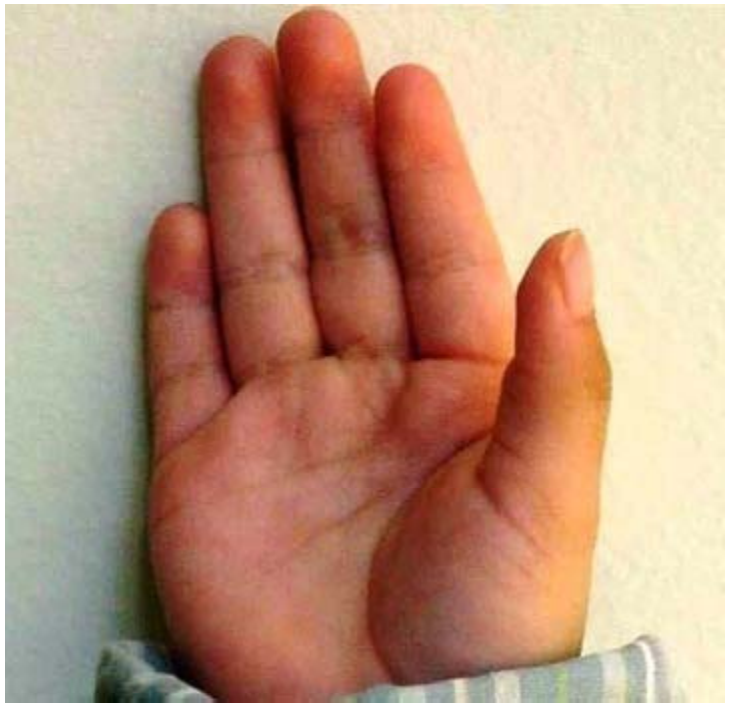
Commonalities across Plains Indian, Italian & South African/Colored populations

Expanding the structural defects

Jones et al. Am J Med Genet 152A:2731, 2010

"Railroad Track"
Ear configuration

"Hockey Stick"
Palmar crease



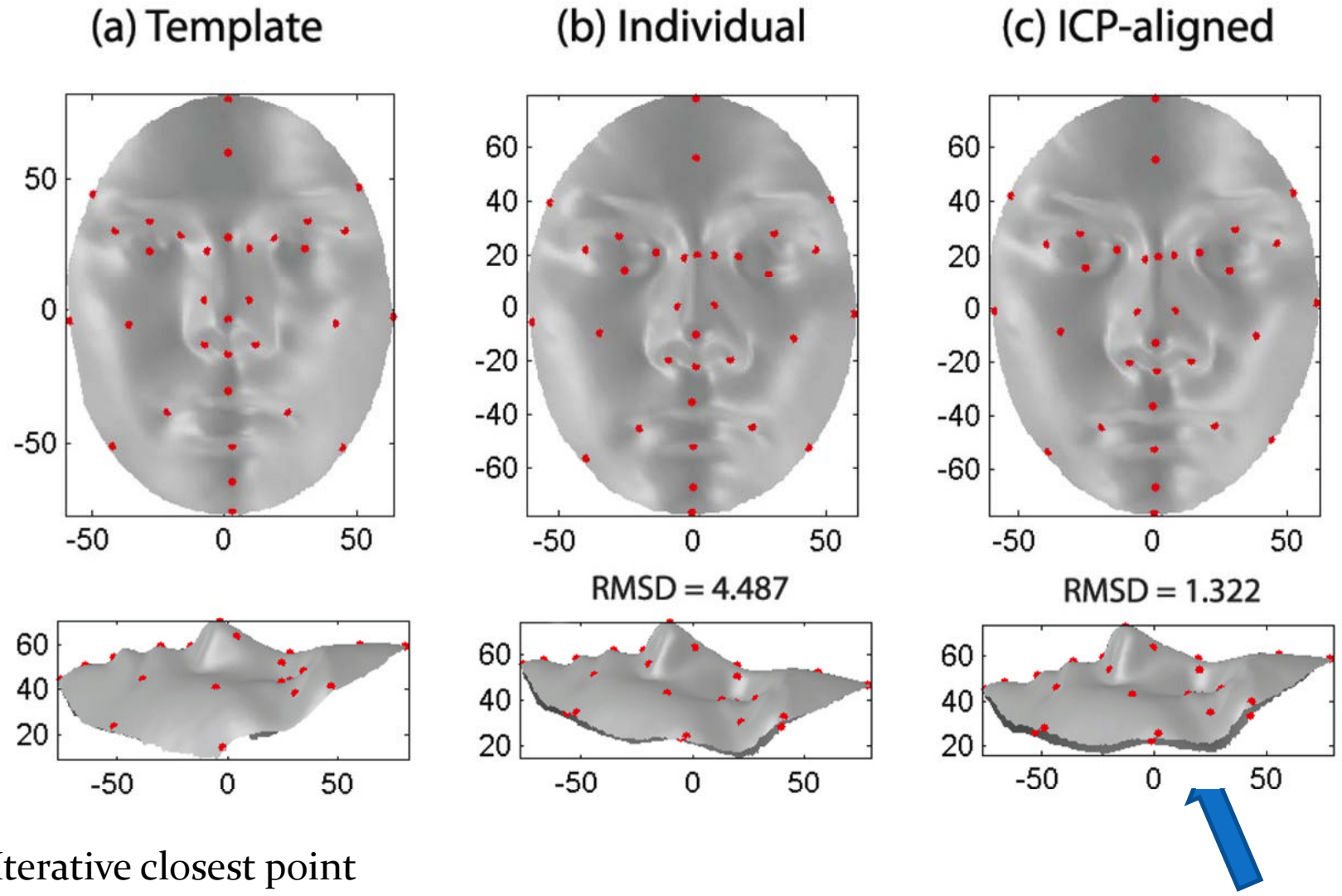
Fifth Finger
Clinodactyly

Expanding the structural defects

Jones et al. Am J Med Genet 152A:2731, 2010

Feature		FAS	Deferred	No FAS	P-value
Railroad track ears	11.8%	4.1%	1.8%	<0.001	
Ptosis	12.2%	3.7%	1.2%	<0.001	
Heart murmur	10.2%	2.3%	1.5%	<0.001	
Decreased elbow pronation/supination	14.7%	4.6%	1.2%	<0.001	
Decreased finger extension	6.7%	16.4%	6.1%	<0.001	
Other joint contractures	2.5%	0.5%	0.3%	0.028	
Hockey stick crease	21.6%	8.7%	5.3%	<0.001	
Other palmar crease defects	15.5%	7.3%	3.8%	<0.001	

