1

Special Thanks to:

Bill Dunty

Joe Wang

Michael Charness

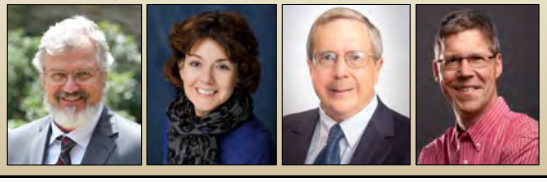
Jennifer Thomas

Jill Vander Velde

Thank You

Publications and Data Sharing Committees

Science Advisory Board



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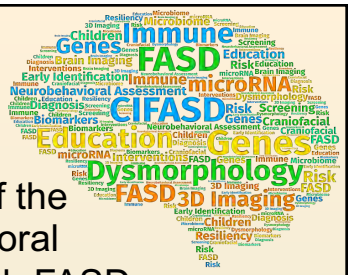
CIFASD4 RFA Goals



To enhance diagnoses of FASD at different stages of the lifespan based on biological, physical, and/or behavioral assessment and improve outcomes in individuals with FASD.

- Improve screening, case recognition and diagnosis of FASD (Face, Brain, Behavior, Biomarker)
- Assess impact of having an FASD across the lifespan
- Identify factors that impart risk/resiliency to FASD
- Develop intervention for FASD
- Employ eHealth technologies so that our research and its applications can be more broadly disseminated

4

CIFASD ADMINISTRATIVE CORE

PI, Coordinator:	Ed Riley, SDSU
Scientific Director:	Michael Charness, Harvard
Admin. Specialist:	Jennifer Thomas, SDSU
Admin. Coordinator:	Jill Vander Velde, SDSU

SCIENCE ADVISORY BOARD

John Hannigan
Sara Jo Nixon
James Reynolds
Daniel Savage
TBD Member

NIAAA ADVISORS

Bill Dunty, Project Scientist
Joe Wang, Program Officer

STEERING COMMITTEE
Chaired by Charness and Riley

C. Chambers	S. Parnell*/
C. Coles	J. Eberhart*
T. Foroud	C. Petrenko*/
A. Noble*/	C. Tapparello*
M. Suttie*	J. Weinberg
K.L. Jones	J. Wozniak
S. Mattson	

* Multiple PI project

Affiliated Scientists: K. Donald, R. Miranda, D. Sarkar, and E. Sowell
Recent UH2 PIs: K. Hashimoto-Torii, M. Torii, T. Blanchard, and S. Mooney

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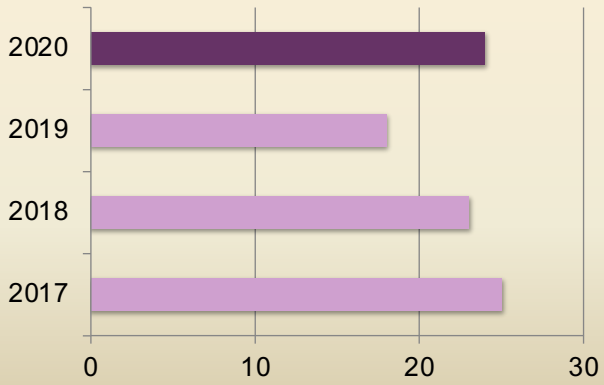
Publication Productivity of CIFASD

Publications citing **CIFASD** funding in PubMed
2017 to present = 90
2020 = 25



Total PubMed
CIFASD Publications = **299**

CIFASD investigators had significant contributions in high impact journals, such as:

- ***Lancet – Neurology***
- ***Nature***
- ***Trends in Cognitive Sciences***
- ***Journal of Neuroscience Development***
- ***Journal of Pediatrics***
- ***Proceedings of the National Academy of Sciences***

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June 2020-Present New CIFASD Publications n=9

- Moore EM, Glass L, Infante MA, **Coles CD, Kable JA, Jones KL, Riley EP, Mattson SN**. Cross-Sectional analysis of spatial working memory development in children with histories of heavy prenatal alcohol exposure, *Alcohol Clin Exp Res*., 2020 Nov 15; In press.
- Aamodt P, **Wetherill L,** Delk P, Torres-Martinez W, Vance GH, Wesson M. Positive and negative professionalism experiences of genetic counseling students in the United States and Canada, *J Genet Couns.,* 2020 Oct 3; In press.
- Quirin K, Hines KA**, Wetherill L**. Genetic counseling for advanced paternal age: A survey of genetic counselors' current practice, *J Genet Couns*., 2020 Sep 23; In press.
- Salem NA, Mahnke AH, Wells AB, Tseng AM, Yevtushok L, Zymak-Zakutnya N, Wertlecki W, **Chambers CD, Miranda RC**; **CIFASD**. Association between fetal sex and maternal plasma microRNA responses to prenatal alcohol exposure: evidence from a birth outcome-stratified cohort, *Biol Sex Differ*., 2020 Sep 10;11(1):51. PMC7488011.
- Bandoli G, **Jones K**, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, Granovska I, Plotka L, **Chambers C**; **CIFASD**. Patterns of prenatal alcohol exposure and alcohol-related dysmorphic features, *Alcohol Clin Exp Res*., 2020, Aug 9; In press.
- Everson JL, Batchu R**, Eberhart JK**. Multifactorial genetic and environmental hedgehog pathway disruption sensitizes embryos to alcohol-induced craniofacial defects, *Alcohol Clin Exp Res*., 2020, Aug 7; In press.
- Boschen KE, Ptacek TS, Simon JM, **Parnell SE**. Transcriptome-wide regulation of key developmental pathways in the mouse neural tube by prenatal alcohol exposure, *Alcohol Clin Exp Res*., 2020, Aug;44(8):1540-1550. PMC7484470.
- Wedderburn CJ, Subramoney S, Yeung S, Fouche JP, Joshi SH, Narr KL, Rehman AM, Roos A, Ipser J, Robertson FC, Groenewold NA, Gibb DM, Zar HJ, Stein DJ, **Donald KA.** Neuroimaging young children and associations with neurocognitive development in a South African birth cohort study, *Neuroimage*., 2020, Oct 1;219:116846. PMC7443699.
- Gupta A, Bansal A, **Hashimoto-Torii K.** HSP70 and HSP90 in neurodegenerative diseases, *Neurosci Lett*., 2020, Jan 18;716:134678. PMC7336893.

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AdminC 2020 Publications n=10

- Moore EM, Glass L, Infante MA, **Coles CD, Kable JA, Jones KL, Riley EP, Mattson SN**. Cross-sectional analysis of spatial working memory development in children with histories of heavy prenatal alcohol exposure, *Alcohol Clin Exp Res*., 2020 Nov 15; In press. PMCID: PMC Journal - In Process
- Wedderburn CJ, Subramoney S, Yeung S, Fouche JP, Joshi SH, Narr KL, Rehman AM, Roos A, Ipser J, Robertson FC, Groenewold NA, Gibb DM, Zar HJ, Stein DJ, **Donald KA**. Neuroimaging young children and associations with neurocognitive development in a South African birth cohort study, *Neuroimage*., 2020 Oct 1;219:116846. PMCID: PMC7443699
- Krueger AM, Roediger DJ, Mueller BA, Boys CA, Hendrickson TJ, Schumacher MJ, **Mattson SN, Jones KL, Riley EP**, Lim KO, **Wozniak JR.** Para-limbic structural abnormalities are associated with internalizing symptoms in children with prenatal alcohol exposure, *Alcohol Clin Exp Res*., 2020 Aug;44(8):1598-1608. PMCID: PMC7484415
- Sullivan EV, Moore EM, Lane B, Pohl KM, **Riley EP**, Pfefferbaum A. Graded cerebellar lobular volume deficits in adolescents and young adults with fetal alcohol spectrum disorders (FASD), *Cereb Cortex,* 2020 Jul 30;30(9):4729-4746. PMCID: PMC7391273
- Roos A, Fouche JP, Ipser JC, Narr KL, Woods RP, Zar HJ, Stein DJ, **Donald KA.** Structural and functional brain network alterations in prenatal alcohol exposed neonates, *Brain Imaging Behav*., 2020 Apr 18:10.1007/s11682-020-00277-8. PMCID: PMC7572489
- Inkelis SM, Moore EM, Bischoff-Grethe A, **Riley EP**. Neurodevelopment in adolescents and adults with fetal alcohol spectrum disorders (FASD): A magnetic resonance region of interest analysis, *Brain Res*., 2020 Apr 1;1732:146654. PMCID: PMC7067519
- Dou X, Lee JY, **Charness ME**. Neuroprotective peptide NAPVSIPQ antagonizes ethanol inhibition of L1 adhesion by promoting the dissociation of L1 and ankyrin-G*, Biol Psychiatry*, 2020 Apr 1;87(7):656-665. PMCID: PMC7056560
- **Kable JA, Coles CD, Mattson SN.** Neurodevelopmental outcomes associated with prefrontal cortical deoxygenation in children with fetal alcohol spectrum disorders, *Dev Neuropsychol*., 2020 Jan-Feb;45(1):1-16. PMCID: PMC7080191
- Swartz ME, Lovely CB, McCarthy N, Kuka T, **Eberhart JK.** Novel ethanol-sensitive mutants identified in an F3 forward genetic screen, *Alcohol Clin Exp Res*., 2020 Jan;44(1):56-65. PMCID: PMC6980918
- Bodnar TS, Raineki C, Wertelecki W, Yevtushok L, Plotka L, Granovska I, Zymak-Zakutnya N, Pashtepa A, Wells A, Honerkamp-Smith G, **Coles CD, Kable JA, Chambers CD, Weinberg J; CIFASD**. Immune network dysregulation associated with child neurodevelopmental delay: Modulatory role of prenatal alcohol exposure, *J Neuroinflammation*, 2020 Jan 28;17(1):39. PMCID: PMC6988366

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Web of Science Search

Showing **5,932** records for **TITLE:** (fetal alcohol) *OR* (prenatal alcohol) *OR* (pregnancy alcohol)
1,726 of the records within this search include grant number information

Indicates a grant funded to a current or former CIFASD Investigator

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CIFASD Visibility

Symposia and Talks Postponed from 2020 to 2021

Research Society on Alcoholism

ISBRA

New Orleans 2020 ➡ San Antonio 2021

CIFASD studies on the role of Genetics in FASD

- Edward Riley - Introduction
- Amanda Mahnke (Miranda lab)
- Johann Eberhart
- Scott Parnell
- Olivia Weeks
- Tatiana Foroud - Discussant
- Michael Charness – Moderator & Discussant

EUROPEAN FASD ALLIANCE

EUFASD

Postponed due to Covid-19 till 12 to 15 September 2021 Arendal, Norway

Using technology to move forward on the recognition and treatment of FASD

- Edward Riley
- Mike Suttie
- Sarah Mattson
- Christie Petrenko

Alcoholism and Stress: A Framework for Future Treatment Strategies
Volterra, Italy - May 2021

Graded regional cerebellar volume deficits in adolescents and adults with Fetal Alcohol Effect and Fetal Alcohol Syndrome

- Edward Riley

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CIFASD Visibility

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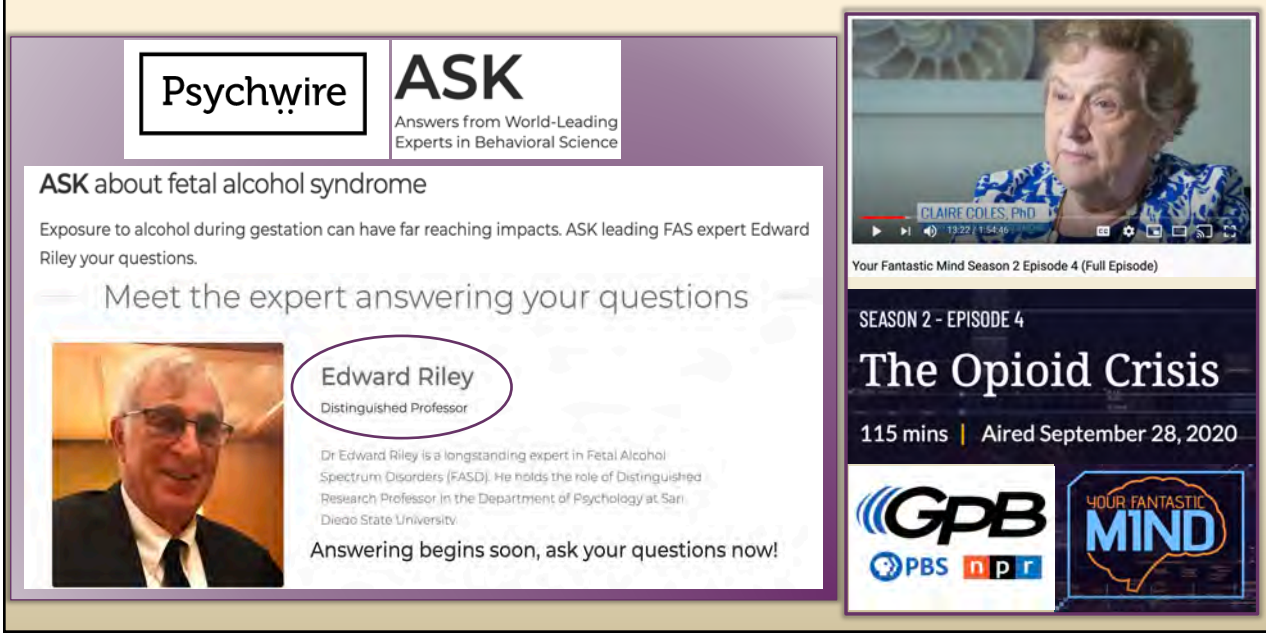
CIFASD Outreach and Education



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CIFASD Outreach and Education

PR%F Alliance

ProofCon 2020: FASD in a New Era

DATES October 22-23, 2020 LOCATION Online

Society for Birth Defects Research & Prevention
Honoring Teratology's Roots, Growing a Healthier Future

2020 VIRTUAL

60th Annual Meeting

June 25–July 2, 2020

Free Live Webinar

Co-hosted by the OTIS Organization of Teratology Information Specialists

COVID-19 and Pregnancy: What Do We Know and How Will We Learn More

Thursday, June 11, 2020 · 12:30 PM–2:00 PM Eastern Daylight Time (US)

Speakers

Sonja A. Rasmussen
MD, MS
University of Florida

Christina D. Chambers
PhD, MPH
University of California–San Diego

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CIFASD in the Headlines

UNIVERSITY of ROCHESTER

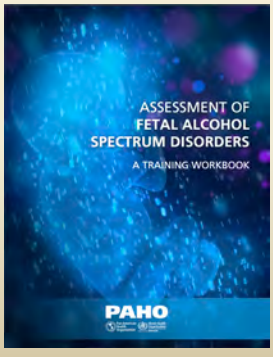
Newscenter

Expert team creates training manual to help providers recognize fetal alcohol spectrum disorders

June 12, 2020

Download the free training manual

Assessment of Fetal Alcohol Spectrum Disorders: A Training Workbook from the Pan American Health Organization's website.



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CIFASD in the Headlines

The feature article highlighted research by the following CIFASD investigators:

- **Kazue Hashimoto-Torii**'s work on molecular mechanisms and motor deficits
- **Jeff Wozniak**'s choline supplementation studies
- **Christie Petrenko** and **Cristiano Tapparello**'s intervention app in a featurette on CIFASD

The issue also included 5Qs with the CIFASD Project Scientist, Bill Dunty

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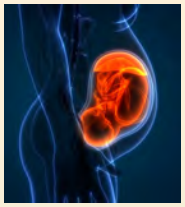
Dr. Koob's FASD Goals



"Research on FASD is a priority for NIAAA, and for many years we've supported studies to understand how alcohol disrupts prenatal development and how FASD can be prevented, diagnosed, and treated," says NIAAA Director George F. Koob, Ph.D. "Basic, translational, and clinical research are providing valuable insight into the mechanisms that underlie the learning deficits and health problems associated with FASD, thereby shedding light on potential intervention strategies."

"Prenatal alcohol exposure contributes to an array of lifelong physical, cognitive, and behavioral problems," says Dr. Koob. "These detrimental effects highlight the need for strategies to improve FASD prevention, screening, diagnosis, and treatment. NIAAA's recent efforts towards the development of a consensus FASD overarching research classification system could accelerate progress in these areas."

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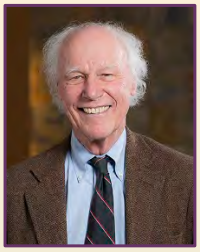
Monthly Meeting - Stigma and FASD

Sylvia Roozen, Ph.D.
FASD Researcher
Maastricht University



Ken Jones, M.D.
FOUNDATIONS of SCIENCE

Tom Donaldson and Kathy Mitchell, NOFAS

Bill Dunty, Ph.D., NIAAA

Understanding the Social Stigma of Fetal Alcohol Spectrum Disorders: From Theory to Interventions

Sylvia Roozen[1] · Sarah E. Stutterheim[2] · Arjan E. R. Bos[3] · Gerjo Kok[1,2] · Leopold M. G. Curfs[1]

N·O·FAS
National Organization on Fetal Alcohol Syndrome
STAMP OUT STIGMA

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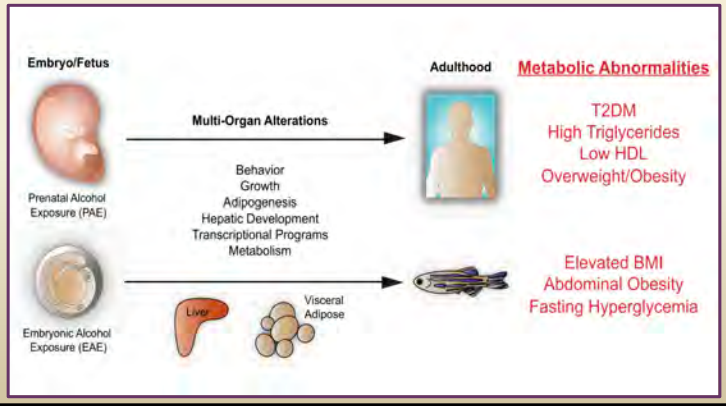
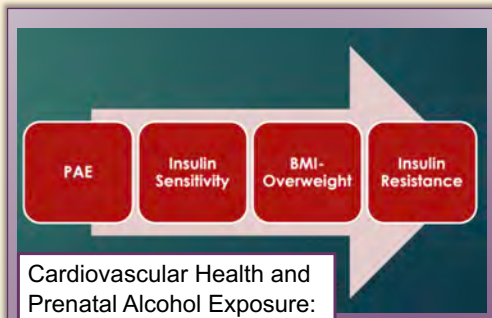
Monthly Meeting Invited Speakers

Olivia Weeks, Ph.D.
Postdoctoral Fellow
HARVARD MEDICAL SCHOOL
BRIGHAM AND WOMEN'S HOSPITAL

Metabolic Abnormalities in Adults with FASD

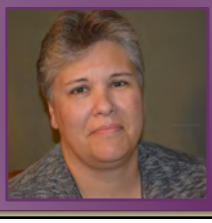




Cardiovascular Health and Prenatal Alcohol Exposure: Alterations in Insulin

EMORY UNIVERSITY SCHOOL OF MEDICINE

Julie Kable, Ph.D.
Assistant Professor, Psychiatry and Behavioral Sciences



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Monthly Meeting Invited Speakers

VA CENTER OF EXCELLENCE
CESAMH
STRESS AND MENTAL HEALTH
UC San Diego

Jessica Bomyea, Ph.D.
Research Health Science Specialist, VASDHS CESAMH
Assistant Professor of Psychiatry, UCSD

Executive Functioning Training to Address Cognitive and Emotional Dysfunction

Applications of cognitive training to FASD

Enhancing	Adapting	Optimizing	Integrating
Enhancing compliance, acceptability • "Gamifying"	Adapting to individualized skills • Titrating difficulty based on baseline ability given broad range • Currently testing simple algorithm based on 85% mark	Optimizing dose/transfer	Integrating within existing treatment frameworks • E.g., goFAR