Surface-Based Morphometry



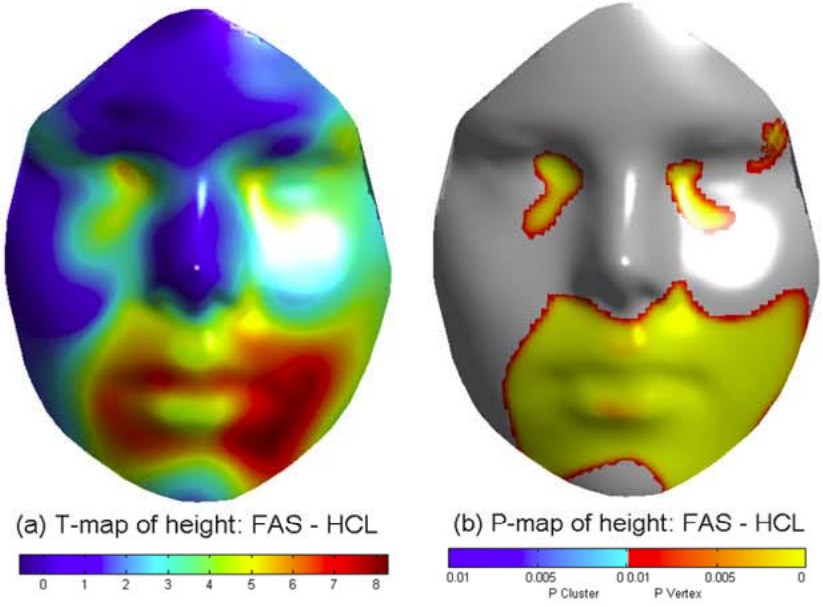
ICP: Iterative closest point

Wan et al. 2010, *Lect Notes Comput Sci*

Surface-Based Morphometry

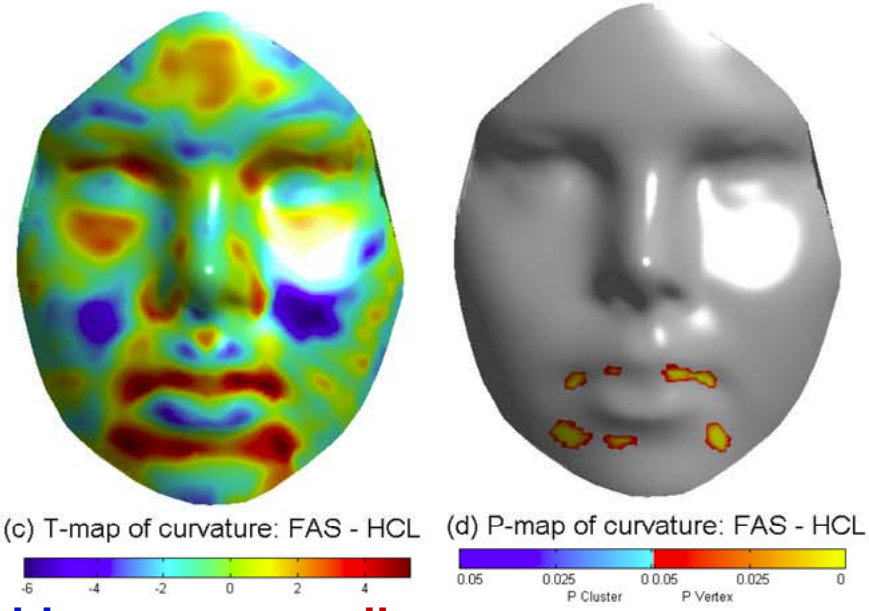
Final result: mean of 44 FAS faces

Height Differences



bigger **smaller**

Curvature Differences



bigger **smaller**

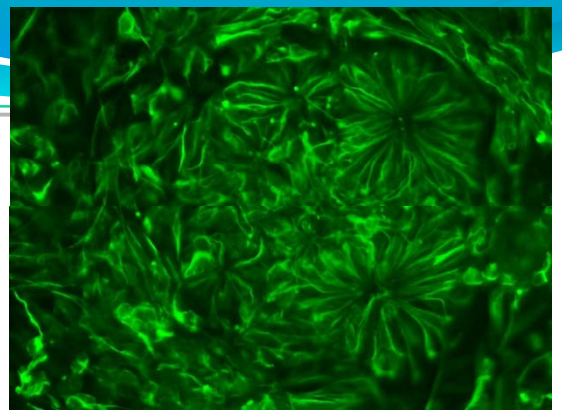
Blue is expanded relative to non-FAS
Red is contracted relative to non-FAS

Biomarkers for PAE

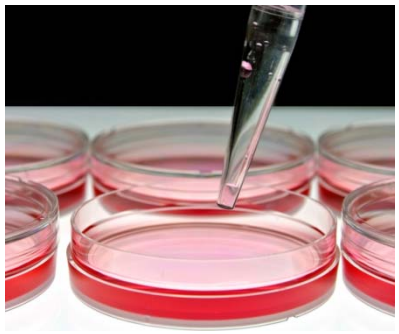
Identification of at-risk pregnancies

Identification of alcohol-exposed offspring

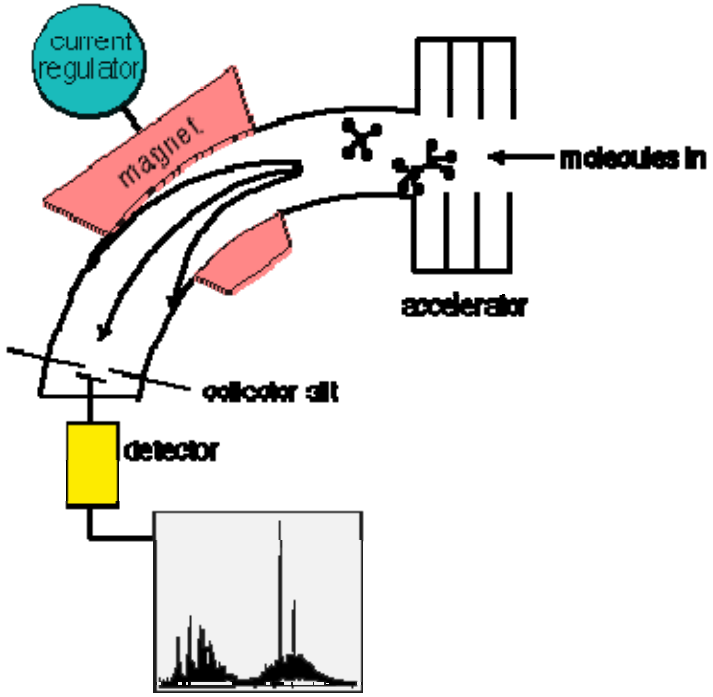
Metabolic Profile of PAE "Metabolomics"



Human neural stem cells + 0.3% ethanol

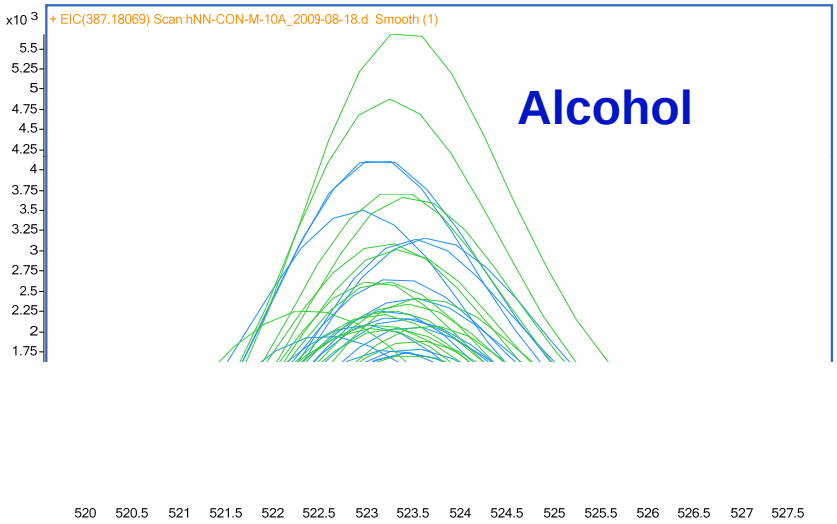


Identify biomolecules in culture medium using Mass Spectrometry

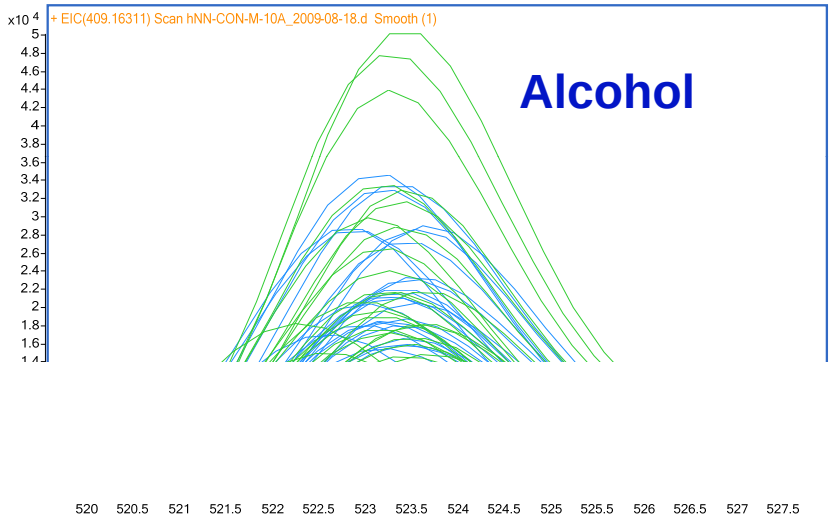


Palmer, Poenitzsch, Smith, West, Cezar, in preparation

Metabolome Analysis of PAE using Human Neural Stem Cells



386.1734
Incr 3.4x by Ethanol



408.1558
Incr 2.8x by ethanol

Palmer, Poenitzsch, Smith, West, Cezar, in preparation

Toward a FASD Neurobehavioral Profile

Mattson et al. 2010 ACER 34:1640

- CIFASD: 48 FASD vs. 46 control vs. 38 FASD-deferred
- Finland & US
- 22 neurobehavioral tests & 547 variables collected
- Identified 22 variables having medium effects or better between groups
- Correctly identified 92% of those with FASD having physical features
- Correctly identified 85% of nondysmorphic PAE