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Recruited into the FASD Field - New

- Alex Tseng
- Alison Noble
- Annika Montag
- Carl Keen
- Carson Kautz-Turnbull
- Catherine Lebel
- Charles Ben Lovely
- Charlis Raineki*
- Chris Nellaker
- Christopher Garcia
- Cleber Trujillo
- Desirè Buckley
- Diego Mesa
- Dorothy Strickland
- Eileen Moore
- Elizabeth Godin
- Florence Roussotte
- Gaby Ritfeld
- Ganz Chockalingam
- Gretchen Bandoli
- John Colby
- Katherine Narr
- Kelly Frazer
- Kristina Uban
- Laura Parfrey
- Li Shen
- Miguel del Campo*
- Mike Suttie
- Nirelia Idrus
- Peter Hammond
- Puja K. Mehta
- Ralf Haesuler
- Rob Lipinski
- Shameena Bake
- Shantanu Joshi
- Smita Paranjape
- Stefanie Bodison
- Tamara Bodnar
- Tom Rackham
- Utku Demir
- Yaling Yang
- Yun Liang
- Zeyu Fu

* Working in alcohol field previously, but recruited to FASD and/or CIFASD research

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Recent CIFASD Investigator Awards & Honors

Sandra Mooney, Co-PI with Susan Smith, UNC

- Funding from the Nutrition Research Institute to examine the "*Disruption of Maternal Microbiome as a Contributor to Altered Nutrient Needs in a Mouse Model of PAE*"

Christie Petrenko and Cristiano Tapparello, URMC

- Received $5,000 from a local private donor to support initial development of the FMF Connect Teacher Companion website that a grad student, Carson Kautz-Turnbull, will lead

Claire Coles, U01 Administrative Supplements

- Diversity supplement to Gaby Ritfeld
- COVID-19 supplement
- Claire named Interim Director of the Emory Autism Center

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Recent CIFASD Investigator Awards & Honors

Joanne Weinberg

- Renewal of R01 AA022460-06A1
- Aim 4 of builds CIFASD U01 and will recontact adults with FASD who participated in the U01 for follow up assessment

Charlis Raineki

- Joanne's former Research Associate received faculty position at Brock University as an Assistant Professor in the Department of Psychology beginning January 1, 2021

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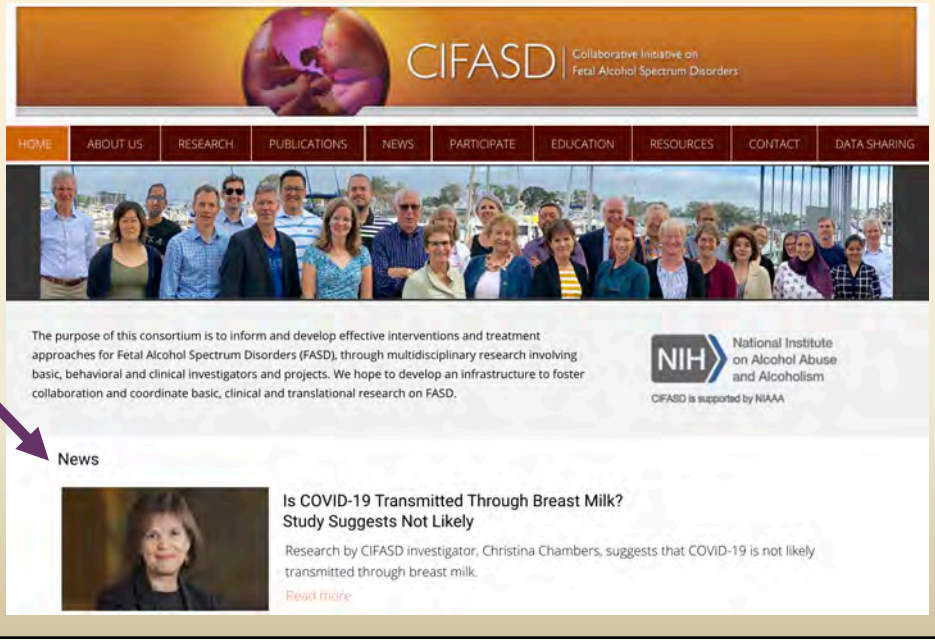
www.CIFASD.org



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CIFASD.org Data Sharing

ACCESSING CIFASD RESEARCH DATA

The CIFASD makes archived data available for discovery and validation research, with the ultimate goal of improving diagnoses, interventions, and treatment of FASD. Archived data from the previous three Phases of CIFASD vary in terms of population studied and outcome variables.

For more information on each Phase and the type of data that are available, please click on the appropriate cell within the Table below.

PHASE	DEMOGRAPHICS	DYSMORPHOLOGY	3D FACIAL IMAGING	NEUROBEHAVIOR	GENETIC DATA	BRAIN VOLUME	INFANT DATA	CYTOKINE DATA
Phase 1 (2003-2007)	✔	✔	✔	✔				
Phase 2 (2007-2012)	✔	✔	✔	✔	✔	✔	✔	
Phase 3 (2012-2017)	✔	✔	✔	✔	✔	✔	✔	✔

To request data, an application for data use must be submitted online via the CIFASD Data Access Request Form.

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CIFASD Publications Policy

CIFASD Publication Process

Policies and forms are housed within the secure section of the CIFASD website.

Concept Proposal
Complete the online
Concept Proposal Form

CIFASD Investigators
Review Concept Proposal:
Provide comments, indicate interest, define proposed contribution

Review Comments/ Respond to CIFASD Investigators

Analyses Proceed/ Manuscript Prepared
Provide updates to CIFASD ~ every 6 months to ensure progress

Prior to Submission
Complete the online
Manuscript Submission Template Form

Post-Acceptance
Complete the online
Post-Acceptance Form

Ensure Compliance
NIH Public Access Policy

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CIFASD4 Progress Tracking

Coles U01 Adults	Current Month	Cumulative Total	May 2021 Goal	% to Goal	Overall Goal	Completion Goal Date	May 2018 Goal	May 2019 Goal	May 2020 Goal	May 2021 Goal	May 2022 Goal
Enrollment											
Number of adult registry enrollees (Atlanta and Seattle)	2	265	393	67%	500	5/31/2022	33	153	273	393	500
Questionnaires - Demographics and Health											
ATL Qs completed - FASD or PAE	1	65	131	50%	166	5/31/2022	12	50	91	131	166
ATL Qs completed - CON	2	45	65	69%	83	5/31/2022	5	25	45	65	84
SEA Qs completed - FAS	0	48	66	73%	84	5/31/2022	6	26	46	66	83
SEA Qs completed - FAE	5	70	66	106%	84	5/31/2022	6	26	46	66	84
SEA Qs completed - CON	0	37	65	57%	83	5/31/2022	4	25	45	65	83
Questionnaires - Total	*8*	*265*	*393*	*67%*	*500*	*5/31/2022*	*33*	*152*	*273*	*393*	*500*
Biosamples and Neurobehavioral Testing (NIH Tool Box and Qs)											
ATL Biosamples and NB - FASD	1	23	32	72%	40	1/1/2022	0	8	20	32	40
ATL Biosamples and NB - PAE	2	28	32	88%	40	1/1/2022	0	8	20	32	40
ATL Biosamples and NB - CON	2	35	32	109%	40	1/1/2022	0	8	20	32	40
SEA Biosamples and NB - FAS	0	24	32	75%	40	1/1/2022	0	8	20	32	40
SEA Biosamples and NB - FAE	2	41	32	128%	40	1/1/2022	0	8	20	32	40
SEA Biosamples and NB - CON	0	18	32	56%	40	1/1/2022	0	8	20	32	40
Biosamples and NB Testing Total	*7*	*171*	*192*	*89%*	*240*	*1/1/2022*	*0*	*48*	*120*	*192*	*240*
	Start	**End**					Cumulative Goal at the end of each year.				
Current month (defined by project) =	10/27/2020	11/20/2020									
Date of project numbers update entry =	11/20/2020										

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Internal CIFASD4 Project Reviews

- Following the CIFASD4 Progress Meeting in June 2020, internal reviews were completed by members of the Advisory Committee based on project presentations, April 2020 NIH progress reports (RPPRs) and the Google Drive progress tracking tables
- Review feedback was drafted and collated by the Science Advisory Board on the consortium as a whole and individual projects
- Reviews were distributed to Project PIs by the Consortium Coordinator late summer 2020

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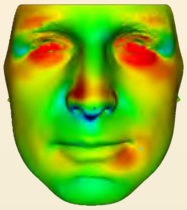
Resource Sharing

UC San Diego



UNIVERSITY of ROCHESTER

UNIVERSITY OF OXFORD

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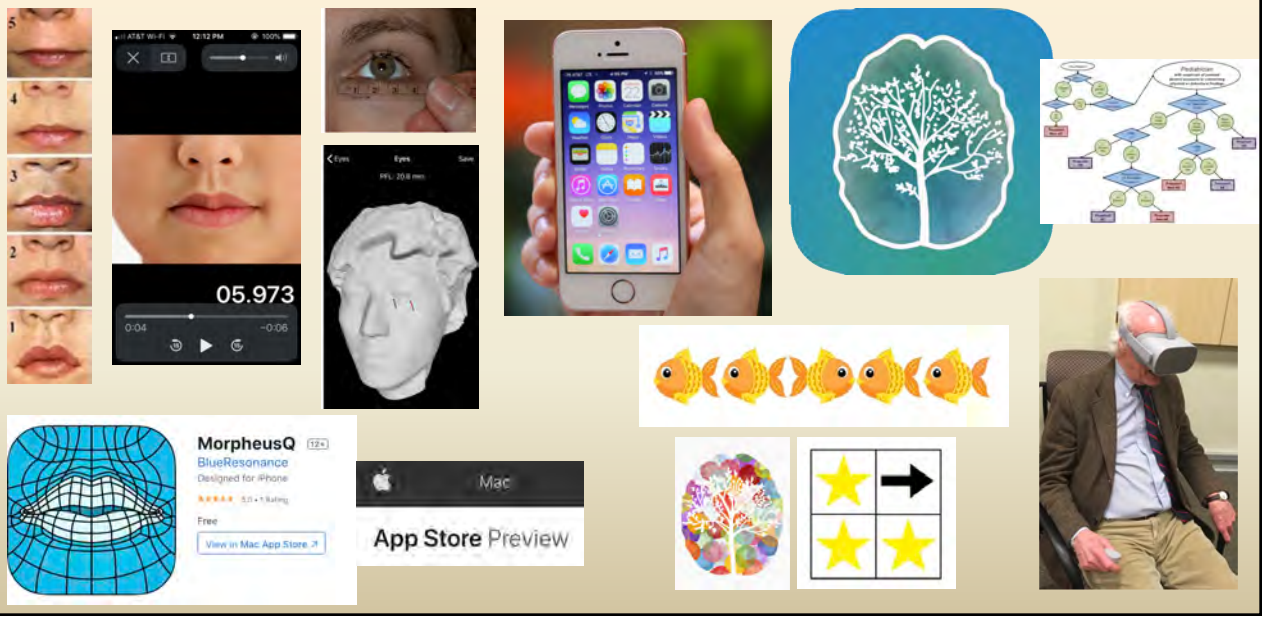
eHealth and App Development Subaward



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Impact of COVID-19

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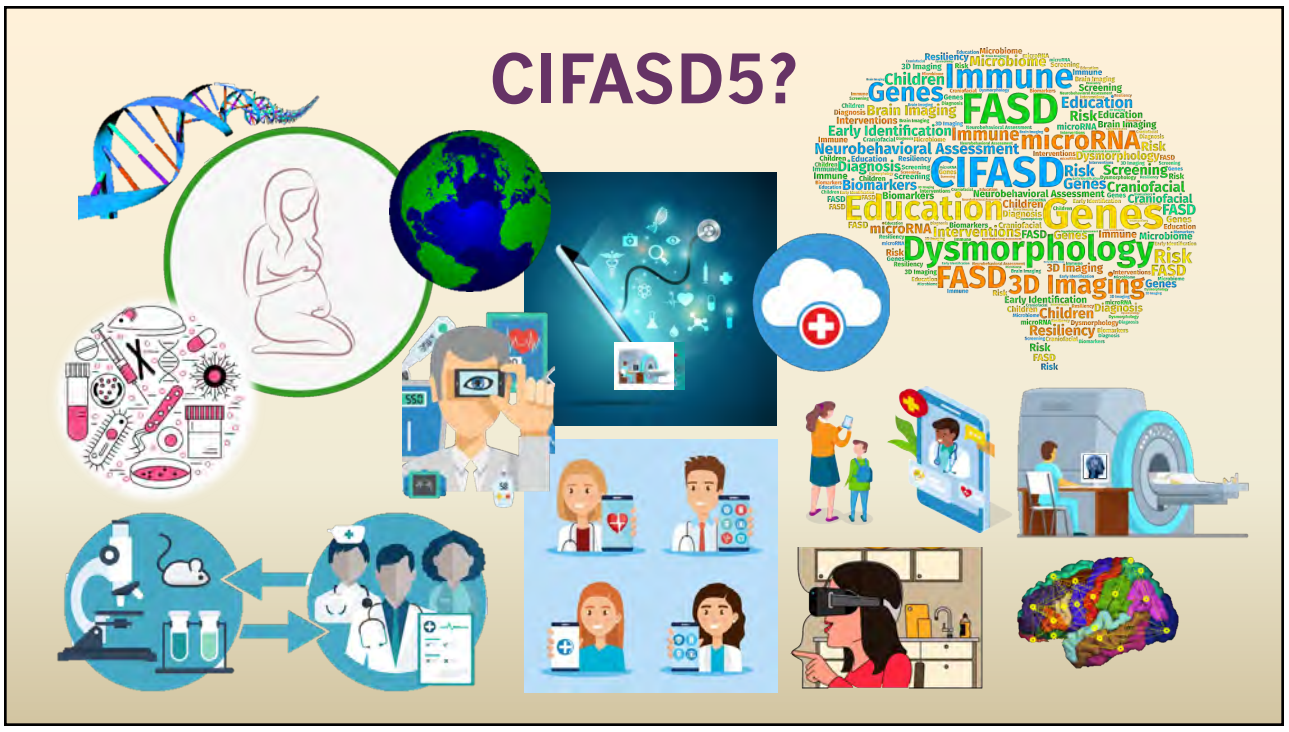

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Thank You

NIH National Institute on Alcohol Abuse and Alcoholism

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Dysmorphology Research Resource

Miguel del Campo, MD and Kenneth Lyons Jones, MD
University of California, San Diego
School of Medicine
La Jolla, California

1

DYSMORPHOLOGY RESEARCH RESOURCE
New Findings June 2020 – December 2020

Significant Results from the Last 6 months

- Aim #1: Assure consistency and accuracy in recognition of FASD at all CIFASD project sites.
  - No subjects were evaluated at any of the Clinical sites in CIFASD
- Aim #2: Further develop and refine the telemedicine approach.
  - Completed a paper entitled "The Use of Telemedicine for the Physical Examination of Fetal Alcohol Spectrum Disorder" and submitted it on September 16, 2020 to Alcoholism: Clinical and Experimental research. It is now in final review. The study documented that Telemedicine is a valid and reliable method for examination of the physical features of FASD.
- Aim #3: Expand on the the San Diego FASD research subject pool that we have established at UCSD Rady Children's Hospital
  - We have recruited 20 subjects prenatally exposed to alcohol seen in our UCSD/Rady Children's Hospital FASD Clinic for a total of 250 subjects recruited overall.
  - We have recruited and referred 27 subjects to Dr. Sarah Mattson's U01 Decision Tree at SDSU.
  - No additional specimens have been sent to Dr. Joanne Weinberg's U01.
  - No additional families have been sent to Dr. Christie Petrenko's U01.

2

Plans for the Remainder of Year 4

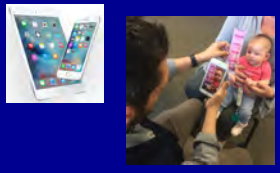
- Hopefully be able to evaluate subjects in Vancouver, Atlanta and Minneapolis by Telemedicine
- Schedule in real time telemedicine training with physicians and other healthcare providers in Alaska to ensure expertise in both standard assessments of the facial features with a ruler and lip-philtrum guide, as well as with the different features of the Morpheus Q App. We will then be able to develop a cadre of physicians and other healthcare providers in Alaska that will allow us to test the Morpheus Q App in hopes of establishing an FASD Prevention Program in Alaska in the future
- See patients by Telemedicine and Face-to-Face at our UCSD/Rady Children's Hospital FASD Clinic, continue to add subjects to our Research Registry, continue to recruit and refer subjects to Dr, Sarah Mattson's U01 Decision Tree at SDSU and to other clinical studies when they are requested as well as blood and urine samples from our biorepository

3

Using Telemedicine (TM) for physical examination in FASD

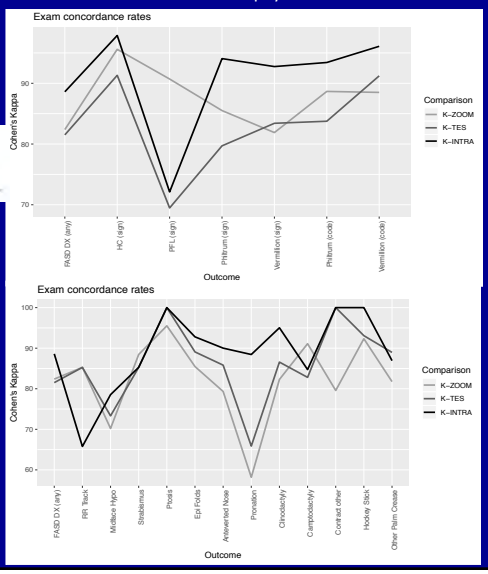
Transportable exam system for TM (TES)

Handheld smart device system for TM (ZOOM)



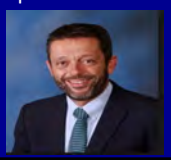
Submitted to Alcoholism: clinical and experimental research. Final review

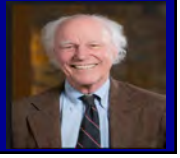
Agreement between face to face (F2F) and Telemedicine (TM) exams for the evaluation of the physical features of FASD



Results and conclusion

Telemedicine using TES or hand held devices is reliable and valid for the exam of the physical features of FASD. **We believe more precise measurements and more objective assessment of the features is necessary even face to face. We are trying new tools to improve precision and objectivity.**
The use of TM will increase the ability to make a diagnosis for all affected patients at an earlier age, in order to provide prompt services and improve outcomes





4

Future plans 1
Training of physicians via Telemedicine

- Pediatric residents
- Genetics fellows
- Indian Health services Valley Center San Diego county
- Alaskan providers. FASD diagnostic teams network and neurodevelopmental partners meeting

5

Future plans 2
Alaska collaborations for CIFASD

- Hope Filkenstein

The State of Alaska Department of Health & Social Services funds a network of regionally based multidisciplinary/interdisciplinary FASD diagnostic teams. There is a limited number of FASD informed medical providers in the State.