Toward a FASD Neurobehavioral Profile

Mattson et al. 2010 ACER 34:1640

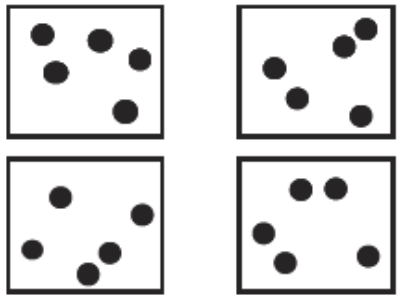
- Tests that were discriminatory
  - Executive Function
    - Working memory, verbal fluency, planning, sequencing, cognitive flexibility, emotional executive function
  - Spatial Reasoning
    - Recognition memory, working memory, learning, visual-motor integration
- Tests that were not discriminatory
    - Basic motor, rule learning, object memory, interhemispheric transfer
- IQ only 55.3% accurate for FAS

Teratogenic Effects:
Understanding Alcohol's Damage

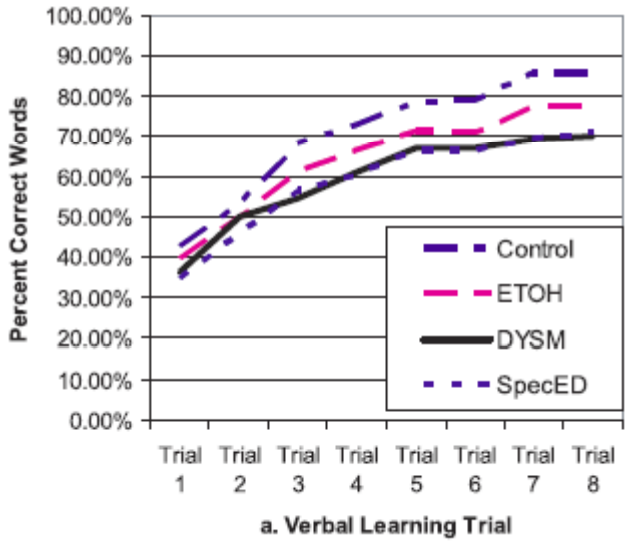
Verbal & Nonverbal Memory

Coles et al. 2010 ACER 34:897

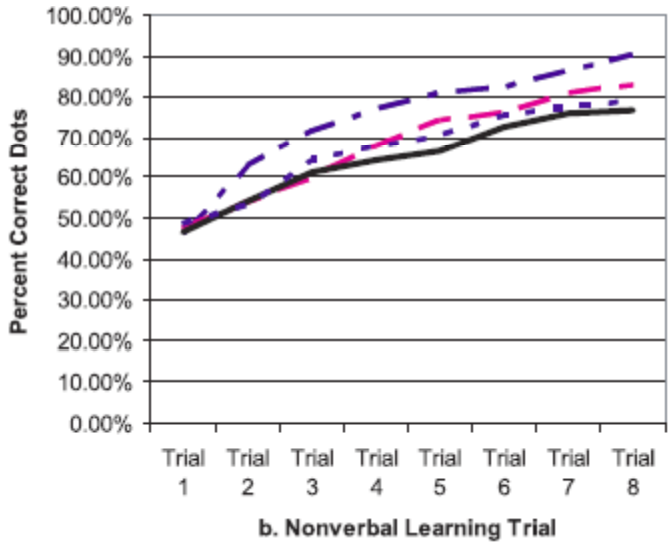
- Memory formation (encoding) vs. memory recall
- Verbal vs. non-verbal memory
- 234 adults, 22yrs, matched for SES & IQ (75-85)
- Control vs. Ethanol (>20 drink/wk) vs. Ethanol + Dysmorphology vs. Special Education
- Verbal memory: Recall 12 unrelated words in 8 trials
- Nonverbal memory:



Verbal Memory



Non-Verbal Memory



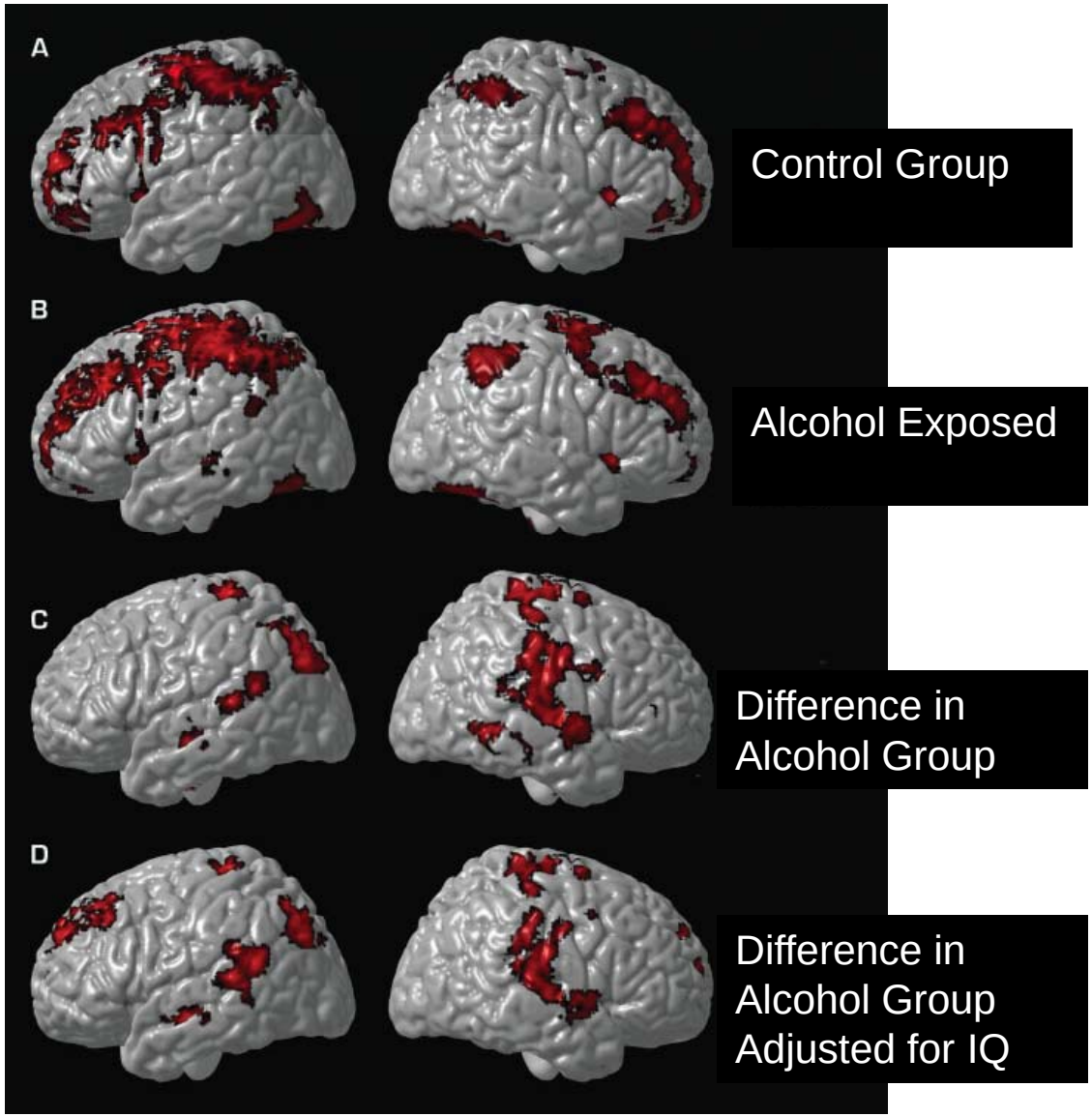
- Verbal affected more than non-verbal/spatial
- Alcohol not different from special-educated adults
- Alc+Dysmorph more affected than Alc-No Dysmorph
- Problems in encoding the memory, not forgetting
- Not a problem of memory but of learning

What is happening in the FASD brain?

Wozniak et al. 2008 ACER 32:1732

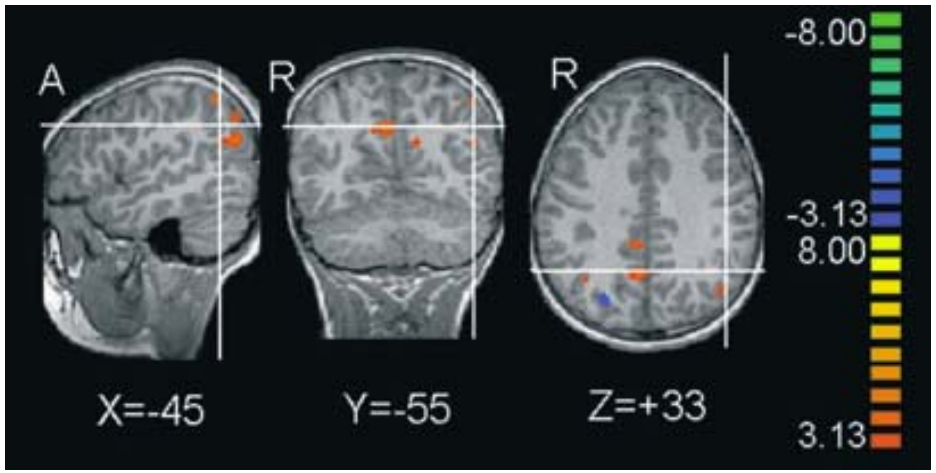
Verbal Working Memory Activation

- Alcohol-exposed subjects display greater activation relative to control subjects
- Suggests that frontal-parietal processing during verbal WM is less efficient in alcohol-exposed individuals.

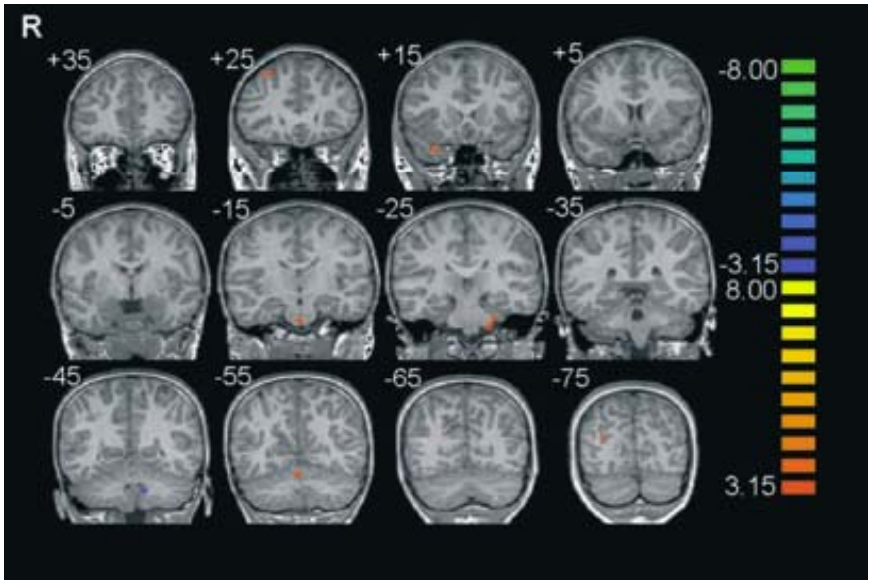


Specific Deficits in Number Processing

Meintjes et al. 2010 ACER 34:1450



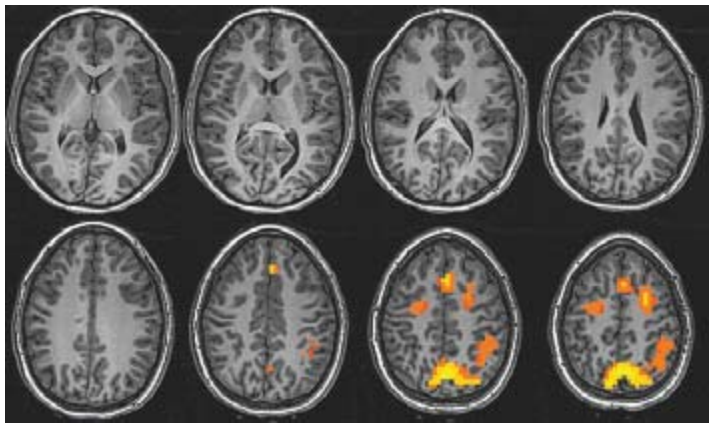
Number Proximity Judgment
Group differences FAS vs Control
Greater activation in FAS brains

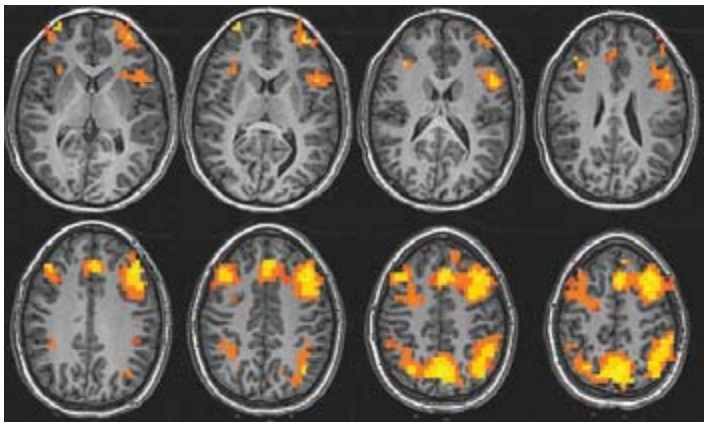


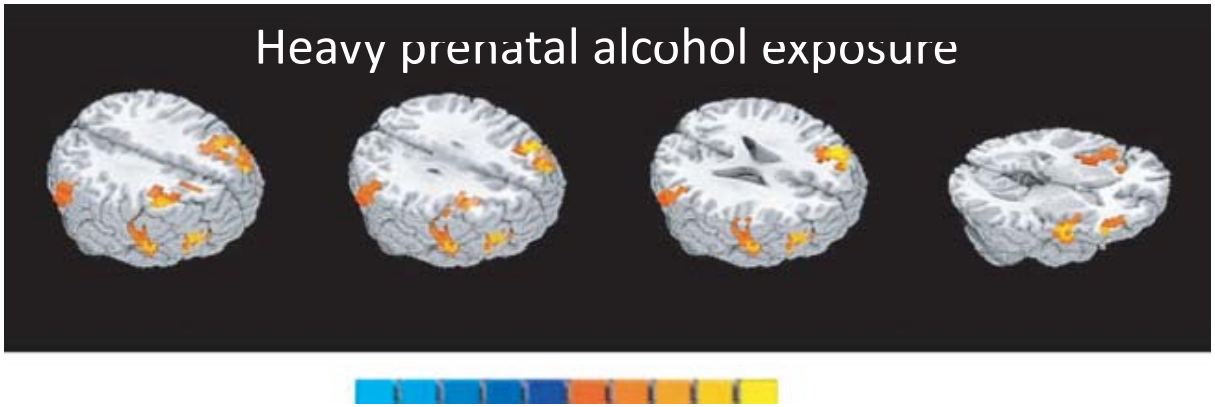
Exact Addition Task
Group differences FAS vs Control
Greater activation in FAS brains

Yellow = greater activation in alcohol-exposed individual

Functional MRI (fMRI) Assessment of Blood Oxygen Level Dependent (BOLD) Response in Spatial Working Memory Task