- Marilyn Pierce Bolger

State of AK sponsored Neurodevelopmental Partners meeting

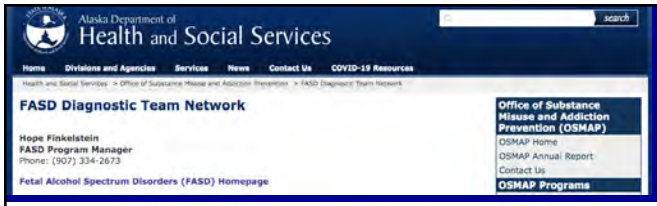
Ptarmigan Connections

Providence Hospital

Regional Native health clinics

Ryan Ray Alaska

6



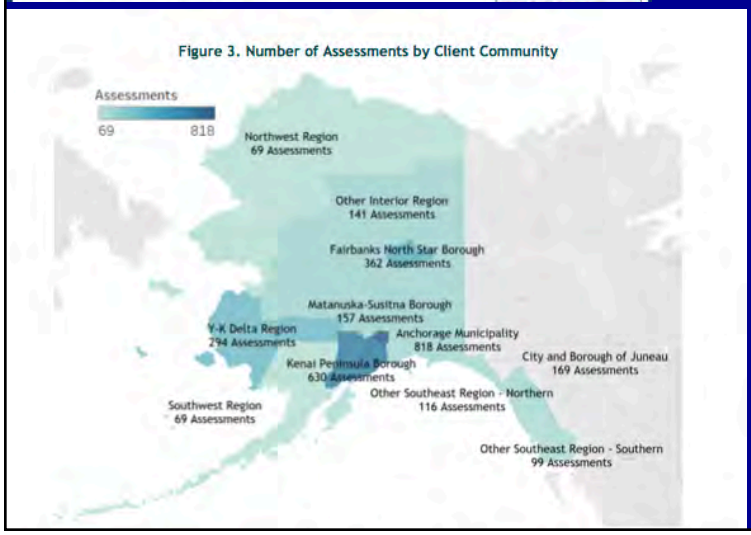


Table 1. Alaska Behavioral Health Regions

Behavioral Health Region	Borough/Census Area
Anchorage Municipality	Anchorage Municipality
Fairbanks North Star Borough	Fairbanks North Star Borough
City and Borough of Juneau	City and Borough of Juneau
Kenai Peninsula Borough	Kenai Peninsula Borough
Matanuska-Susitna Borough	Matanuska-Susitna Borough
Northwest Region	Nome Census Area
	North Slope Borough
	Northwest Arctic Borough
Other Interior Region	Denali Borough
	Southeast Fairbanks Census Area
	Valdez-Cordova Census Area
	Yukon-Koyukuk Census Area
Other Southeast Region – Northern	Haines Borough
	Hoonah-Angoon Census Area
	Petersburg Borough
	Sitka City and Borough
	Skagway Municipality
	Wrangell City and Borough
Other Southeast Region – Southern	Yakutat City and Borough
	Ketchikan Gateway Borough
	Prince of Wales-Hyder Census Area
Y-K Delta Region	Bethel Census Area
	Kusilvak Census Area
Southwest Region	Aleutians East Borough
	Aleutians West Census Area
	Bristol Bay Borough
	Dillingham Census Area
	Kodiak Island Borough
	Lake and Peninsula Borough

Source: Alaska Division of Public Health

7

Examination techniques

- Precise measurements
- Subjective evaluation of features

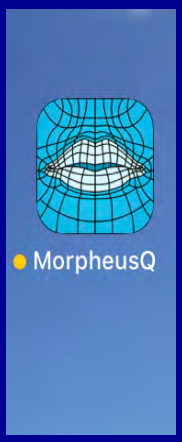
- 3 key features
  - Short palpebral fissure length
  - Smooth philtrum
  - Narrow vermillion of upper lip with loss of Cupid's bow shape

Figure 4. A and B. Correct measurement of the palpebral fissures with a hard ruler measuring between the two canthi, placing the ruler at the right angle of the face, parallel to the line tha joins both canthi. C. Using the philtrum and lip guide and looking with a 45 degree angle.

8

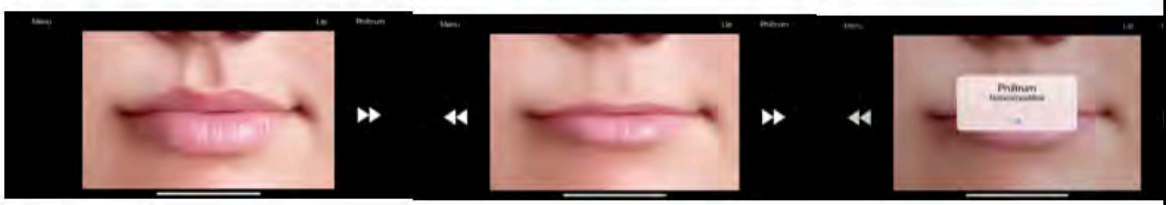
How to improve assessment of physical features

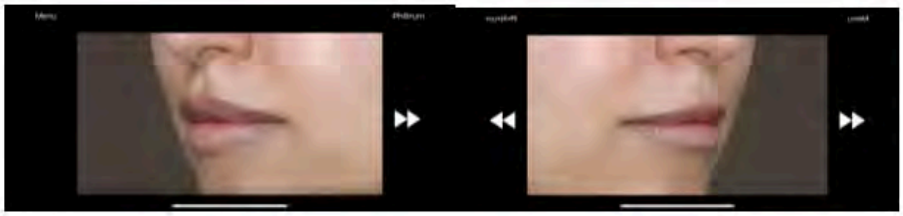
Precise measurement in 3-D photo



9

Continuous Morph scales for shapes of philtrum and upper lip





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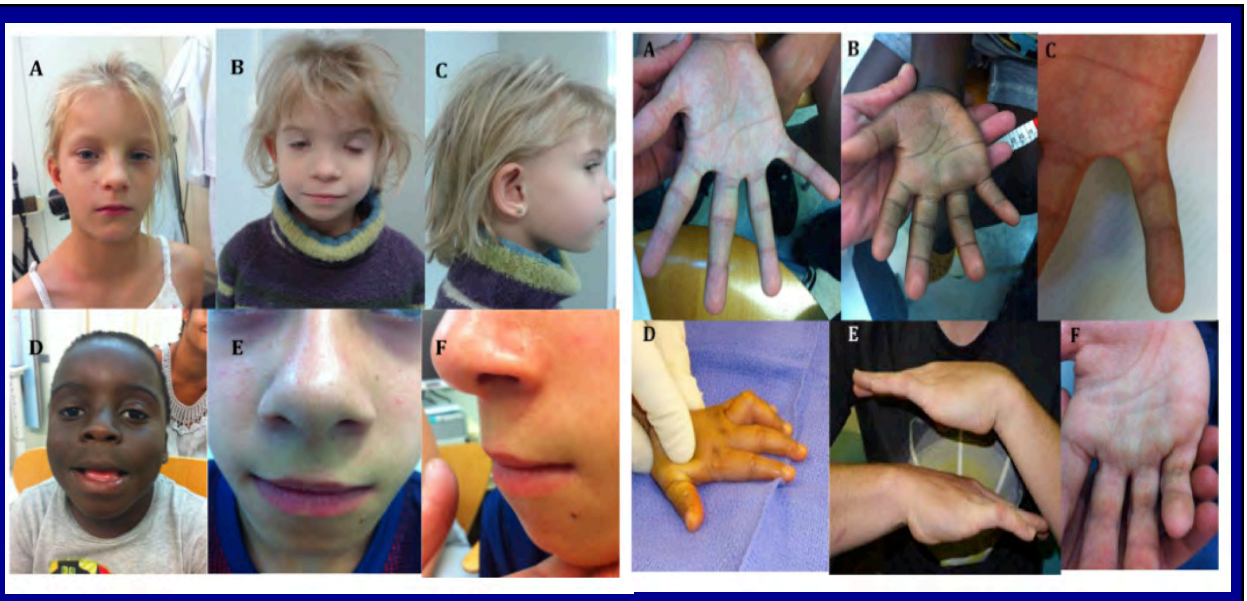


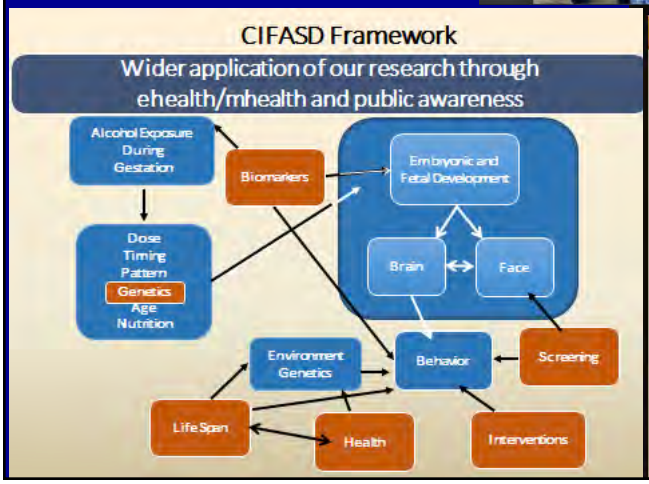
12 additional physical features: ptosis, epicanthal folds, midface hypoplasia, shot nose with anteverted nares, railroad track ears, retrognathia, joint contractures, limitation elbow pronosupination, camptodactyly, clinodactyly, abnormal palmar creases, hockey stick crease

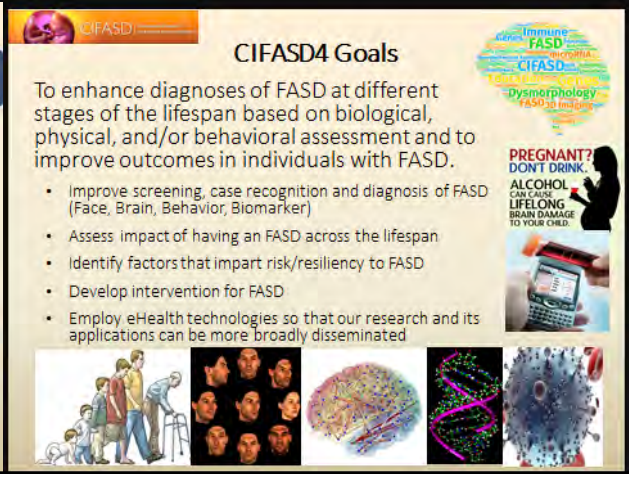
11

Watch 3 D image taken by Morpheus Q real time.

12

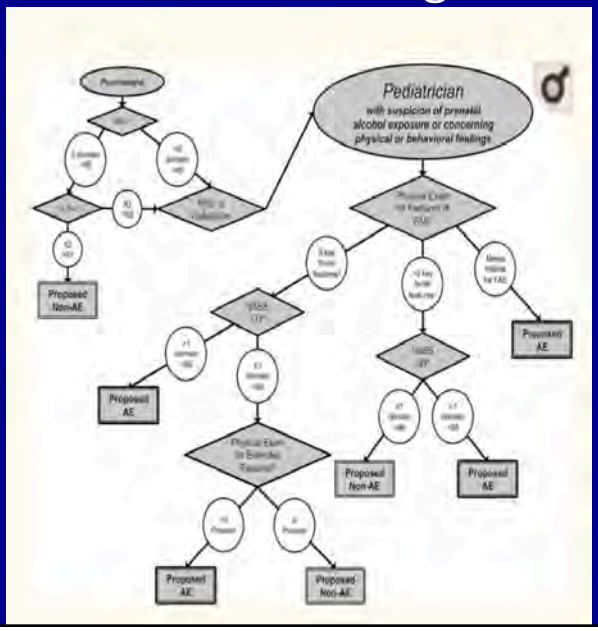
Future plans 3. Extend the collaboration to other clinical groups in the consortium CIFASD 5?





13

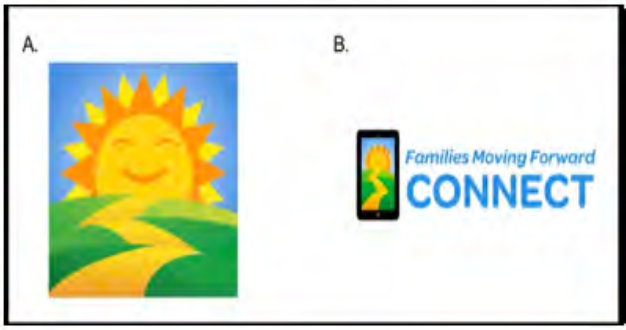
Online neurobehavioral testing and Decision Tree



Sarah Mattson, PhD

14

Remote intervention



Christie Petrenk0 Christian Taparello

15

STIGMA: A major reason FASD is being ignored

An attribute that is deeply discrediting and reduces the individual from a whole and usual person to a tainted discounted one

4 Types of Stigma
- Public Stigma
- Stigma by Association
- Self Stigma
- Structural Stigma

16

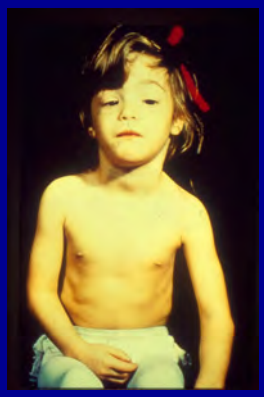
Publications:
Stigma of Fetal Alcohol Spectrum Disorders

- Corrigan PW, Juana Lorena Lara, Binoy Bien Shah, Kathleen T. Mitchell, Diana Simmes, Kenneth L. Jones. The Public Stigma of Birth Mothers of Children of with FASD. Alcohol Clin Exp Res 41: 2017: 1166 – 1173.
- Corrigan PW, Binoy Bien Shah Juana Lorena Lara,, Kathleen T. Mitchell, Diana Simmes, Kenneth L. Jones. Addressing the Public Health Concerns of FASD: Impact of Stigma and Health Literacy. Drug and Alcohol Dependence https://doi.org./10.1016/j.drugalcdep.2017.12.027.
- Corrigan PW, Binoy Bien Shah Juana Lorena Lara,, Kathleen T. Mitchell, Peggy Coombs-Way, Diana Simmes, Kenneth L. Jones. Stakeholders Perspectives on the Stigma of FASD. Addiction Research and Theory.

https://doi.org/10.1080/16066359.2018.1478413.

17

How Does Public Stigma Impact FASD Leading To FASD Being all but Ignored



Government support and philanthropy are very difficult to obtain for a condition that is so stigmatized

Because of stigma children with FASD do not get proper help through the school system

Stigma leads to obstetricians being loath to even ask a pregnant women If she is drinking alcohol

Stigma leads to Pediatricians being loath to give a child a diagnosis of FASD because they feel it will insult the mother

Because of stigma judges believe that individuals with FASD cannot be rehabilitated

Because of stigma individuals with FASD are not treated equally before the law

Lack of early diagnosis is directly related to worse outcome

Lack of DX leads to Insurance Companies unwilling to pay for medical care without a diagnosis

Stigma leads to lack of a diagnosis of FASD leading to a failure to be referred for appropriate services

18

Development of an Anti-Stigma Program: Two Approaches to Changing Stigma

- Provide Education
- Contact Interventions – Challenge stereotypes by providing presentations of "lived experience" of a health condition by high-functioning persons with the health condition, followed by interactions with the targeted audience. We have developed an AEP/FASD anti-stigma education and contact intervention program..

19

Using Contact Interventions

- Kathie Mitchelle and Peggy Combs-Way have developed a training program for birth mothers, those with "lived experience", to talk with the participating primary care pediatricians and obstetricians to demystify the alcohol screening process from their unique perspective.

20

Active Approach to Partnerships

- The anti-stigma approach borrows from the science of **Community Based Participatory Research** which represents principles that form a partnership between investigators and stakeholders involved in the **community** in which health concerns lie.
- The **community** in this case encompasses biologic mothers of children with an FASD, women who drink alcohol during their pregnancies,and foster and adoptive mothers and primary care pediatricians and obstetricians.

21

Two Year CDC Funding Methodology: Year 1

- Recruitment of Community Based Participatory Research team:
  7 to 10 members comprised of persons with a lived experience and targeted healthcare providers. (Pediatricians and Obstetricians)

- Primary Objectives:

1) Dispel provider stereotypes about the prevalence of FASD and the reasons, characteristics, and risk factors associated with drinking alcohol during pregnancy
2) Decrease the percentage of providers who view stigma as a barrier to screening their patients.
3) Increase alcohol use screening rates for obstetric patients using a validated screening tool
4) Increase pediatric prenatal alcohol screening tools
5) Develop a formal birth mothers training curriculum focused on addressing stigma issues and empowerment
6) Develop an anti-stigma manual to provide structure for presentations on the lived-experience of FASD

22

Methodology Year 1 (continued)

- Five Focus Groups were established and held:
  1) Biologic mothers
  2) Pediatricians
  3) Obstetricians
  4) Adoptive and Foster Mothers in San Diego

Purpose: To elucidate the key issues surrounding stigma and bias as it pertains to alcohol exposed pregnancies and FASD and as it relates to the individuals in each focus group.

23

Methodology: Year 2

- Implementation: Components of the anti-stigma program were finalized by the CBPP team and the implementation of the contact program with the targeted population is ready to commence.
- This will begin with presentation of the contact program to both Pediatricians and Obstetricians by woman with the lived experience
- The presentation will take only 30-45 minutes

24

Contact Interventions for Reducing Stigma: Two Core Components

1) Person with the condition introduces the topic. e.g. Disparities in Care – and then presents to the Target Audience how providers stigmatizing attitudes may lead to disparities in care.

2) The person with the lived experience relates what she has gone through with the Target Audience including struggles with the condition, recovery, and resilience, and that successful recovery is possible.

25

Primary Objectives

- decrease primary care pediatricians and obstetricians stereotypes about women who drink alcohol during pregnancy
- decrease the percentage of primary care pediatricians and obstetricians who report stigma/bias as a barrier to screening their patient

26

Research Design

- Subjects (Primary Care Pediatricians and Primary Care Obstetricans) will be randomized to one of two conditions - education or contact.
- Participants in the education and contact conditions will each be randomized to one of two arms - one additional booster, or two additional boosters.
- Boosters for the education condition will be a 15-minute power point review of myths and challenging facts about mothers of children with FASD. The 15-minute contact condition will be two separate presentations of recovery by two biological mothers of children with FASD;
- Data will be collected at baseline, day 2 (immediately post-test and day 30.
- Research participants will complete measures of stigma, knowledge of FASD (FASD literacy scale), and familiarity with FASD, at each of the assessment time points of themselves historically? Or typically or????

27

Early Predictors of FASD in Ukraine

Christina Chambers, Claire Coles, Julie Kable, Rajesh Miranda, Amanda Mahnke, Nihal Salem, Marisa Pinson, Gretchen Bandoli, Todd Coleman, Marcelo Aguilar-Rivera, Ken Jones, Wladimir Wertelecki, Lyuba Yevtushok, Natalya Zymak-Zakutnya

Collaborative Initiative on Fetal Alcohol Spectrum Disorders
Fall 2020 Meeting

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CIFASD4 Aims

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2

Early Predictors of FASD in Ukraine

Develop a panel of prenatal/infancy physiologic and biologic markers that can predict FASD using existing data and 200 newly enrolled pregnant women/infants

- miRNAs
- COR paradigm
- Cytokines

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Early Predictors of FASD in Ukraine

Develop risk/resilience profiles based on early markers and other factors that will adequately predict preschool and school age performance using existing data and 200 newly enrolled pregnant women/infants

- Growth, social, environmental, economic, health, & other available data in base models
- Add early physiology/biomarkers to profiles
- Test prediction model to extent possible in CIFASD2 and 3 retrospective samples

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Early Predictors of FASD in Ukraine

Collaborate with others in the CIFASD consortium

- Provide data, biological samples and analytical support to Weinberg project
- Provide data, biological samples and analytical support to Torii project
- Provide data to Mattson project
- Provide data, 3D images and ultrasounds to Suttie and Noble projects

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Early Predictors of FASD in Ukraine

Supplements/XO/Complementary R01

- Biomarkers to validate maternal report of alcohol exposure
- HIV and alcohol
- WGS of mother/child pairs
- COR adaptation for clinical administration/scoring

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Recruitment Status

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Activity	N Recruited	N Required
New Pregnant Women	140	200
Infant Testing	30 at 6 months 11 at 12 months	180
School Age Testing	96	150
Blood Samples Woman	140	200
Blood Samples Infant	4	180
Blood Samples School Age	55	75
Ultrasound	136	200
3D Image (1 site)	35	90
Blood Samples Research Repository	32	--

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HIV Supplement – Lutsk Province

Characteristics	Children 3-10 years N =112	Population Reference in Ukraine
Male	63 (56.3%)	
Female	49 (43.8%)	
Birthweight <2500 g	12 (10.7%)	4.3%
OFC at birth <32 cm	16 (14.3%)	3.3%-4.1%
Maternal alcohol consumption first month of pregnancy **any** **3 to 4 occasions**	 40 (36%) 18 (16%)	
Maternal concerns about development **Learning** **Behavior**	 7 (6.3%) 14 (12.5%)	

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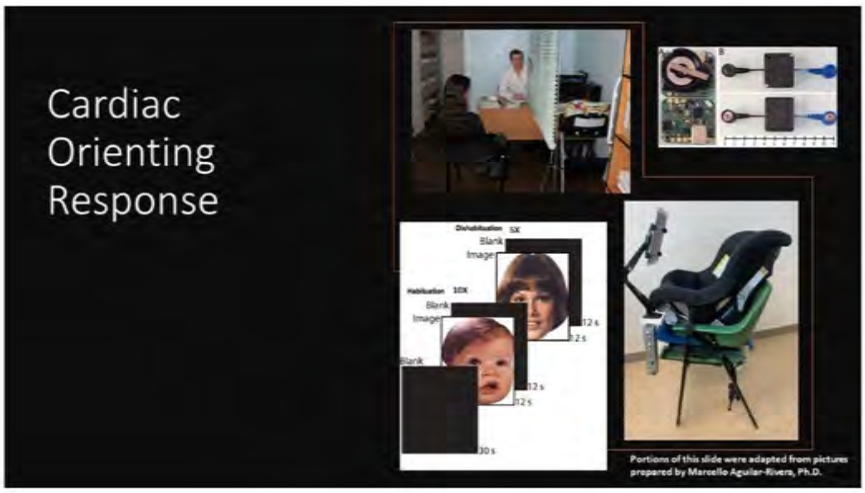
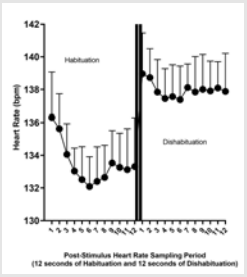
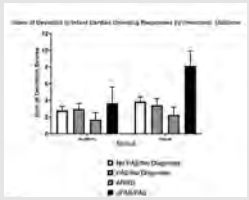


10

Infant Heart Rate Responses While Processing Novel Information Predict Later pFAS/FAS Status





- Receiver operating characteristic curve analysis of the visual response yielded an area under the curve value of .765 for predicting to pFAS/FAS status.
- In comparison, routine breast cancer screening methods have area under the curve values that range from the .60-.70's

11

Salem et al. Biology of Sex Differences (2020) 11:51
https://doi.org/10.1186/s13293-020-00307-2

Biology of Sex Differences

RESEARCH Open Access

Association between fetal sex and maternal plasma microRNA responses to prenatal alcohol exposure: evidence from a birth outcome-stratified cohort

Nihal A. Salem[1,2], Amanda H. Mahnke[1,3], Alan B. Wells[4,5], Alexander M. Tseng[1], Lyubov Yevtushok[6,7,8], Natalya Zymak-Zakutnya[8,9], Wladimir Wertelecki[5,8], Christina D. Chambers[4,5,*†], Rajesh C. Miranda[1,2,3*†] and Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD)

Abstract

Most persons with fetal alcohol spectrum disorders (FASDs) remain undiagnosed or are diagnosed in later life. To address the need for earlier diagnosis, we previously assessed miRNAs in the blood plasma of pregnant women who were classified as unexposed to alcohol (UE), heavily exposed with affected infants (HEa), or heavily exposed with apparently unaffected infants (HEua). We reported that maternal miRNAs predicted FASD-related growth and psychomotor deficits in infants. Here, we assessed whether fetal sex influenced alterations in maternal circulating miRNAs following prenatal alcohol exposure (PAE). To overcome the loss of statistical power due to disaggregating maternal samples by fetal sex, we adapted a strategy of iterative bootstrap resampling with replacement to assess the stability of statistical parameter estimates. Bootstrap estimates of parametric and effect size tests identified male and female fetal sex-associated maternal miRNA responses to PAE that were not observed in the aggregated sample. Additionally, we observed, in HEa mothers of female, but not male fetuses, a network of co-secreted miRNAs whose expression was linked to miRNAs encoded on the X-chromosome. Interestingly, the number of significant miRNA correlations for the HEua group mothers with female fetuses was intermediate between HEa and UE mothers at mid-pregnancy, but more similar to UE mothers by the end of pregnancy. Collectively, these data show that fetal sex predicts maternal circulating miRNA adaptations, a critical consideration when adopting maternal miRNAs as diagnostic biomarkers. Moreover, a maternal co-secretion network, predominantly in pregnancies with female fetuses, emerged as an index of risk for adverse birth outcomes due to PAE.

Keywords: Bootstrap resampling, Sex as a biological variable, Extracellular miRNAs, Fetal alcohol spectrum disorders, Maternal miRNA co-secretion

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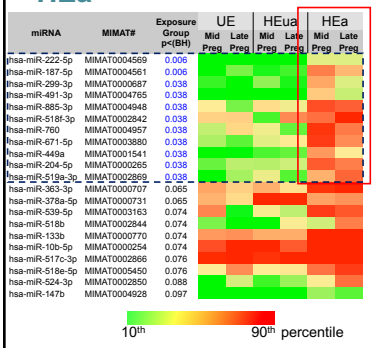
HEamiRNAs and Placental Development



Balaraman S, Schafer JJ, Tseng AM, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, et al. (2016) Plasma miRNA Profiles in Pregnant Women Predict Infant Outcomes following Prenatal Alcohol Exposure. PLoS ONE 11(11): e0165081. https://doi.org/10.1371/journal.pone.0165081

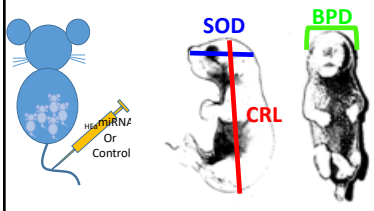
Published Online: 4 March, 2019 | Supp Info: http://doi.org/10.26508/lsa.201900252
Downloaded from life-science-alliance.org on 4 March, 2019

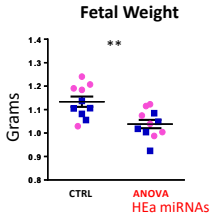
Research Article

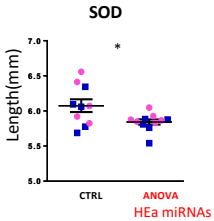
Life Science Alliance

Maternal circulating miRNAs that predict infant FASD outcomes influence placental maturation

Alexander M Tseng[1], Amanda H Mahnke[1], Alan B Wells[2,3], Nihal A Salem[1], Andrea M Allan[4], Victoria HJ Roberts[5], Natali Newman[6], Nicole AR Walter[6], Christopher D Kroenke[6], Kathleen A Grant[6], Lisa K Akison[7], Karen M Moritz[7], Christina D Chambers[2,3], Rajesh C Miranda[1], Collaborative Initiative on Fetal Alcohol Spectrum Disorders







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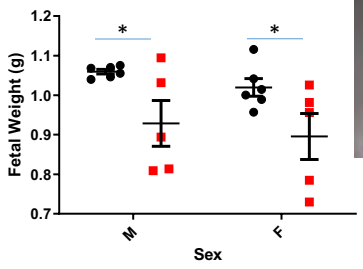
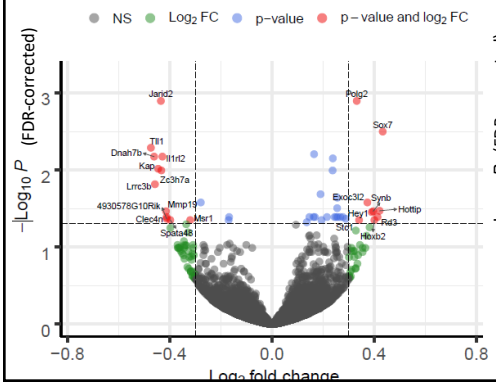
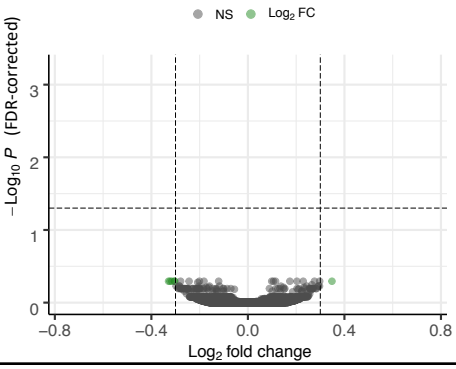
HEamiRNAs compared to PAE: Placental transcriptome



HEamiRNA vs Control



PAE vs Control



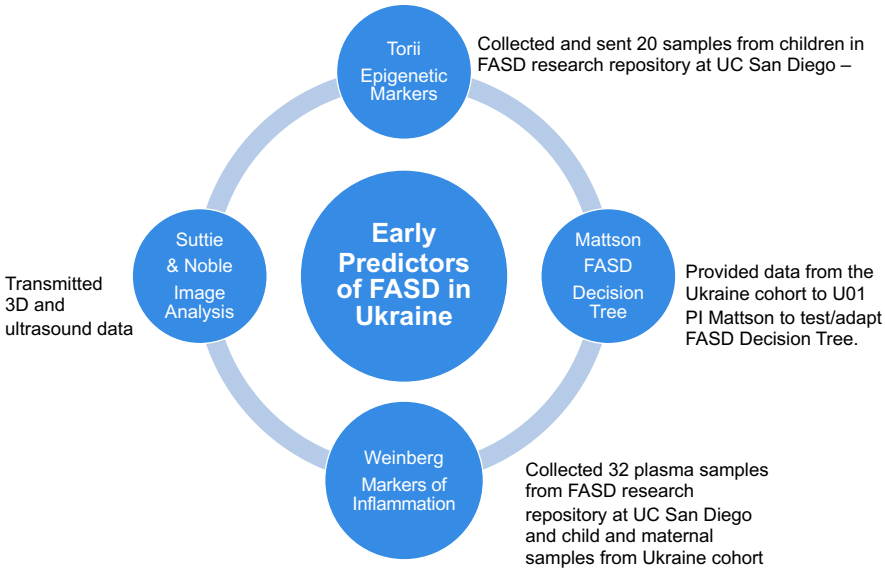
14

Progress

- Placenta transcriptomics (effects of $_{HEa}$miRNAs and PAE)
  - manuscript in preparation
  - Presentation planned for RSA2021
- Maternal miRNAs:
  - 93 analyzed
  - 30 additional received = 123
  - 56 mother/child dyads
  - 97 overlap with JW's data.
- Child miRNAs:
  - 57 child samples completed
  - 1 new sample received
  - Additional samples expected
  - 20 overlap with JW's data

15

Synergy Across the Consortium



16

Training

- Bandoli – K01
- Salem - F99/K00
- Pinson - F30
- Tseng - F31

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Publications Accepted or In Press

- Kable JA, Coles CD, Jones KL, Yevtushok L, Kulikovsky Y, Zymak-Zakutnya N, Dubchak I, Adhmedzhanova D, Wertelecki W, Chambers CD, and the CIFASD. Infant Cardiac Orienting Responses Predict Later FASD in the Preschool Period. ACER In press

- Salem NA, Mahnke AH, Wells AB, Tseng AM, Yevtushok L, Zymak-Zakutnya N, Wertlecki W, Chambers CD, Miranda RC; Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). Association between fetal sex and maternal plasma microRNA responses to prenatal alcohol exposure: evidence from a birth outcome-stratified cohort. Biol Sex Differ. 2020 Sep 10;11(1):51. doi: 10.1186/s13293-020-00327-2.PMID: 32912312

- Bandoli G, Jones K, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, Granovska I, Plotka L, Chambers C; CIFASD. Patterns of Prenatal Alcohol Exposure and Alcohol-Related Dysmorphic Features. Alcohol Clin Exp Res. 2020 Aug 9. doi: 10.1111/acer.14430. Online ahead of print. PMID: 32772389

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Publications Accepted or In Press

- Sowell KD, Holt RR, Uriu-Adams JY, Chambers CD, Coles CD, Kable JA, Yevtushok L, Zymak-Zakutnya N, Wertelecki W, Keen CL; CIFASD. Altered Maternal Plasma Fatty Acid Composition by Alcohol Consumption and Smoking during Pregnancy and Associations with Fetal Alcohol Spectrum Disorders. J Am Coll Nutr. 2020 Mar-Apr;39(3):249-260. doi: 10.1080/07315724.2020.1737984. Epub 2020 Apr 2.PMID: 32240041
- Bodnar TS, Raineki C, Wertelecki W, Yevtushok L, Plotka L, Granovska I, Zymak-Zakutnya N, Pashtepa A, Wells A, Honerkamp-Smith G, Coles CD, Kable JA, Chambers CD, Weinberg J; and the CIFASD. Immune network dysregulation associated with child neurodevelopmental delay: modulatory role of prenatal alcohol exposure. J Neuroinflammation. 2020 Jan 28;17(1):39. doi: 10.1186/s12974-020-1717-8.PMID: 31992316
- Tseng AM, Mahnke AH, Wells AB, Salem NA, Allan AM, Roberts VH, Newman N, Walter NA, Kroenke CD, Grant KA, Akison LK, Moritz KM, Chambers CD, Miranda RC; Collaborative Initiative on Fetal Alcohol Spectrum Disorders. Maternal circulating miRNAs that predict infant FASD outcomes influence placental maturation. Life Sci Alliance. 2019 Mar 4;2(2):e201800252. doi: 10.26508/lsa.201800252. Print 2019 Apr.PMID: 30833415

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Publications Accepted or In Press

- Sarkar DK, Gangisetty O, Wozniak JR, Eckerle JK, Georgieff MK, Foroud TM, Wetherill L, Wertelecki W, Chambers CD, Riley E, Zymak-Zakutnya N, Yevtushok L. Persistent Changes in Stress-Regulatory Genes in Pregnant Women or Children Exposed Prenatally to Alcohol. Alcohol Clin Exp Res. 2019 Sep;43(9):1887-1897. doi: 10.1111/acer.14148. Epub 2019 Aug 6.PMID: 31329297
- Bandoli G, Coles CD, Kable JA, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, Wells A, Granovska IV, Pashtepa AO, Chambers CD; CIFASD. Patterns of Prenatal Alcohol Use That Predict Infant Growth and Development. Pediatrics. 2019 Feb;143(2):e20182399. doi: 10.1542/peds.2018-2399. Epub 2019 Jan 4.PMID: 30610099
- Coles CD, Kable JA, Granovska IV, Pashtepa AO, Plotka LD, Dolhov VB, Wertelecki W, Jones KL,Chambers CD; CIFASD. Gestational age and socioeconomic status as mediators for the impact of prenatal alcohol exposure on development at 6 months. Birth Defects Res. 2019 Jul 15;111(12):789-796. doi: 10.1002/bdr2.1408. Epub 2018 Oct 31.PMID: 30378744

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20

Publications Accepted or In Press

- Bodnar TS, Raineki C, Wertelecki W, Yevtushok L, Plotka L, Zymak-Zakutnya N, Honerkamp-Smith G, Wells A, Rolland M, Woodward TS, Coles CD, Kable JA, Chambers CD, Weinberg J; Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). Altered maternal immune networks are associated with adverse child neurodevelopment: Impact of alcohol consumption during pregnancy. Brain Behav Immun. 2018 Oct;73:205-215. doi: 10.1016/j.bbi.2018.05.004. Epub 2018 May 5.PMID: 29738852
- Sowell KD, Uriu-Adams JY, Van de Water J, Chambers CD, Coles CD, Kable JA, Yevtushok L, Zymak-Zakutnya N, Wertelecki W, Keen CL; Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). Implications of altered maternal cytokine concentrations on infant outcomes in children with prenatal alcohol exposure. Alcohol. 2018 May;68:49-58. doi: 10.1016/j.alcohol.2017.08.006. Epub 2017 Aug 12.PMID: 29453023

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Publications Submitted or in Preparation

- Kautz C, Petrenko CLM, Handley ED, Coles CD, Kable JA, Wertelecki W, Yevtushok L, Zymak-Zakutnya N, Chambers CD, and CIFASD. Partner influence as a factor in maternal alcohol consumption and depressive symptoms, with subsequent effects on infant neurodevelopmental outcomes. Submitted to ACER.
- Kable, JA, Coles, CD, Keen, CL, Uriu-Adams, JY, Jones, KL, Yevtushok, L., Kulikovsky, Y, Wertelecki, W., Pedersen, TL, Chambers, CD. & and the CIFASD. The impact of micronutrient supplementation in alcohol-exposed pregnancies on reaction time responses in Ukrainian preschoolers. Submitted to Alcohol.
- Coleman TP, Kable JA, Aguilar-Rivera M, Coles CD, Jones KL, Yevtushok L, Kulikovsky Y, Zymak-Zakutnya N, Akhmedzhanova D, Wertelecki W, Chambers CD. Infant cardiac orienting response as a predictor of neurodevelopmental risk. In preparation.
- Raineki, C., Bodnar, T., Wertelecki, W., Yevtushok, L., Plotka, L., Granovska, I., Zymak-Zakutnya, N., Pashtepa, A., Wells, A., Honerkamp-Smith, G., Coles, C.D., Kable, J.A., Chambers, C.D., Weinberg, J., and the CIFASD. Differential associations between maternal and child Immune milieus in alcohol-dependent and alcohol-independent neurodevelopmental delay. In preparation.

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Future Directions

- Test of hypothesis that PAE results in premature aging which can be tested in children and adults
  - Markers of premature aging
    - Cell-free telomere length
    - T-cell exhaustion phenotype
    - Serum amyloid
    - CDKN2A/P16NK4A
- Determine the predictive validity of the COR collected in infancy to the 7-10 year-old neurodevelopmental outcomes (when the 150 children have completed testing as part of original aims in Phase 4)
- Assess health outcomes in children retained in the study from 0-15 years of age and possibly their mothers, including markers of peripheral vascular functioning
  - Relate markers of vascular functioning to fNIRS and neurobehavioral outcomes

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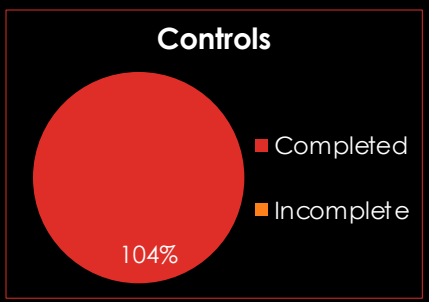
NEUROIMAGING PROJECT UPDATE

Jeff Wozniak, Ph.D.
University of Minnesota
December 2020

1

PHASE 1: BASELINE MRI AND NEUROCOGNITIVE ASSESSMENT

Target: recruit groups of 45 (PAE) and 45 (controls)
Age range: 8 – 16 years old at enrollment
Dysmorphology; MRI scan; neurocognitive testing
Second scan after 15 month interval



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PHASE 2: 15-MONTH FOLLOW-UP MRI

- Returning on a rolling basis (2019-2022)
  - Controls = 16 of 45 completed (53% toward May, 2021 goal)
  - Prenatal alcohol = 26 of 45 completed (87% toward May, 2021 goal)
- Scanning and neuropsychological evaluations re-initiated in October, 2020
  - Nov: 42 (70%)
  - Dec: +4 (76%)
  - Jan: +6 (86%)
  - Feb: +3 (92%)
  - Mar: +1 (93%)
  - Apr: +2 (97%)
  - May: +2 (100%)
  - June: 4 (71% of overall goal) ------→

3

PUBLICATIONS

4

Para-limbic Structural Abnormalities Are Associated With Internalizing Symptoms in Children With Prenatal Alcohol Exposure

Alyssa M. Krueger, Donovan J. Roediger, Bryon A. Mueller, Christopher A. Boys, Timothy J. Hendrickson, Mariah J. Schumacher, Sarah N. Mattson, Kenneth L. Jones, Edward P. Riley, Kelvin O. Lim, and Jeffrey R. Wozniak

Background: Prenatal alcohol exposure (PAE) is associated with a variety of structural abnormalities in the brain, including several within the para-limbic system. Children with PAE have higher rates of internalizing disorders, including depression and anxiety, which may be related to underlying limbic system anomalies.