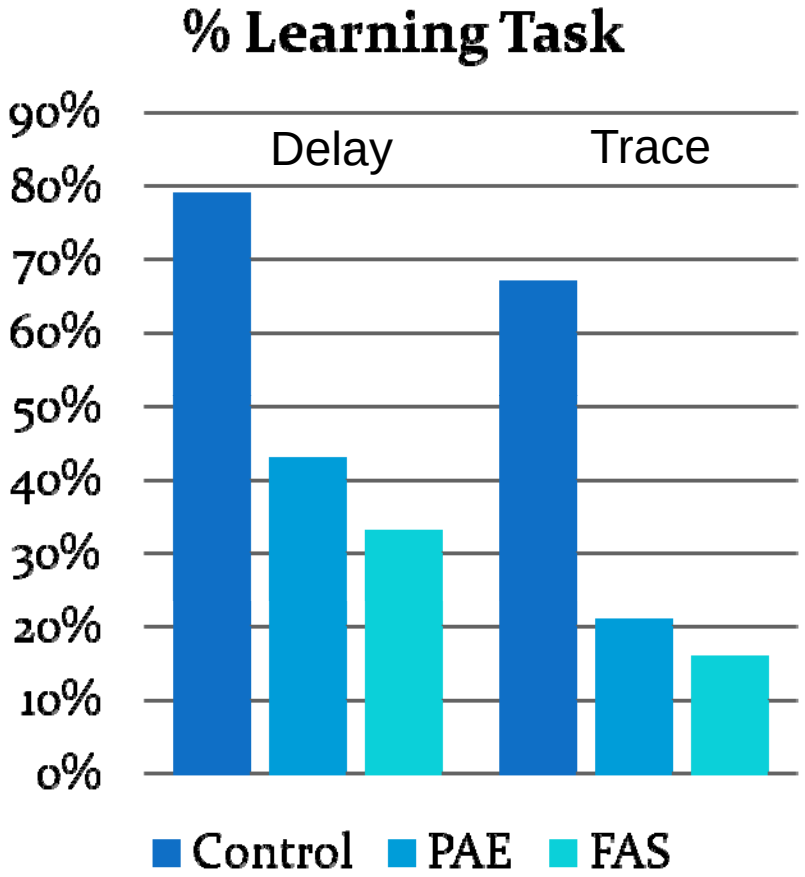


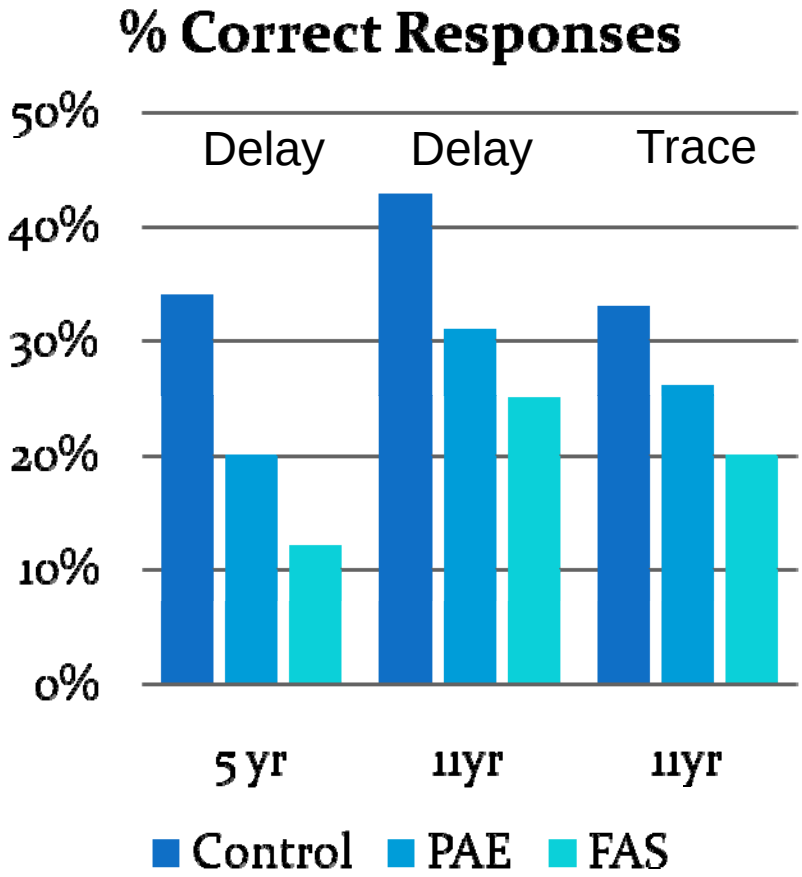
Yellow = greater activation in alcohol-exposed individual