Methods: Children aged 8 to 16 with PAE ($n = 41$) or without PAE ($n = 36$) underwent an magnetic resonance imaging of the brain and parents completed behavioral questionnaires about their children. Semi-automated procedures (FreeSurfer) were used to derive para-limbic volumes from T1-weighted anatomical images.

Results: There were significant group differences (PAE vs. nonexposed controls) in the caudate, hippocampus, and the putamen; children with PAE had smaller volumes in these regions even after controlling for total intracranial volume. A trend-level association was seen between caudate volume and internalizing symptoms in children with PAE; smaller caudate volumes (presumably reflecting less optimal neurodevelopment) were associated with higher levels of anxiety and depression symptoms in these children.

Conclusions: Caudate structure may be disproportionately affected by PAE and may be associated with the later development of internalizing symptoms in those affected by PAE.

Key Words: Fetal Alcohol Spectrum Disorder, Brain, Anxiety, Depression, Children.

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Para-limbic Region	Estimated Marginal Mean	SE	F	p-value	Corrected p-value	Cohen's d
Hippocampus	PAE= 7918.32	98.02	9.917	.002	.006**	.78
	Control= 8377.23	104.82				
Caudate	PAE= 7403.13	107.14	17.810	<.001	<.001***	.98
	Control= 8075.31	114.57				
Putamen	PAE= 10596.47	135.31	4.040	.026	.050*	.53
	Control= 11052.03	144.70				
Amygdala	PAE= 3200.55	40.842	3.807	.055	.055	.45
	Control= 3319.02	43.68				

Internalizing Measure	Caudate	Hippocampus	Putamen
CBCL			
Internalizing	-0.374[a*]	0.160	-0.043
Anxious/Depressed	-0.362[a*]	0.118	-0.136
Withdrawn/Depressed	-0.301[b]	-0.058	-0.106
BASC-3CBCL			
Internalizing Problems	-0.276[b]	-0.189	0.001
Anxiety	-0.241[b]	-0.071	-0.021
Depression	-0.277[b]	-0.241*	-0.009

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Roediger, D.J., Krueger, A.M., de Water, E., Mueller, B.A., Boys, C.A., Hendrickson, T.J., Schumacher, M.J., Mattson, S.N., Jones, K.L., Lim, K.O., CIFASD, & Wozniak, J.R. (in press). Hippocampal subfield abnormalities and memory functioning in children with fetal alcohol spectrum disorders. *Neurotoxicology & Teratology; dio:10.1016/j.ntt.2020.106944*.

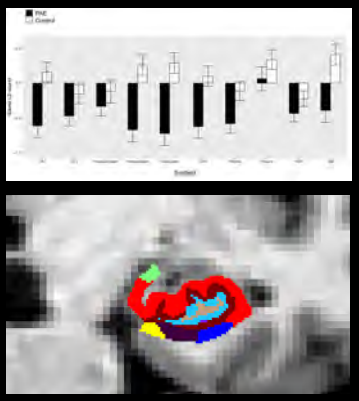

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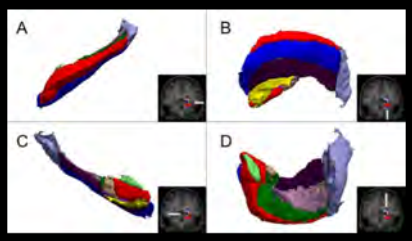
Table 3. Comparison of hippocampal subfield volumes between participants with prenatal alcohol exposure (PAE; n = 40) and control participants (n = 39)

Subfield	Mean		SD		*t*	*p*
	PAE	*Control*	*PAE*	*Control*		
Parasubiculum	132	138	26	29	0.14	0.890
Presubiculum	693	782	101	94	-3.09	0.003
Subiculum	968	1089	136	114	-3.62	0.001
CA1	1599	1760	226	184	-2.48	0.015
CA3	498	523	65	65	-0.72	0.471
CA4	1201	1301	156	135	-2.16	0.034
HATA	96	101	17	14	-0.64	0.523
Fimbria	172	194	37	39	-1.35	0.182
Fissure	197	212	50	41	-0.56	0.579
Tail	1071	1189	163	146	-2.56	0.012

- Compared hippocampal subfield volumes in participants with PAE (*n*=40) vs controls (*n*=39), using a large, age-matched dataset (HCP-Development, *n*=514) for normative standards.
- Five of ten subfields were significantly smaller in PAE group *after* controlling for intracranial volume.
- No correlation between subfield volumes and memory performance.



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Manuscript under review or in preparation

de Water, E., Rockhold, M.N., Roediger, D.J., Krueger, A.M., Mueller, B.A., Boys, C.J., Schumacher, M.J., Mattson, S.N., Jones, K.L., Lim, K.O., CIFASD, & Wozniak, J.R. (**under review**). Social Behaviors and Gray Matter Volumes of Brain Areas Supporting Social Cognition in Children and Adolescents with Prenatal Alcohol Exposure. *Brain Research.*

Rockhold, M.N., Krueger, A.M., de Water, E., Lindgren, C.W., Sandness, K.E., Eckerle, J.K., Schumacher, M.J., Fink, B.A., Boys, C.A., Carlson. S.M., Fuglestad, A.J., Mattson, S.N., Jones, K.L., Riley, E.P., CIFASD, and Wozniak, J.R. (**under review**). Executive and social functioning across development in children and adolescents with prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research*

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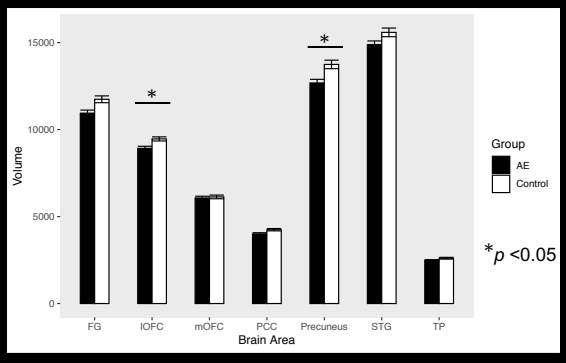
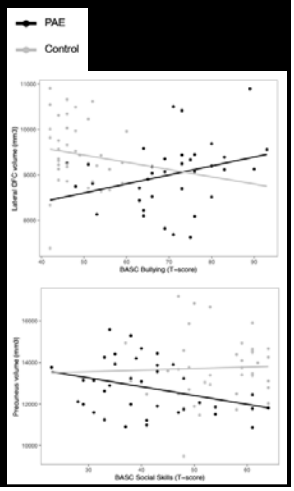
de Water, E., Rockhold, M.N., Roediger, D.J., Krueger, A.M., Mueller, B.A., Boys, C.J., Schumacher, M.J., Mattson, S.N., Jones, K.L., Lim, K.O., CIFASD, & Wozniak, J.R. (under review). Social Behaviors and Gray Matter Volumes of Brain Areas Supporting Social Cognition in Children and Adolescents with Prenatal Alcohol Exposure. *Brain Research.*





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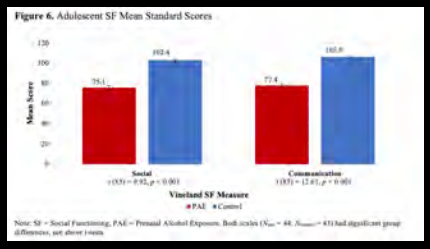
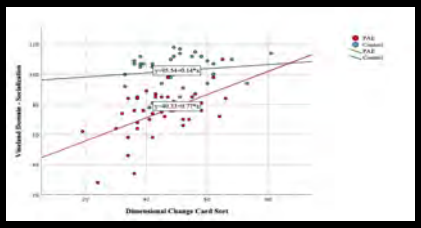
EXECUTIVE AND SOCIAL FUNCTIONING ACROSS DEVELOPMENT

Rockhold, Madeline; Krueger, Alyssa; de Water, Erik; Lindgren, Chris; Sandness, Kristin; Eckerle, Judith; Schumacher, Mariah; Fink, Birgit; Boys, Christopher; Carlson, Stephanie; Fuglestad, Anita; Mattson, Sarah; Jones, K.; Riley, Edward; Wozniak, Jeffrey **(REVISION UNDER REVIEW)**



- Sig. correlations between SF & EF within the adolescent PAE group; not present in the control group or the early childhood PAE group
  - PAE moderated the EF/SF relationship
- At four-year follow-up (M_{age}= 8.5), those originally in the early childhood PAE group also demonstrated this EF/SF relationship



- Examined deficits in SF and EF in young children and adolescents w/ PAE
- Examined the relationship between these deficits in comparison to a control population

May highlight sensitive periods for SF and EF training in children with PAE and may suggest that FASD programs consider targeting EF training as a component in social skill interventions

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ONGOING BRAIN MRI ANALYSES:

Roediger et al. (in prep.)

CIFASD- No Detectable Difference in Cortical Myelination using T1w/T2w ratio

- Donovan J. Roediger, Alyssa M. Krueger, Bryon A. Mueller, Christopher A. Boys, Timothy J. Hendrickson, Sarah N. Mattson, Kenneth L. Jones, Kelvin O. Lim, Mariah J. Schumacher, the CIFASD, and Jeffrey R. Wozniak

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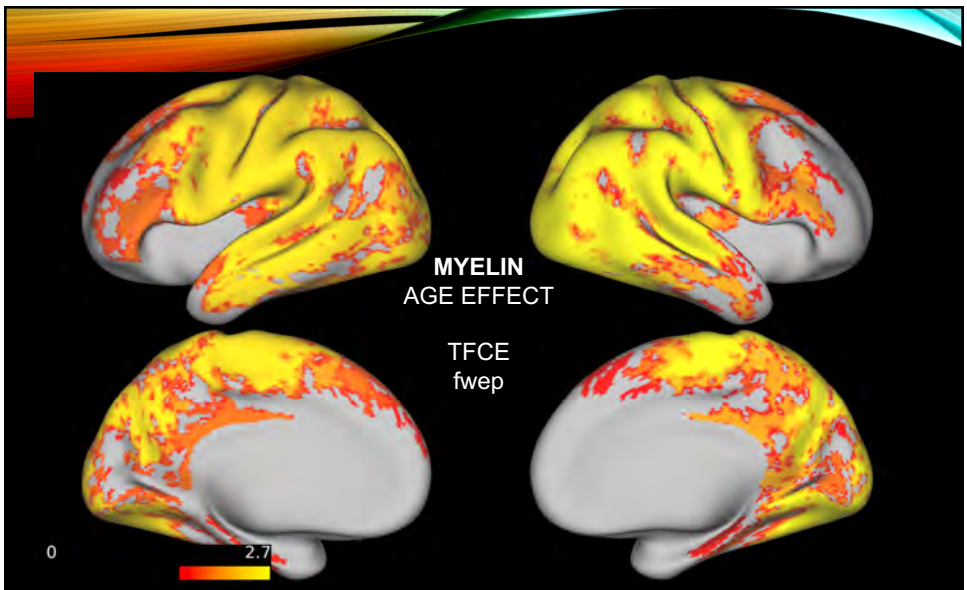

- Clear relationship between age and myelin status (above) [Method test]
- No group differences: PAE vs. Control

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COLLABORATIONS

- **Mattson collaboration:** Neurocognitive data / Decision-tree data: 90 complete
- **Suttie collaboration:** 3D and 2D photos: 90 participants (PAE and controls)
- **Foroud/Wetherill collaboration:** Saliva sent (n=47ish), demographic data uploaded to Central Repository (Box)
- **Weinberg collaboration:** Blood samples for immune function study: 59 samples from 31 individuals sent, along with demographic, treatment, behavioral, and health-related data shared.

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ABSTRACTS
• De Water et al. (2021, Feb.) Social Behaviors and Gray Matter Volumes of Brain Areas Supporting Social Cognition in Children and Adolescents with Prenatal Alcohol Exposure; International Neuropsychological Society
• Rockhold, M.N., Krueger, A.M., Schumacher, M.J., Mattson, S.N., Jones, K.L., Riley, E.P., & **Wozniak, J.R.** (2021, Feb.). *The Association of ADHD Symptoms and Learning Ability in Children with Prenatal Alcohol Exposure*. Poster to be presented at the International Neuropsychological Society Conference, San Diego, CA.
• Krueger, A.M., Rockhold, M.N., Roediger, D.J., Mueller, B.A., Boys, C.A., Hendrickson, T.J., Schumacher, M.J., Mattson, S.N., Jones, K.L., Riley, E.P., Lim, K.O., & **Wozniak, J.R.** (2020, June). *Para-limbic structural abnormalities' association with internalizing symptoms in children with prenatal alcohol exposure.* Poster presented at the Research Society on Alcoholism Annual Scientific Meeting, New Orleans, LA.
• de Water, E., Krueger, A.M., Lindgren, C.W., Fuglestad, A.J., Rockhold, M.N., Sandness, K.E., Eckerle, J.K., Fink, B.A., Boys, C.J., and **Wozniak, J.R.** (2020, June). *Early delay of gratification predicts later inhibitory control and academic performance in children with prenatal alcohol exposure*. Poster presented at the Research Society on Alcoholism Conference, New Orleans, Louisiana.
• Rockhold, M.N., Krueger, A.M., Schumacher, M.J., Boys, C.J., Mattson, S.N., Riley, E.P., Jones, K.L., **Wozniak, J.R**. (2020, June). *Social Behavior and Executive Functioning Deficits in Children Prenatally Exposed to Alcohol*. Research Society on Alcohol Conference, New Orleans, LA.

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U01: A Multisite Neurobehavioral Assessment of Fetal Alcohol Spectrum Disorders

Sarah N. Mattson, Ph.D.
San Diego State University

1

Summary of Major Activities

Archival Data Analysis (Aim 1a): As reported in previous progress reports, we examined the classification accuracy of the eTree app in the San Diego coFASP data set (Chambers, PI). Overall accuracy was 83% but subgroup accuracy varied from 28% to 100%. We are currently examining the role of moderator and mediator variables in this analysis and considering whether alterations to the eTree algorithm would improve accuracy in low-risk samples. We have also obtained data from the other coFASP sites (May, PI) and plan to use that dataset to test the algorithm modifications.

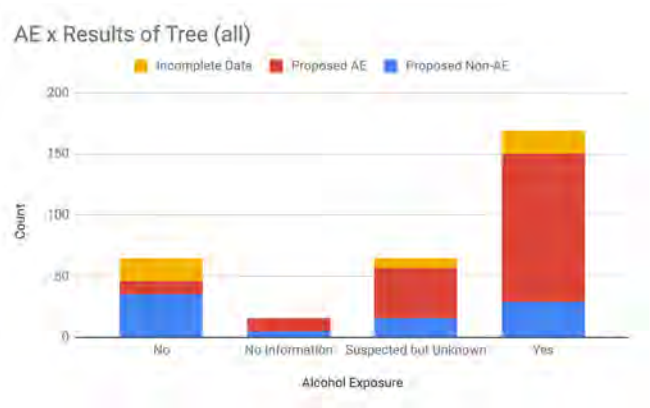
eTree (Aim 1b): We continue to collect data using the eTree. This has been substantially slowed due to the pandemic; however, our current completed sample is 269, which is 87% of our May 2021 goal. Of these subjects, 209 are from San Diego and 60 are from Minneapolis. We are still enrolling subjects that are seen in person in the UCSD clinic (K. Jones) but this has slowed considerably during the pandemic.

Validation of the eTree using in-person neuropsychological testing (Aim 1b): Due to the COVID-19 pandemic, all in-person testing has paused. Our current completed sample is 215, which is 115% of our May 2021 goal. Of these subjects, 114 are from San Diego and 101 are from Minnesota.

BRAIN-online (Aim 2a/2b): Since the last progress report, we have rolled out the Brief Assessment of Individual Neurobehavior – online version (BRAIN-online) which was formerly known as the FONS. We enrolled our first subject on 9/7/20 and have tested 38 subjects so far. This represents 76% of the subjects who were sent invitations. The subjects are 7-17 years old, with an average age of 12.25 years. We started our recruitment for BRAIN-online with subjects that already had eTree and in-person neuropsychological testing data and thus 95% of the BRAIN-online sample also have eTree and neuropsychological test data.

2

eTree Accuracy



	eTree = Exposed	eTree = Not Exposed
Exposed (confirmed or suspected)	161 (78.2%) **Sensitivity**	45 (17.9%) False Negative
Not Exposed	11 (4.4%) False Positive	35 (76.1%) **Specificity**

Overall Accuracy = 78%
PPV = 94%
NPV = 44%

3

Significant Results: Risk Score

- Risk score developed and validated using CIFASD data
  - Developed in CIFASD 2 (N=325)
  - Validated in CIFASD 3 (N=426)
- Risk score ranges from 0-5, with 0-1 = Low Risk and 4-5 = High Risk
- Frequencies of the Alcohol Exposed (AE) and control (CON) subjects in each risk group were significantly different
  - $\chi 2 = 81.97$, $p < .001$
- Subjects in the "high risk" category were more likely to be from the AE group compared to those in the "low risk" group
  - Odds Ratio [OR] = 29.37, 95% CI: 13.74-62.79, $p < .001$,
- Risk Score significantly correlated with IQ and executive function composite
  - EF: AE: $r = -.300$, $p = .002$; CON: $r = -.403$, $p < .001$
  - IQ: AE: $r = -.349$, $p < .001$; CON: $r = -.313$, $p < .001$

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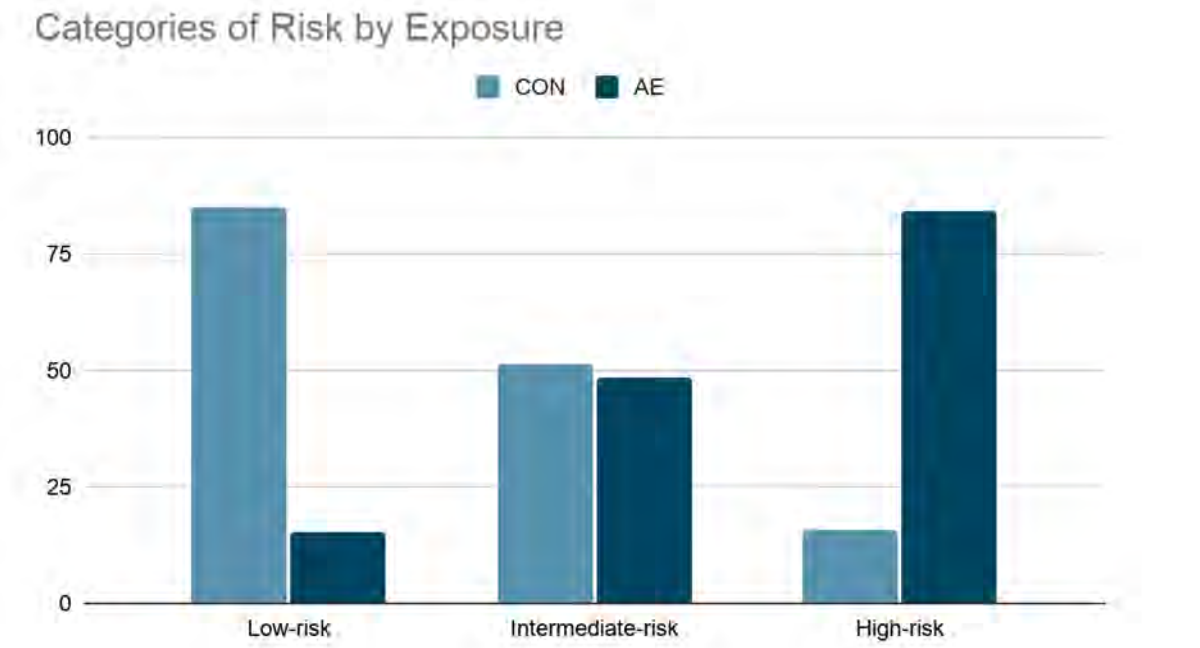

$\chi 2 = 81.97$, $p < .001$

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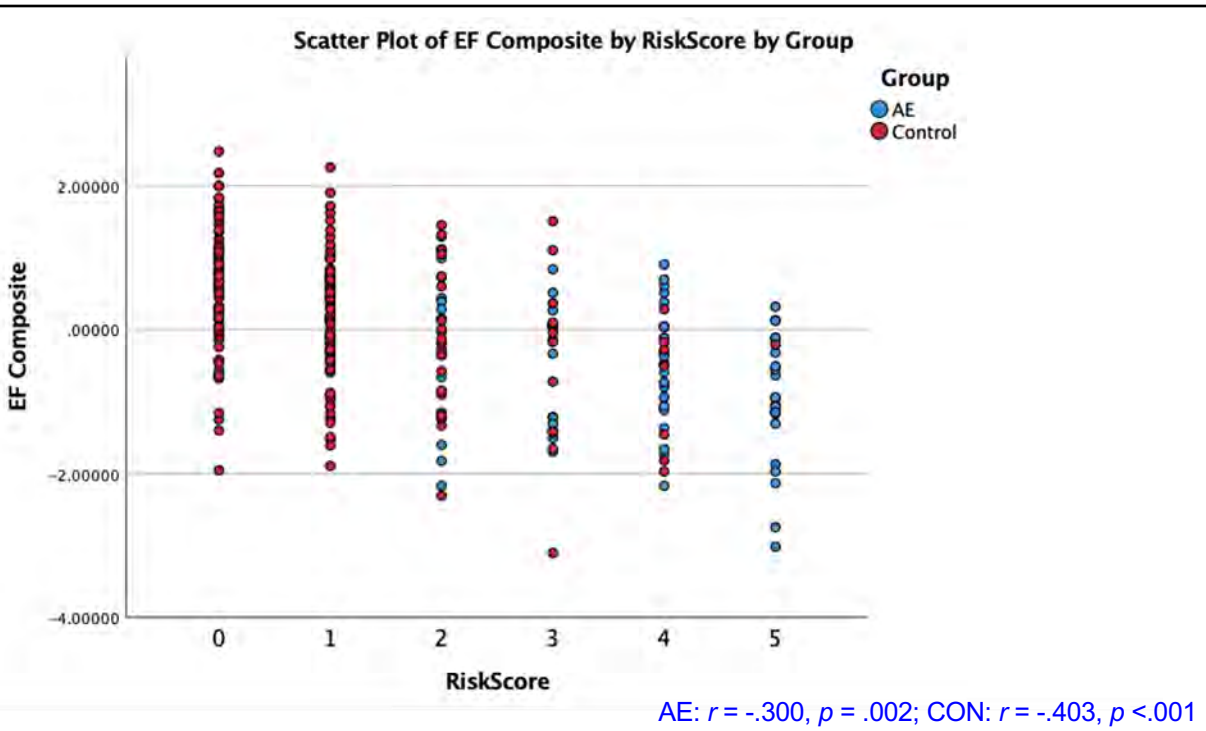

AE: $r = -.300$, $p = .002$; CON: $r = -.403$, $p < .001$

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BRAIN-online

(very) preliminary data

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	CON	AE	*p*
N	8	20	
Age	13.1 (3.18)	11.1 (3.46)	.165
Sex/Gender (Fem.)	5/8	8/20	.281
Race	2 Asian 6 White	1 Am. Indian/Alaska Native 4 Black/African Am. 1 More than one 14 White	.115
Ethnicity (Hispanic/Latino)	0/8	9/20	.045
IQ [M (SD)]	114.8 (16.70)	85.3 (16.26)	<.001
eTree Result (AE)	2/8	17/20	.002
Risk Score [M (SD)]	1.5 (1.60)	3.8 (1.15)	<.001
Risk Score (High)	1/8	14/20	.013

8

Tapping

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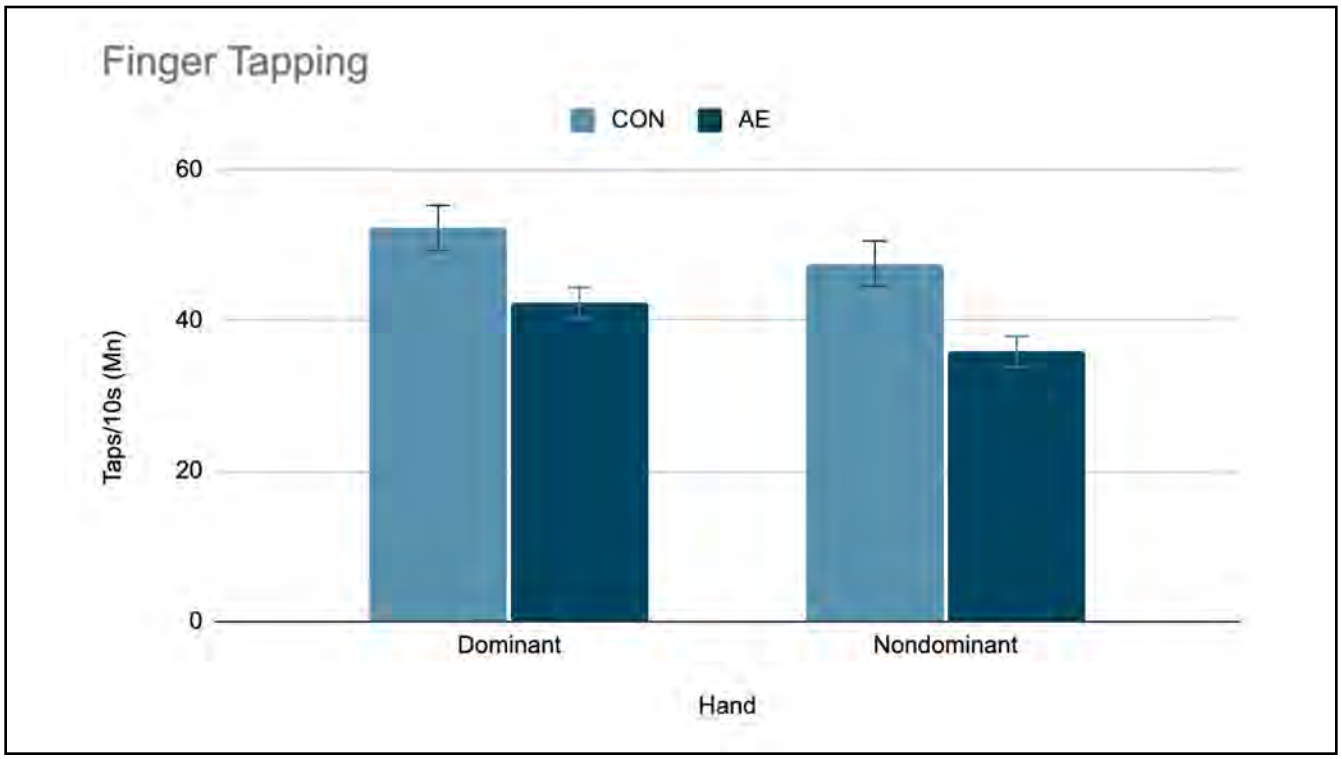
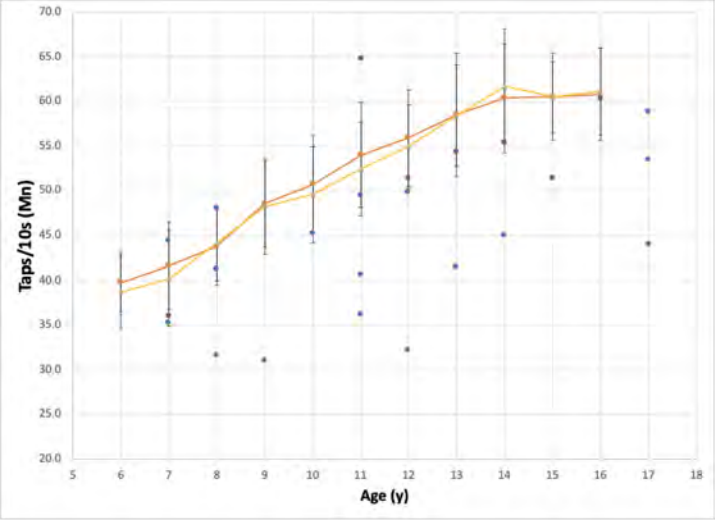

Finger Tapping
CON
AE
60
40
20
0
Taps/10s (Mn)
Dominant
Nondominant
Hand

10

BRAIN-online Compared to Normative Data



https://www.tandfonline.com/doi/full/10.1080/87565641.2018.1495724

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Tapping Correlations

	IQ	Age	Risk Score
Dominant Hand	-.441*	.596**	-.461*
Nondominant Hand	.557**	.565**	-.510**

* p < .05
** p < .01

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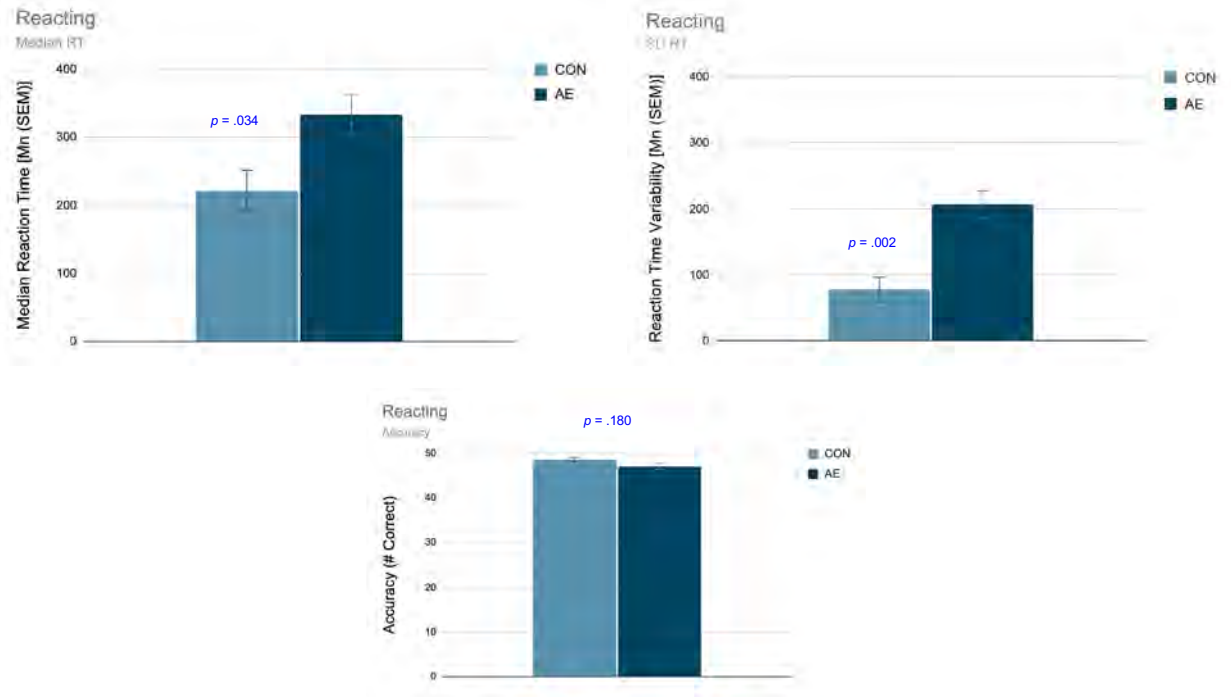
Reacting

13



14

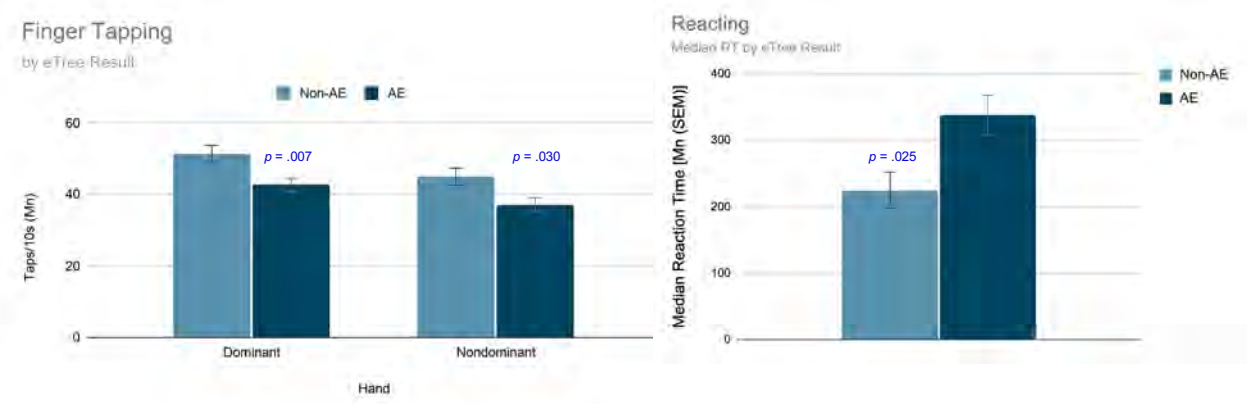
Reacting Correlations

	IQ	Age	Risk Score
Mean RT	-.442*	-.405*	.638**
Median RT	-.386*	-.385*	.600**
SDRT	-.558**	-.452*	.596**

* p < .05
**p < .01

15

Relationship between BRAIN-online and eTree



16

Other Papers in Progress

- Bernes, G.A., Coles, C.D., Kable, J.A., May PA., Kalberg, W.O., Sowell, E.R., Jones, K L., Riley, E.P., Mattson, S.N., and the CIFASD (Submitted 2020). Convergent validity of measures of executive function in children with heavy prenatal alcohol exposure: Correspondence between multiple raters and laboratory measures.
- Bernes, Courchesne, Mattson et al., Development of a Postnatal Risk Score that Identifies Children with Prenatal Alcohol Exposure
- Sobolewski, Courchesne, Hyland, Mattson et al., Validation of BASC in youth with FASD
- Mattson, Duprey, Hyland, et al. Sensitivity and Specificity of an automated decision tree tool for detecting FASD
- Hyland, Duprey, E.E., Chambers, C.D., Mattson, S.N., et al. Validation of an automated decision tree tool for detecting FASD in a low-risk prevalence sample
- Duprey, Hyland, Jones, Mattson et al., Accuracy of an automated decision tree tool for detecting ARND

17

Plans for 2021 and Beyond

- eTree & BRAIN-online
  - Continue to collect eTree and BRAIN-online data
  - Extend use of BRAIN-online to other CIFASD sites, outside of CIFASD, and in clinical settings (IRB)
  - Pursue patent for eTree & BRAIN-online
  - Collect data from school age children from San Diego school
  - Collect data from young adults from SDSU and UCSD
- Data analysis
  - Validate BASC (parent questionnaire) for use in eTree
  - Examine co-occurring maternal alcohol and other substance use (e.g., opioids, cannabis)
- Hopefully
  - Recruit subjects from specialty clinics (developmental-behavioral pediatrics)
  - Complete eTree subjects from Minnesota (32 pending dysmorphology)
  - Begin data collection with 3D camera/morpheus and eTree

18

Effects of COVID-19

- In person data collection paused 3/13/2020
- SDSU had had limited repopulation but human subject research involving minors is not allowed
- Questionnaires are still being collected though in person physical exams were also paused
- BRAIN-online initiated September 2020
- Loss of ½ staff member
- No undergraduate RAs

19

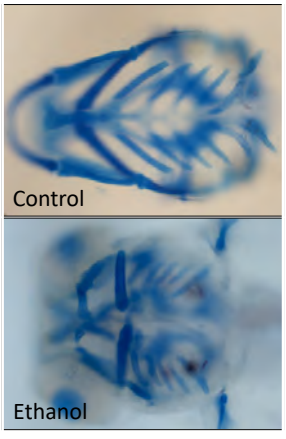
Aim 1. Use strain-specific differences in ethanol sensitivity to characterize modifiers of FASD.

Aim 2. Employ screening approaches to identify and confirm modifiers of gene-ethanol interactions.

1

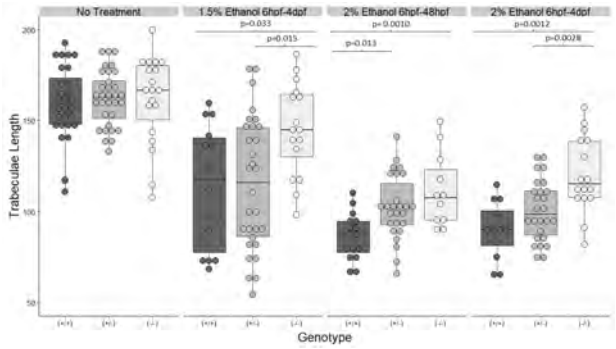
Candidate genes from mouse identify sensitizing and protective mutations

nnt$^{-/-}$



Mazumdar, et al., in prep

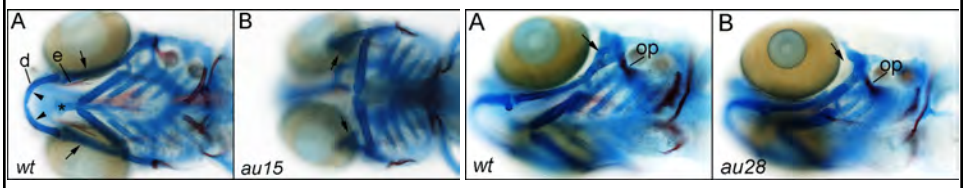
p53



Tucker, Fish, et al., in prep

2

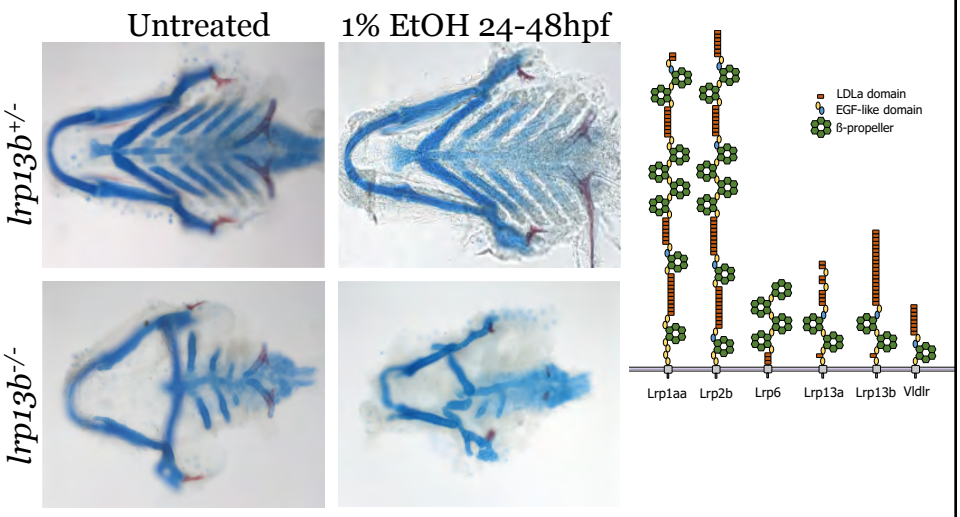
Forward genetic screens identify ethanol-sensitive mutants



(Swartz, et al. ACER 2020)

3

Identification of an uncharacterized member of the Lrp family

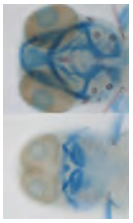


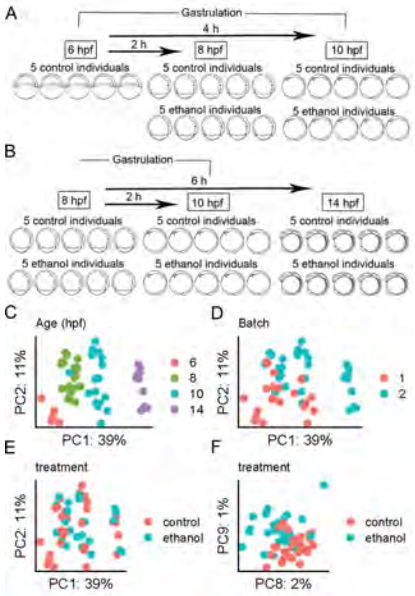
- LRPs have over 50 known ligands, including Bmps, Shh, and Wnt

(Kuka, et al., in prep)

4

Loss of *vangl2* sensitizes embryos to ethanol during early embryogenesis.