Alcoholism Clinical and Experimental Research (2009) 33: 2067

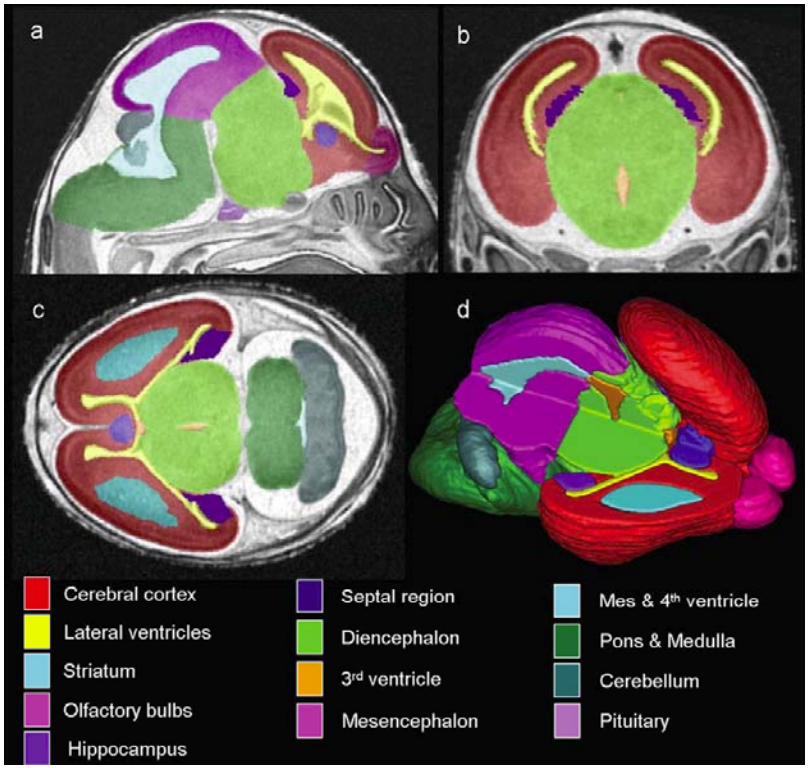
Learning deficits are persistent

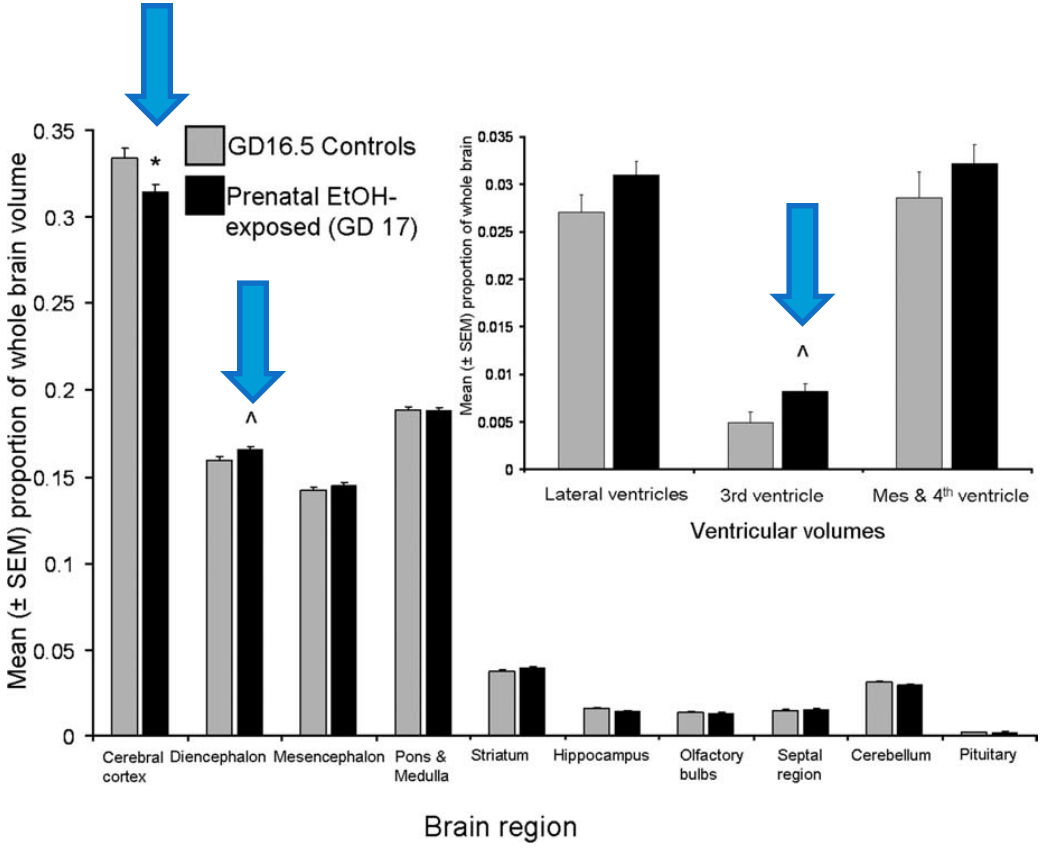
Jacobson et al. 2011 ACER 35:250





Magnetic Resonance Microscopy of FAS Mouse Brain – O'Leary-Moore et al. 2010 BDRA 88:953





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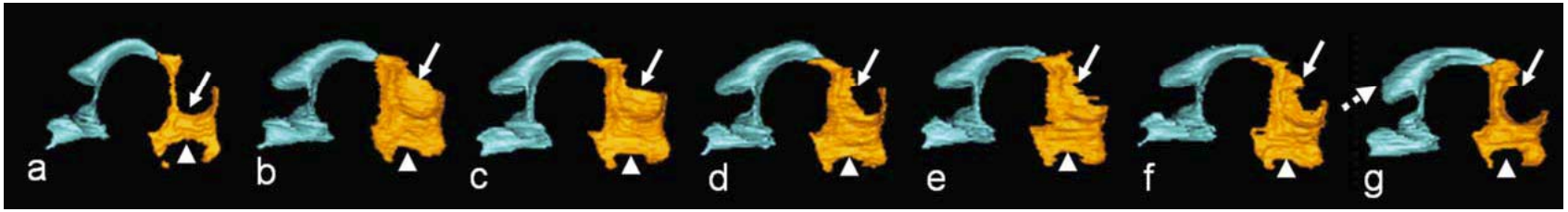
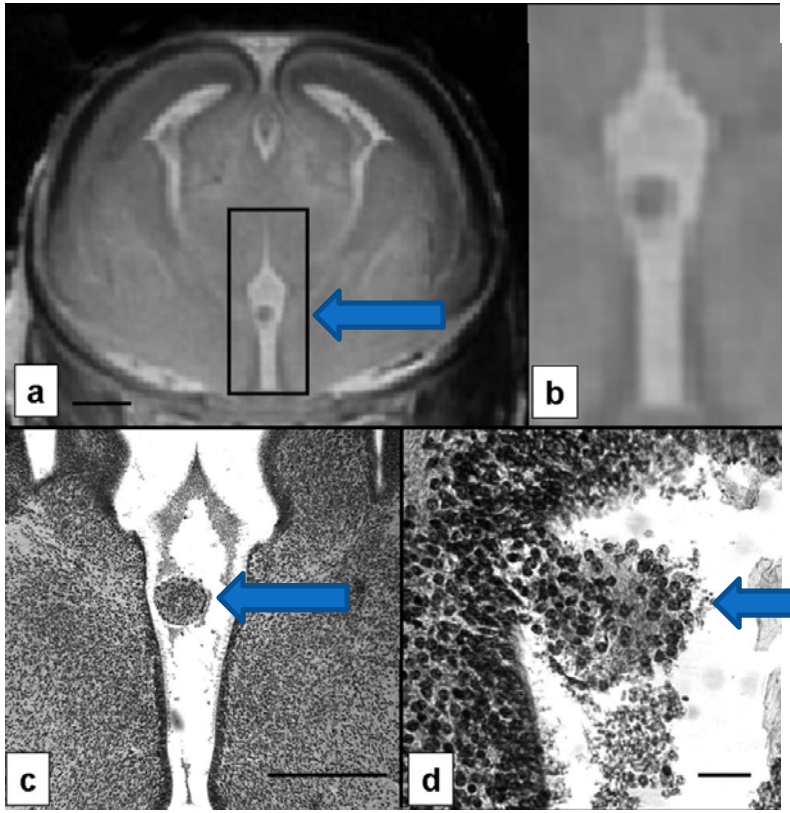




Brain ventricle volume
3rd ventricle is expanded in FAS

Heterotopia in third ventricle of FAS.
Neural heterotopias associated with increased seizure activity.
Found in FAS individuals.

Epigenetics: A parent's experience is transmitted to future generations

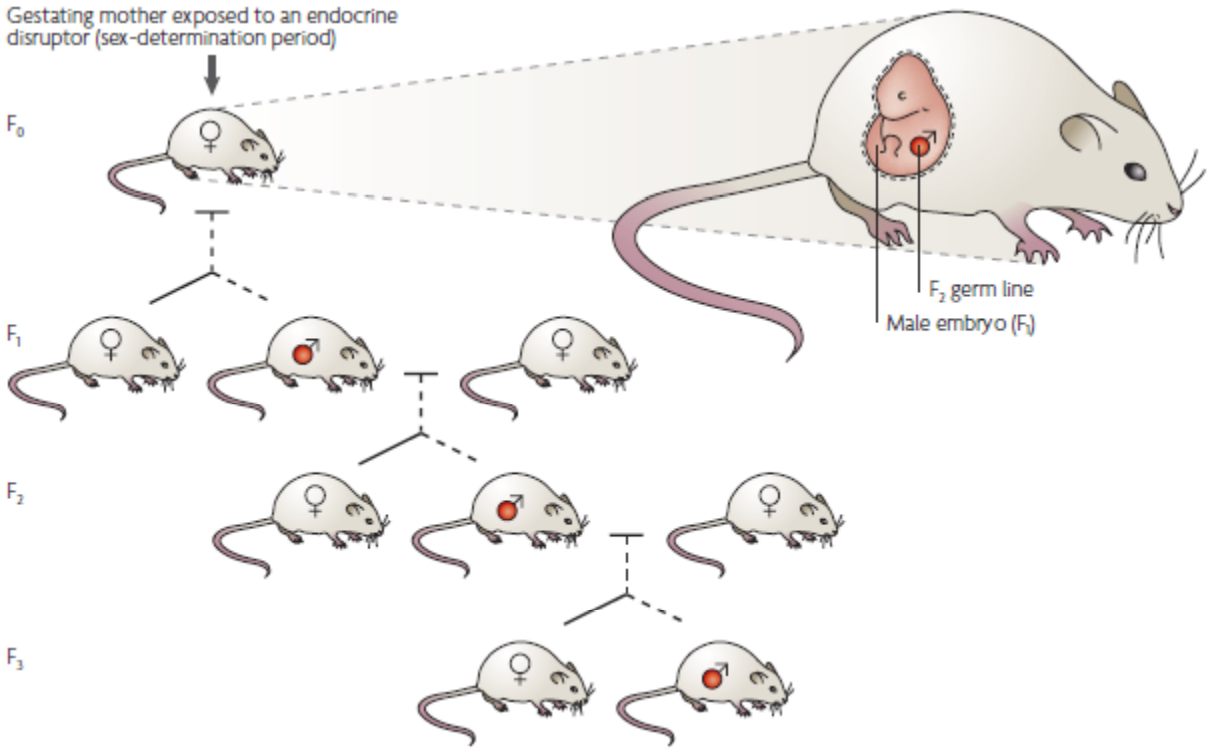


Figure 5 | **Germline transmission of epigenetically regulated transgenerational phenotypes.** In a gestating mother, there is multiple-generation exposure of the F_0 female, the F_1 embryo and the F_2 generation germ line to environmental factors. The transgenerational transmission of disease phenotypes through the male germ line (labelled red) is indicated. Both male and female offspring develop disease, but the transgenerational phenotype is transmitted only paternally after exposure to vinclozolin[96].