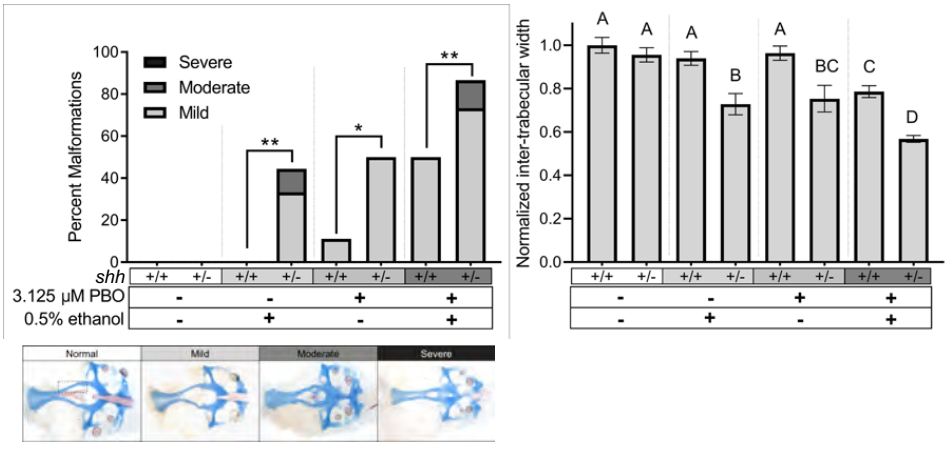




Sidik et al. in revision, BMC Biology

5

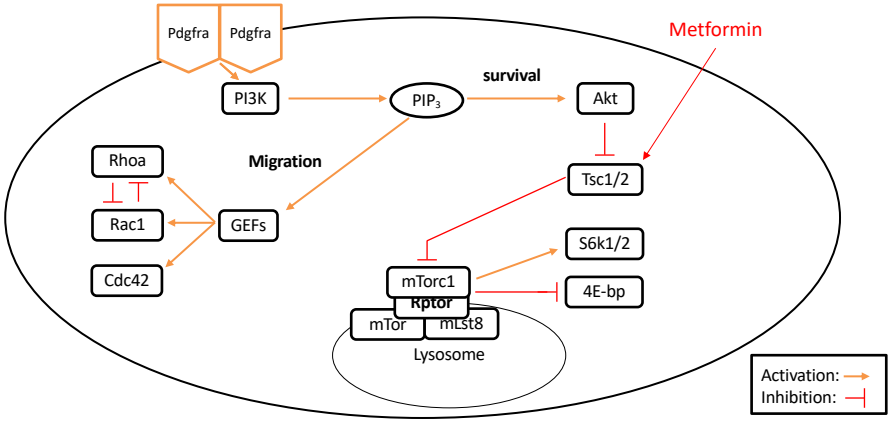
Multifactorial interactions strongly synergize



Everson et al., ACER 2020

6

Pdgf signaling plays dual functions in craniofacial development



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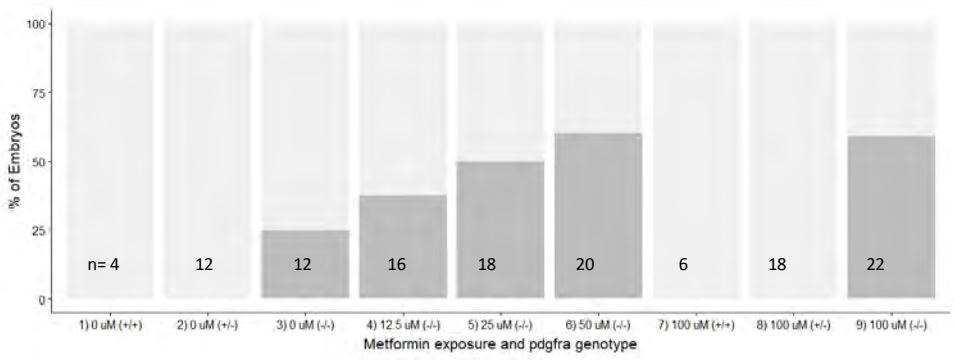
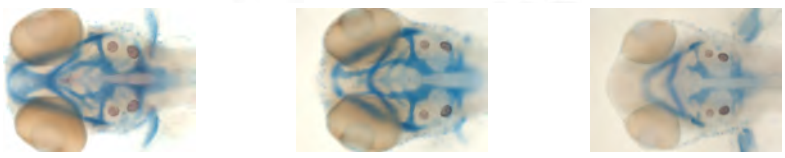


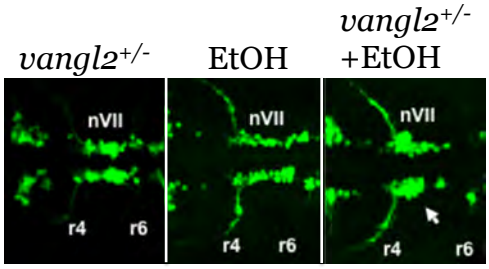


Scott Tucker

8

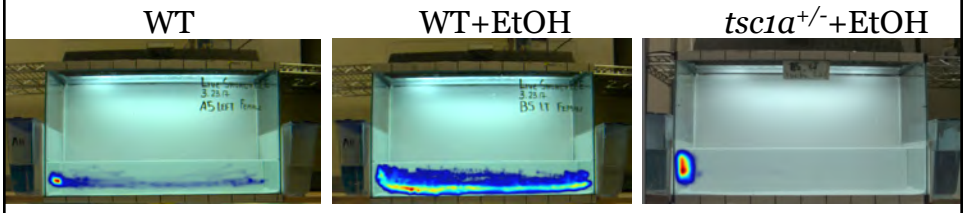
The face can predict neural defects

Wnt/PCP and neuronal migration



Buckley et al., in progress

mTOR and social behavior



Fernandes et al., in progress

9

Near-term goals

- Aim 1:
  - Analyses of Kif2a (from human data) and efcab7 (from mouse data), both associated with cilia function.
- Aim 2:
  - 96-well plate-based screen for chemicals that interact with ethanol.
  - Transposon-based forward genetic screen.

10

Thanks:

11

Exploring the Genetics of FASD in Complementary Mouse and Fish Models

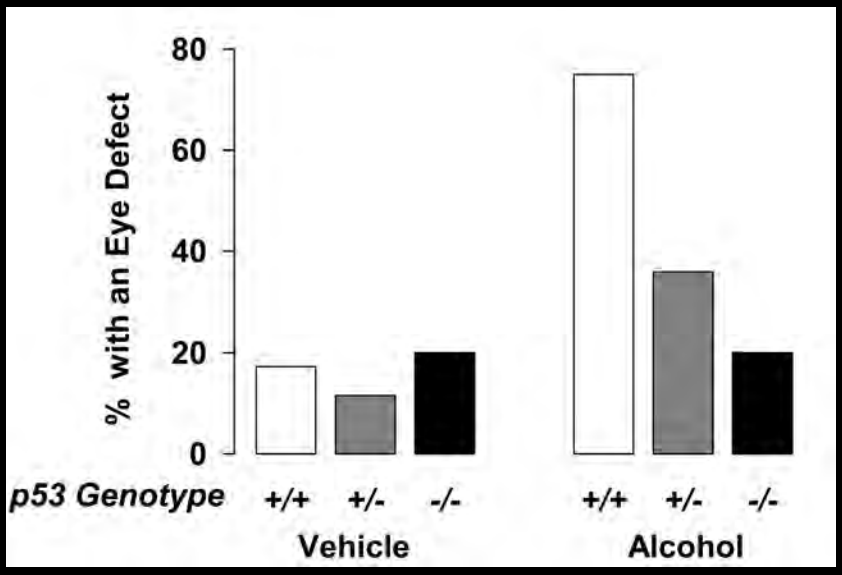
1

C57BL/6J: 46.4%
C57BL/6N: 19.8%

Dou et al, 2013

2

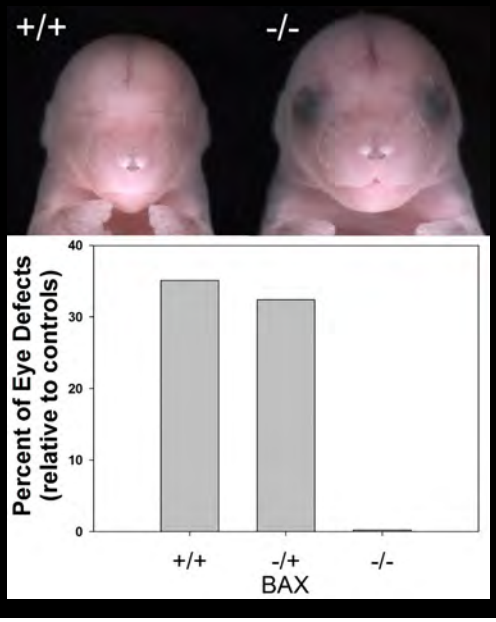
Tumor Protein 53 (*Tp53*)



Fish, Tucker et al., in prep

3

Reducing Bax rescues ethanol's teratogenic effects



Fish et al., in prep

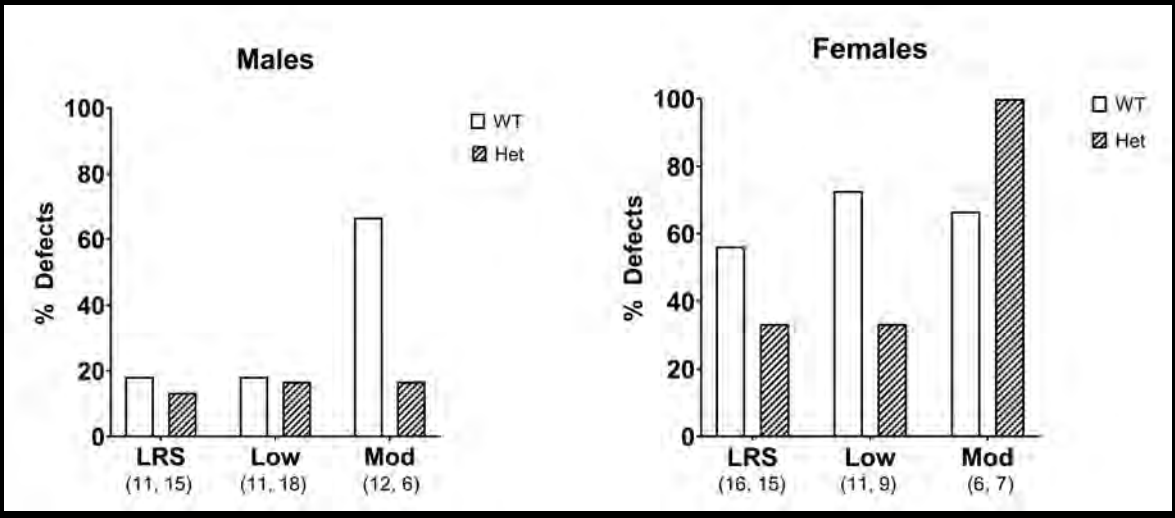
4

IPA: Top 10 Canonical Pathways

Ingenuity Canonical Pathways	p-value	Molecules
L-cysteine Degradation II	0.0024	CTH
Intrinsic Prothrombin Activation Pathway	0.0047	COL1A1,KLK8
Cysteine Biosynthesis/Homocysteine Degradation	0.0048	CTH
Coronavirus Pathogenesis Pathway	0.0058	BAX,IRF3,RPS11
Caveolar-mediated Endocytosis Signaling	0.0135	ITGA7,ITGB4
mTOR Signaling	0.0145	AKT1S1,PLD4,RPS11
Huntington's Disease Signaling	0.0195	BAX,CREB3L4,PENK
Leucine Degradation I	0.0214	BCAT2
Gαs Signaling	0.0275	CREB3L4,RGS2
Paxillin Signaling	0.0282	ITGA7,ITGB4

5

Huntingtin gene (*Htt*)



6

Identifying FAS Risk and Resiliency Candidate Genes in Mice

<u>Baseline C57BL/6J vs. 6N strain comparison</u>

Decreased cell proliferation and increased apoptosis pathways

Numerous large differences in several cilia genes (e.g. Dynlt1 & Efcab7)

<u>Immediate (6hr) response to alcohol</u>

Amplification of abnormal cell proliferation and apoptosis processes in 6J mice

Numerous canonical pathways:

"Neuroimmune" signaling

Primary ciliogenesis

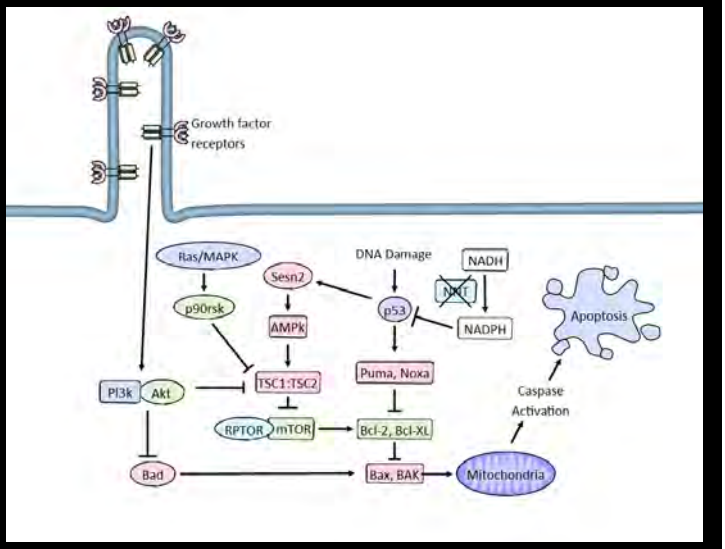
Apoptosis

Altered cell migration pathways in 6N mice

<u>Intermediate (12 hr) response to alcohol</u>

p53 – most up-regulated pathway

Shh – most down-regulated pathway



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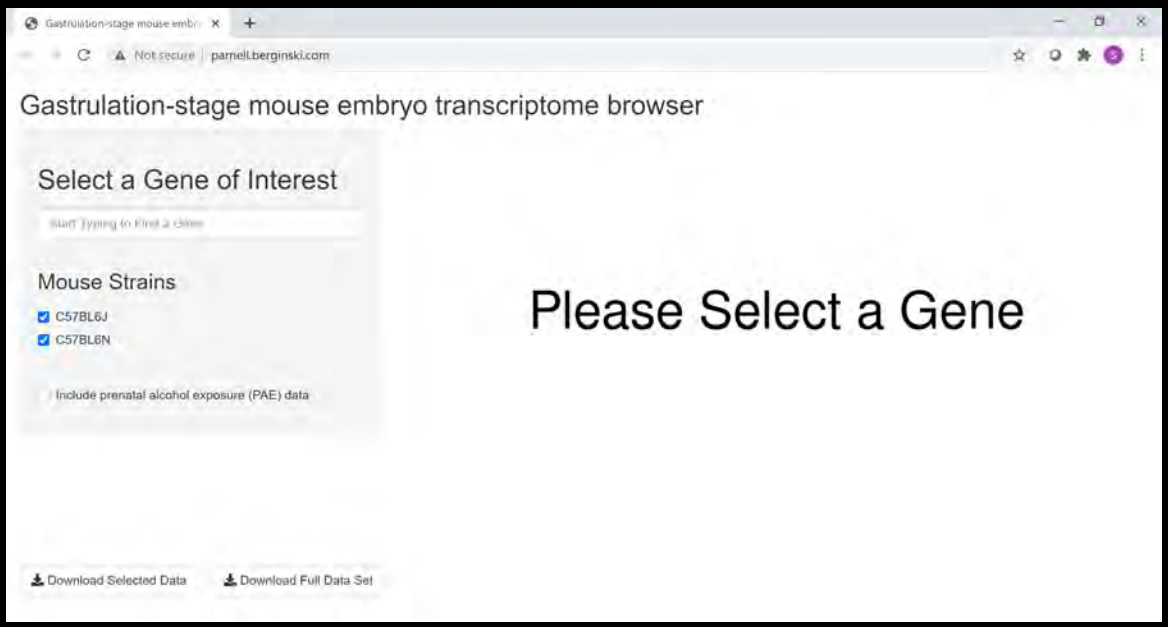
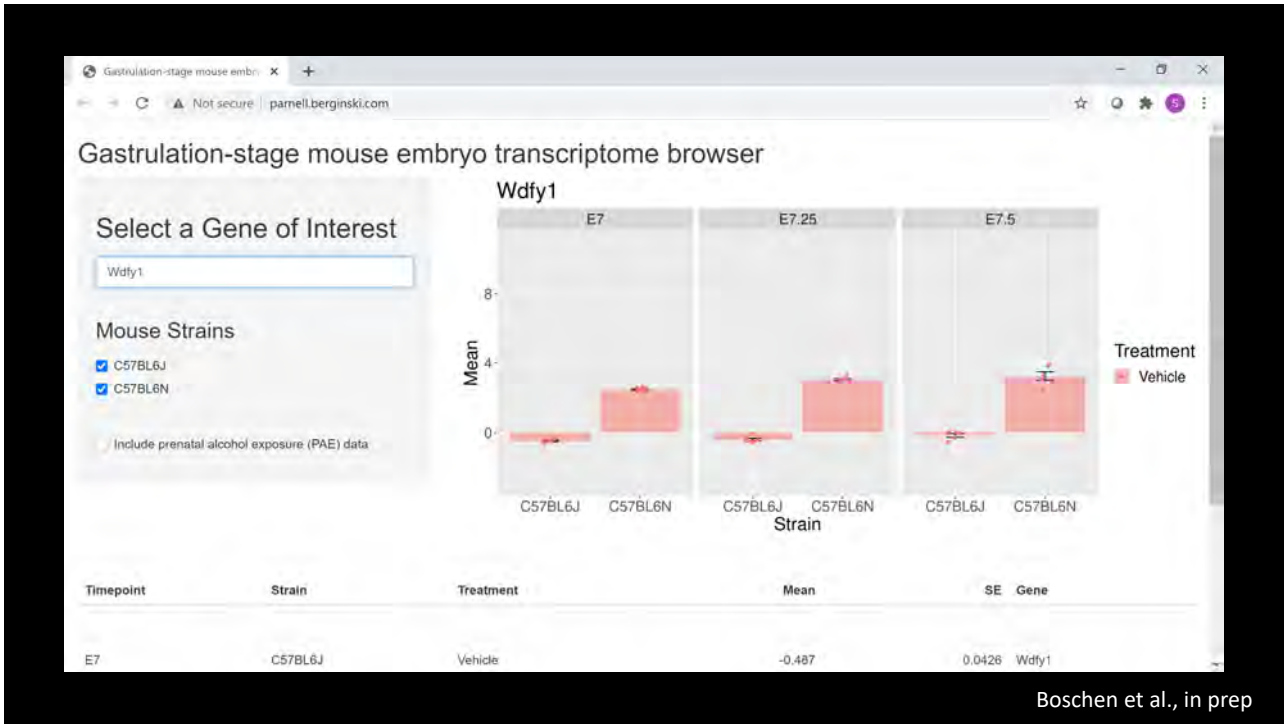