Modification of DNA creates differences despite identical DNA

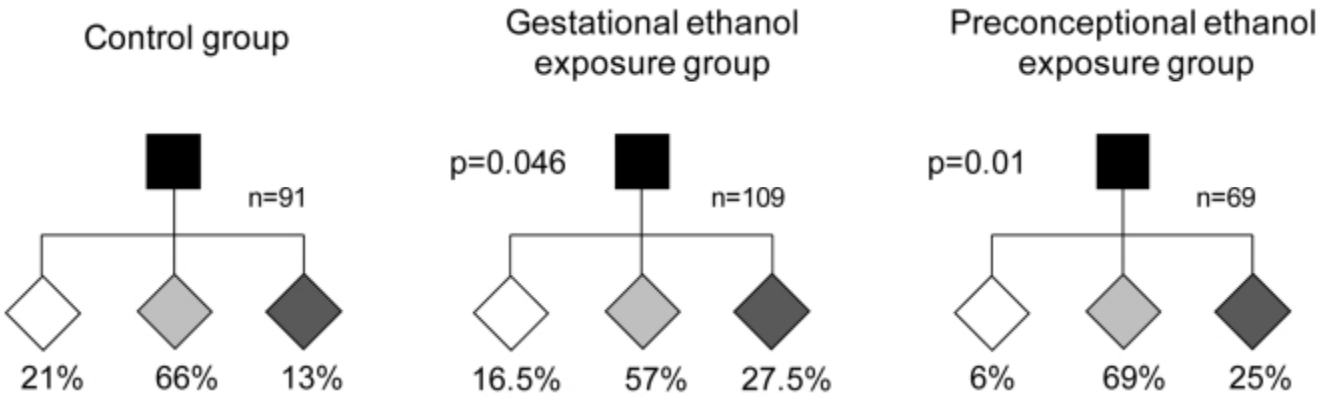
low → high

Yellow | Slightly Mottled | Mottled | Heavily Mottled | Pseudo-agouti

Dolinoy et al. Ped Res 2007

Ethanol alters the epigenome

Kaminen-Ahola et al. 2010 PLoS Genetics 6:e1000811



1st trimester
BAC 0.12%

10wk prior to conception
BAC 0.12%

Ethanol

This gene is silenced by ethanol.
Ethanol increases its methylation.
Does effect persist across generations?

Epigenetics control adult health & disease risk

- Body size at birth and childhood growth trajectory
- Chronic disease
  - Obesity, cardiovascular disease, hypertension
- Cancer risk
- Reproductive defects
- Neurobehavior
  - Nurturing behavior (rodents)
  - Syndromes: Angelman, Prader-Willi, Beckwith-Wiedemann
  - Schizophrenia? Bipolar? Touretts?

Interventions & Treatments

Can we reduce alcohol's damage in utero?

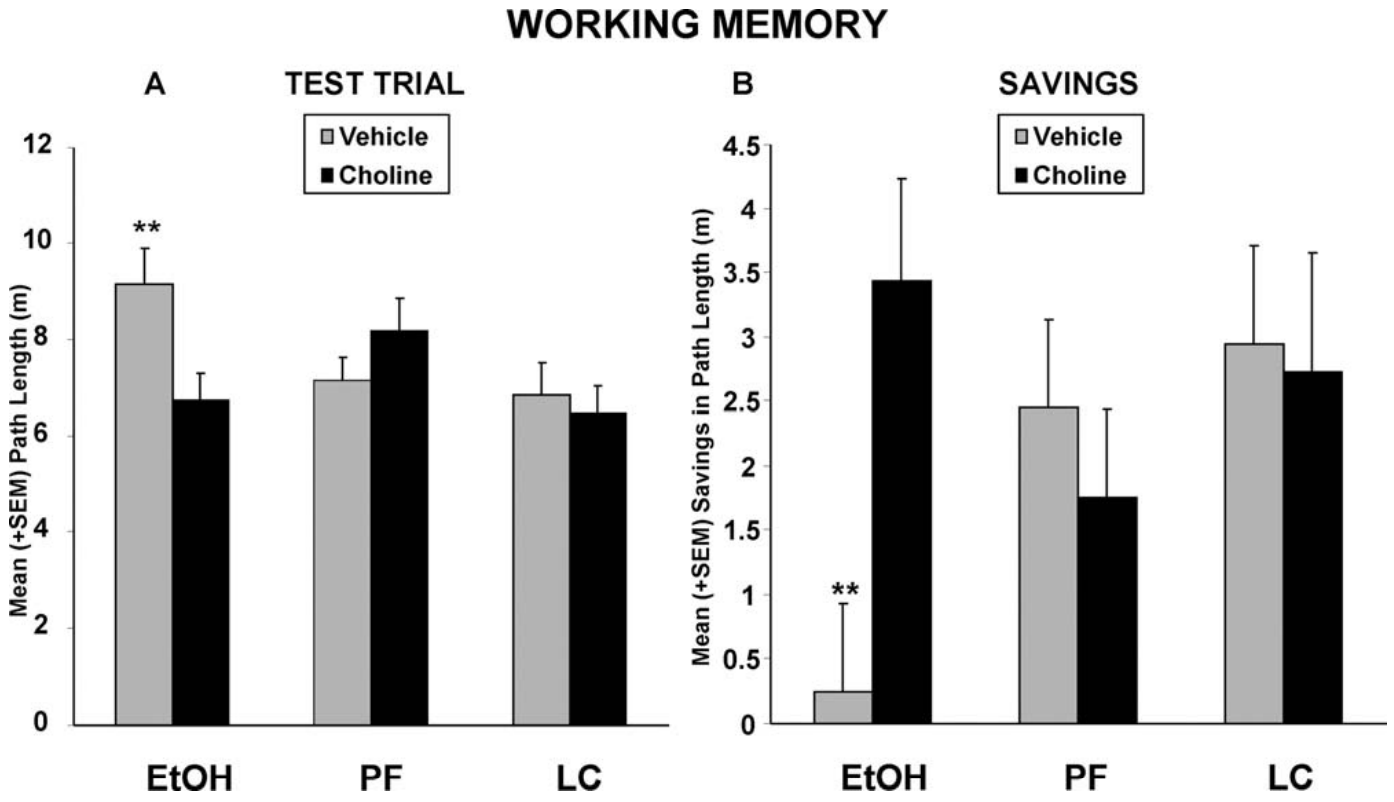
Can we restore cognition & function in later life?

Choline Supplements Mitigate PAE Effects

Thomas et al. 2010 Birth Def Res A 88:827

- Choline is an essential nutrient
- People vary in their ability to synthesize choline
- Essential for healthy brain development
  - Supports cognition, learning, memory
- Used to make acetylcholine, brain fatty acids
- Helps folate & B12 to do their jobs
- Controls gene expression using epigenetics
- Being tested to treat neurodegenerative diseases

Rats given 6 g/kg ethanol during pregnancy ± choline (2-3x normal intake)



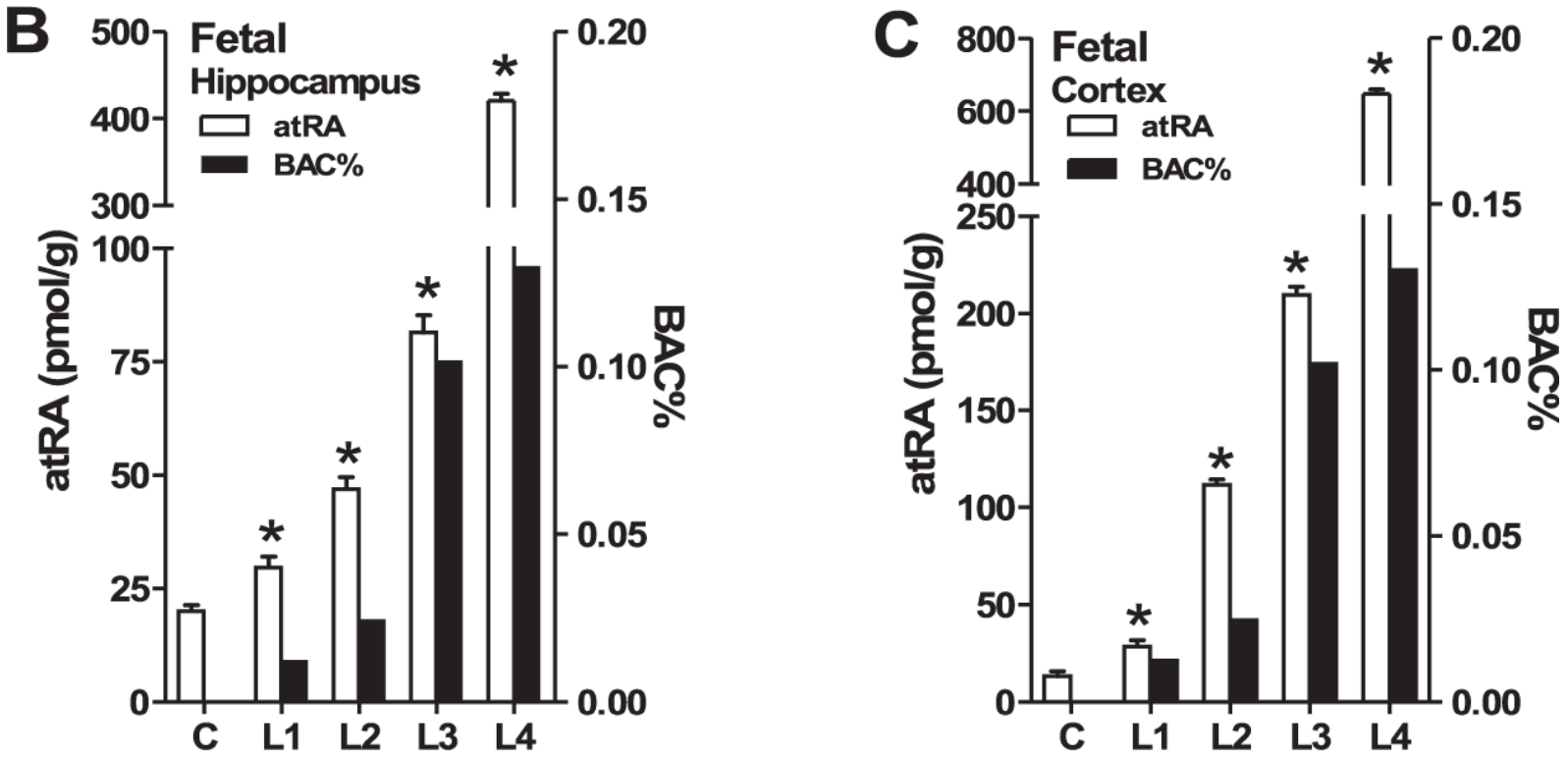
Morris Water Maze: FAS rats fed choline found the platform faster
And used a shorter route to find the platform.

FASD & Vitamin A

- Vitamin A is essential for normal brain and embryo development
- Alcoholics often have low Vitamin A stores
- Alcohol & Vitamin A cross-talk at the molecular level
- Might alcohol cause fetal Vitamin A deficiency?

Alcohol may cause Vitamin A toxicity

Kane et al. 2010 FASEB J 24:823

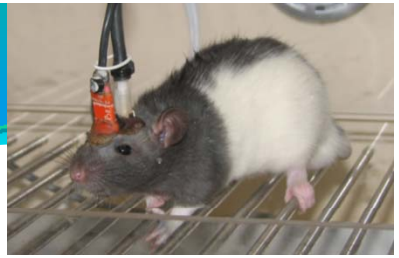


Maternal Nutrient Status in a Prospective FASD Cohort – Keen et al. Biofactors 2010

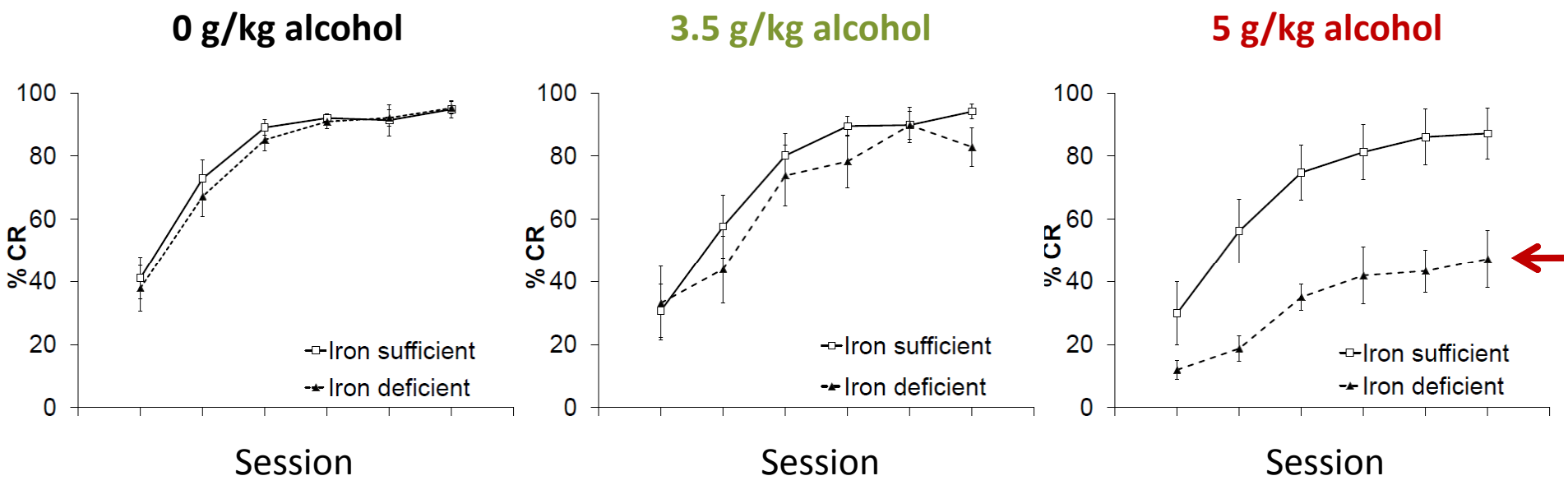
	Russia Sample		Ukraine Sample	
	Alc-Exp	**Alc-Unexp**	**Alc-Exp**	**Alc-Unexp**
Ca (µg/mL)	88.5 ± 3.3	93.8 ± 4.5	83.4 ± 1.2	83.5 ± 0.7
Cu (µg/mL)	2.2 ± 0.2	2.4 ± 0.2	**1.7 ±0.1***	1.9 ± 0.1
Fe (µg/mL)	1.4 ± 0.3	1.1 ± 0.1	0.78 ± 0.06	0.82 ± 0.05
Mg (µg/mL)	18.1 ± 0.7	19.0 ± 1.0	15.9 ± 0.02	16.2 ± 0.2
Zn (µg/mL)	**0.59 ± 0.04***	0.73 ± 0.06	**0.57 ± 0.02***	0.64 ± 0.05

*** P < 0.05**

Maternal Iron Deficiency Worsens FASD Outcome



Associative Learning: Eyeblink Classical Conditioning



Alcohol x Iron status interaction:

$F_{(2,55)} = 4.1$, $P = 0.022$ → SYNERGISM

Rufer, Tran, Andrjewski, Smith, submitted 2011

Thank you!

FETAL ALCOHOL
SPECTRUM DISORDERS
Study Group