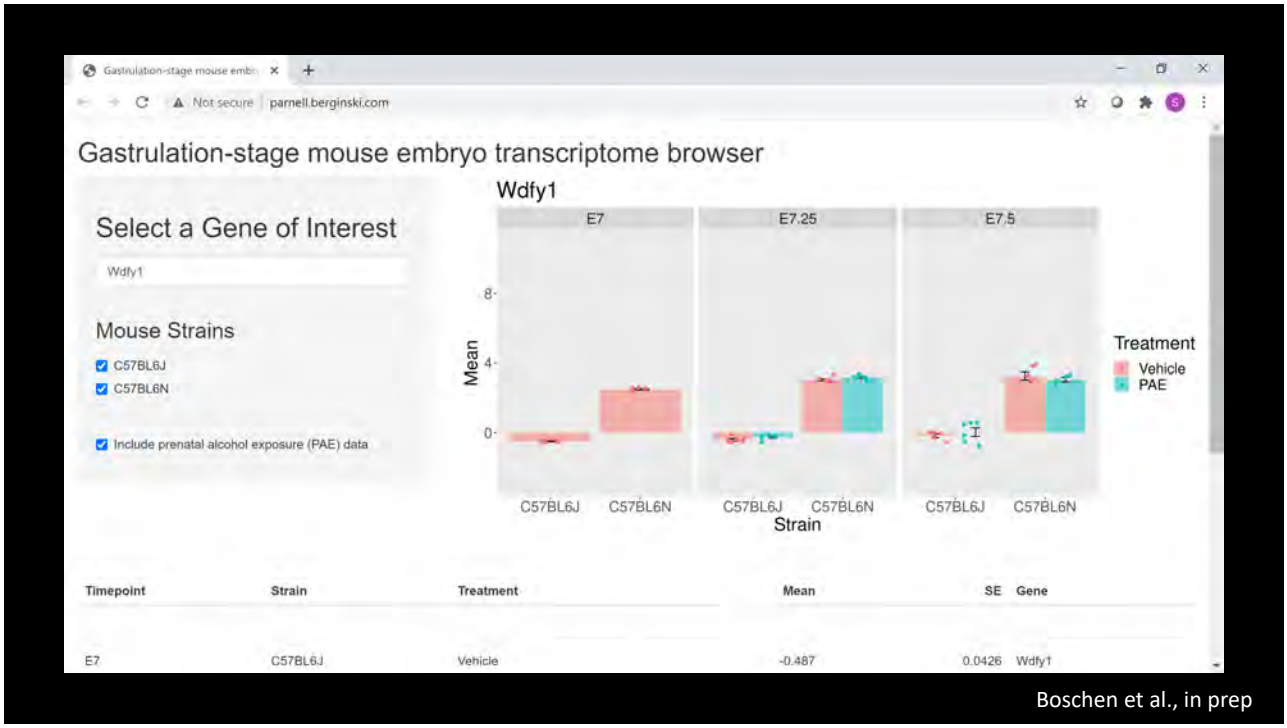
Boschen et al., in prep

8



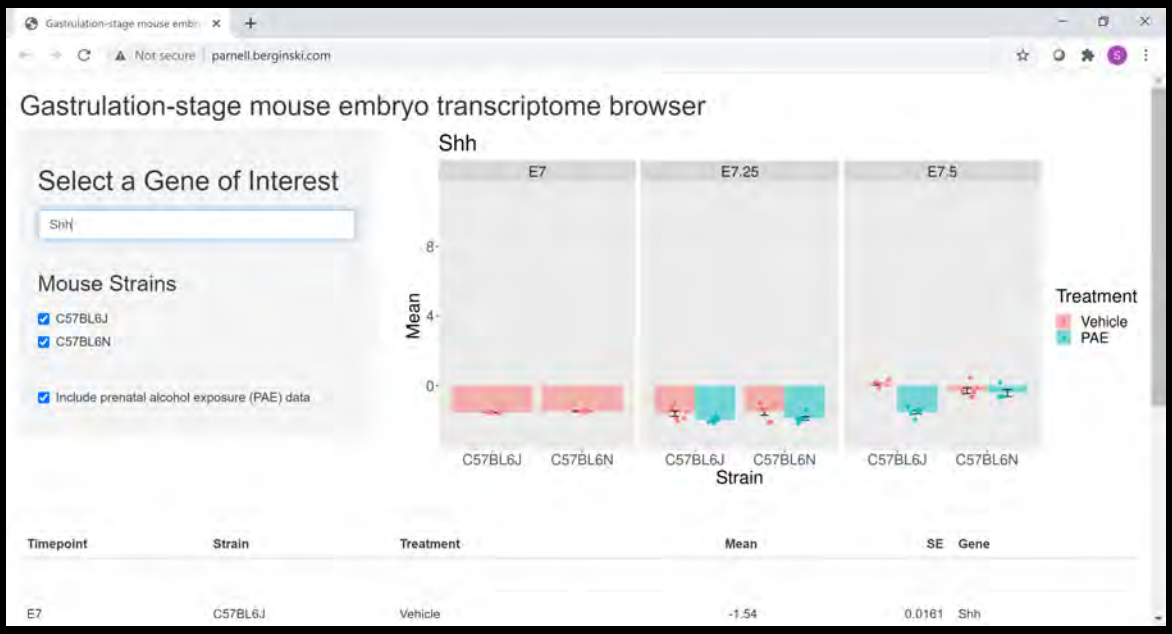
Boschen et al., in prep

9



Boschen et al., in prep

10



Boschen et al., in prep

11

Future Plans

- Collaborative cross
  - Combination of genomics and transcriptomics
    - Maybe start to get into proteomics and RNA splicing?
- Specific strains that may be more susceptible to PAE
  - 129/S2
- Cell culture models to recapitulate specific cellular processes following gastrulation-stage alcohol exposure
  - Rapid transgenic evaluation of the role of specific genes
  - Pharmacological screens to further identify gene/alcohol interactions

12

COVID-19

- UNC is still operating at 50% capacity, but work is commencing.
  - Potential differences in aged mice vs. young mice.

- Two manuscripts almost ready for submission.
  - Fish EW, Tucker SK, Peterson RL, Eberhart JK, Parnell SE. Tp53 is a pathogenic mechanism for gastrulation stage alcohol exposure: studies in mice and zebrafish. (in prep).
  - Boschen KE, Ptacek TS, Simon JM, Parnell SE. Transcriptomic analyses of two closely related substrains of gastrulation-stage mouse embryos with differential susceptibility to prenatal alcohol exposure. (in prep).

13

Families Moving Forward Connect: Development of a Mobile Health Intervention for Caregivers Raising Children with FASD

Christie L. M. Petrenko, Ph.D. & Cristiano Tapparello, Ph.D.

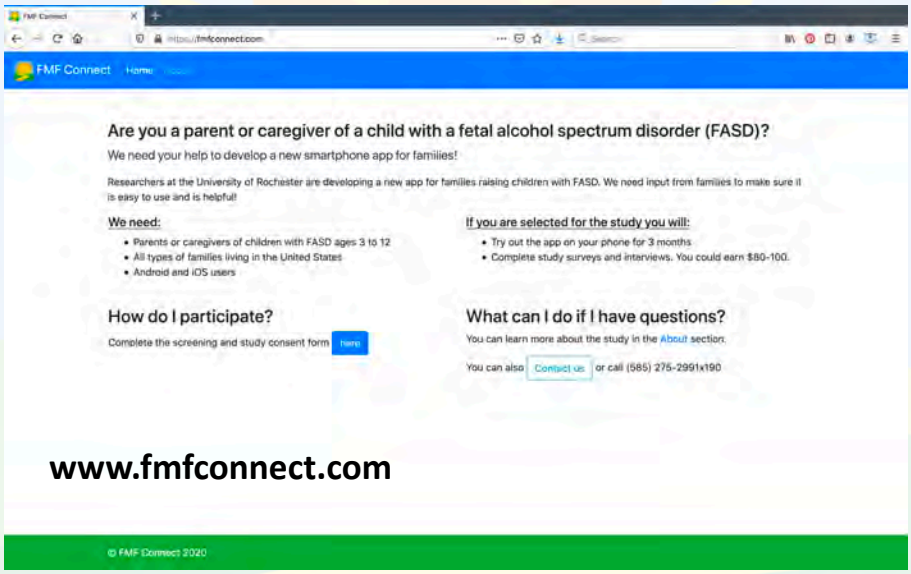
Mt. HOPE family center

UNIVERSITY of ROCHESTER

1

In Progress: Feasibility Trial

Families Moving Forward CONNECT



www.fmfconnect.com

2

2

Families Moving Forward CONNECT

Recruitment

Screening

172 Started Consent

Eligibility

107 Eligible

23 Ineligible

42 Incomplete

Device Type

63 iOS

44 Android

3

3

Families Moving Forward CONNECT

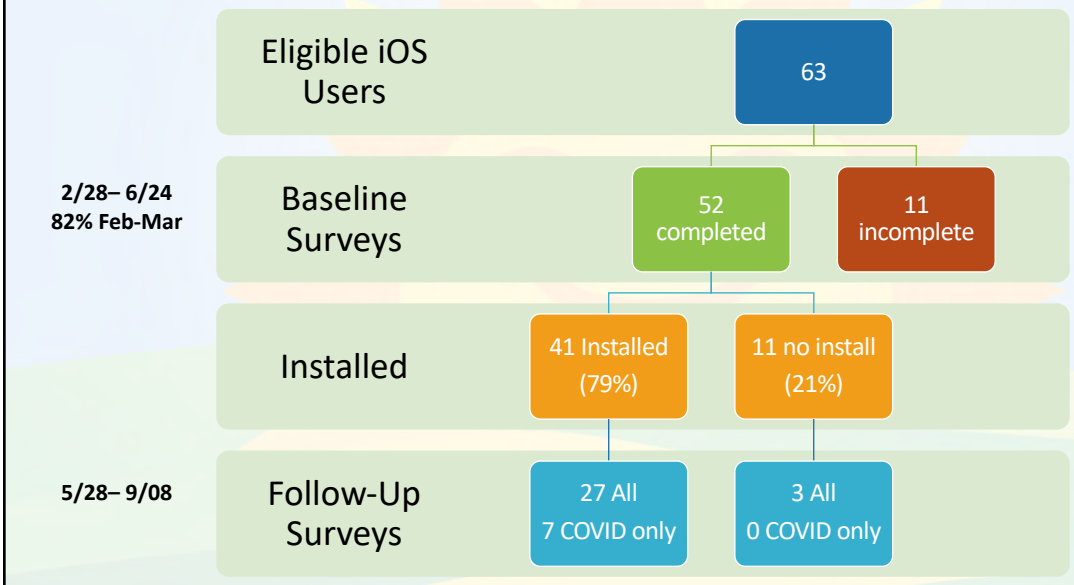
Feasibility Trial

4

4

Families Moving Forward CONNECT

Feasibility Trial: iOS Users (Mar-Oct 2020)

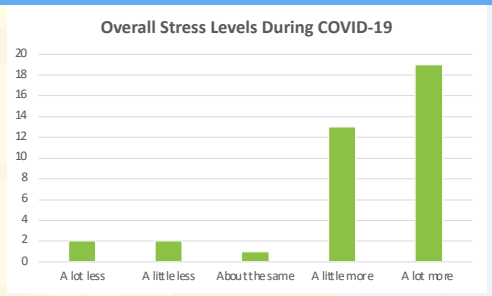


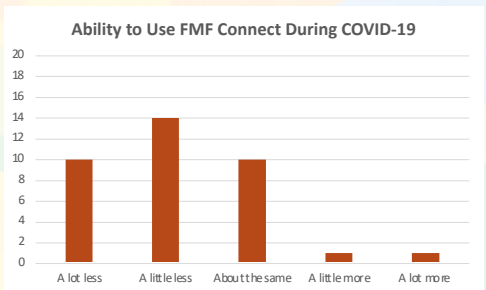
5

Families Moving Forward CONNECT

COVID-19 Impact (n=37)

- iOS version of the app began release days prior to most shut down orders
- Scope of work and staffing has continued with limited interruptions
  - COVID-19 has had variable impact on families and their use of the app
  - Android version of app delayed due to COVID-19 response





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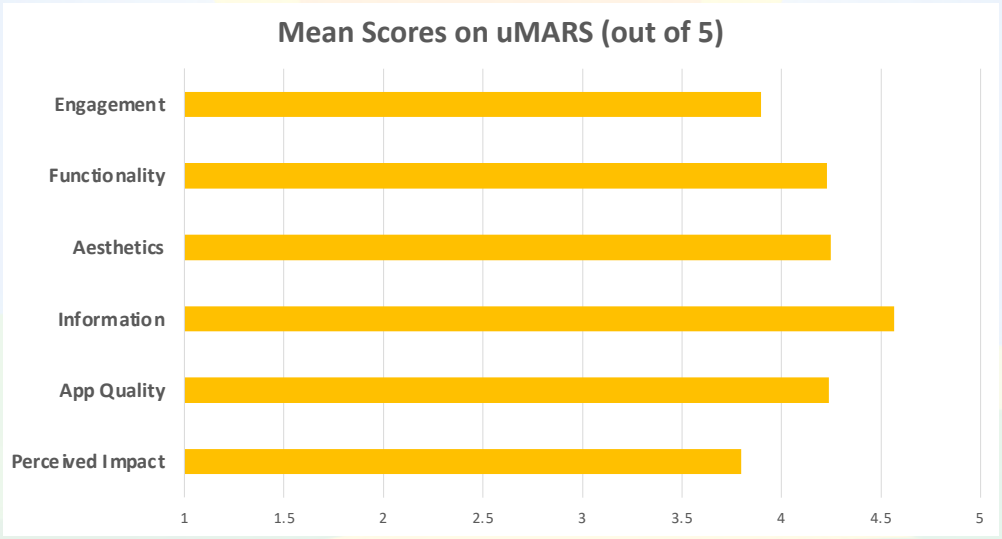
Families Moving Forward CONNECT

Mobile Application Rating Scale: User Version (uMARS)



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7

Families Moving Forward CONNECT

Android Feasibility Trial

- Had to re-write about 60% of code due to changes with Android OS, AWS, and inconsistencies discovered on testing
  - Able to bring on new post-doc in November to assist
- Based on feedback, will unlock all content for users from the start
  - Will provide users more autonomy in self-directing their learning
  - Will test whether this change will increase usage relative to prior tests
- Expect to release Android version to 44 users in next few weeks

8

8

Intensive RCT Planning Meetings

- Reviewed and prioritized 29 possible refinements to app based on user feedback
- Reviewed and revised measurement battery based on preliminary feasibility data
- Reviewed content additions
- Identified new recruitment sources
- In progress of string file review for last 2 modules

- Independent stigma review
- Considering RCT timeline and design elements
  - FMF Connect + coaching
  - FMF Connect
  - Waitlist

Will be able to complete trial prior to end of Year 5

- Timeline will balance making as many refinements as possible

9

9

Publications

Published

- Petrenko, C.L.M., Parr, J, Kautz, C, Tapparello, C., Olson, H. C. (2020). Families Moving Forward Connect mobile health intervention for fetal alcohol spectrum disorders: Development and qualitative evaluation of design and functionalities. *JMIR: mHealth uHealth, 8,* e14721.

Submitted

- Kautz-Turnbull, C., Petrenko, C.L.M., Handley, E.D., Coles, C.D., Kable, J.A., Wertelecki, W., Yevtushok, L., Zymak-Zakutnya, N., Chambers, C.D., & CIFASD. (Under review). Partner influence as a factor in maternal alcohol consumption and depressive symptoms, with subsequent effects on infant neurodevelopmental outcomes.

In Preparation

- Petrenko, C.L.M., Parr, J., Kautz, C., Roth, A., Tapparello, C., Olson, H.C. (in preparation). Results from Two Rounds of Beta-Testing of the Families Moving Forward Connect App for Caregivers Raising Children with FASD.
- Kautz-Turnbull, C., Petrenko, C.L.M., & Rogge, R. (In preparation). Reasons for Children's Behavior: Development and Validation of a New Measure of Parental Attributions.

10

10

Immune dysregulation in FASD: Programming of health and neurobehavioral outcomes

Weinberg Update

With: Tamara Bodnar, Charlis Raineki, Parker Holman, Linda Ellis, Amanda Chao, Tim Oberlander, Christine Loock, Jan Lutke

CIFASD Late Fall 2020 Progress Meeting
December 2-4, 2020

a place of mind
THE UNIVERSITY OF BRITISH COLUMBIA
Faculty of Medicine
Department of Cellular & Physiological Sciences

CIFASD Collaborative Initiative on Fetal Alcohol Spectrum Disorders

NIH National Institute on Alcohol Abuse and Alcoholism

1

Aim 1. Use validation cohorts to confirm the utility of maternal and infant/child immune parameters as possible biomarkers and predictors of alcohol-related health and neurobehavioral outcomes

- In collaboration with Tina - longitudinal study in Western Ukraine:
  - Concept Proposal 90: Raineki, C., Bodnar, T., Wertelecki, W., Yevtushok, L., Plotka, L., Granovska, I., Zymak-Zakutnya, N., Pashtepa, A., Wells, A., Honerkamp-Smith, G., Coles, C.D., Kable, J.A., Chambers, C.D., Weinberg, J., and the CIFASD. **Differential associations between maternal and child Immune milieus in alcohol-dependent and alcohol-independent neurodevelopmental delay.**
  - Data analysis in progress

2

Aim 1 (cont'd)

- **Child study in San Diego with Tina and Ken**
  - Children recruited from San Diego FASD Research Subject Pool (Rady Children's Hospital), and unexposed controls from other UCSD pediatric clinics
  - Samples from 32 children in the FASD registry collected to date
    - 0.5ml plasma aliquots banked for our study
    - Since last report in June, 18 new consents obtained; blood samples to be requested as soon as research is open to do so
- **Analysis of cytokines in plasma samples from children in Jeff's choline clinical trial**
  - 67 samples from 34 unique subjects received in October
  - Cytokine assays and pre-processing of the data have now been completed
  - Analysis ongoing

3

Aim 2. Extend our assessment of the immune system in individuals with FASD into adulthood

Adult Health Study (collaboration with Claire Coles and Therese Grant)

- To date, 72/120 adults recruited:

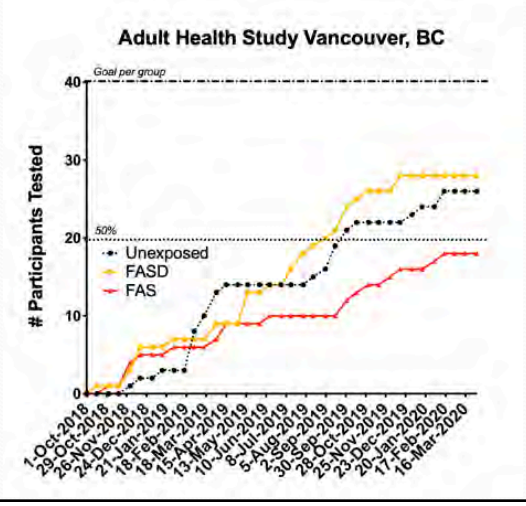
  FAS = 18

  FASD/ARND = 28

  Unexposed = 26
- Mean age:

  Exposed – 37.5 yr

  Unexposed – 32 yr
- We have not been able to resume in person testing



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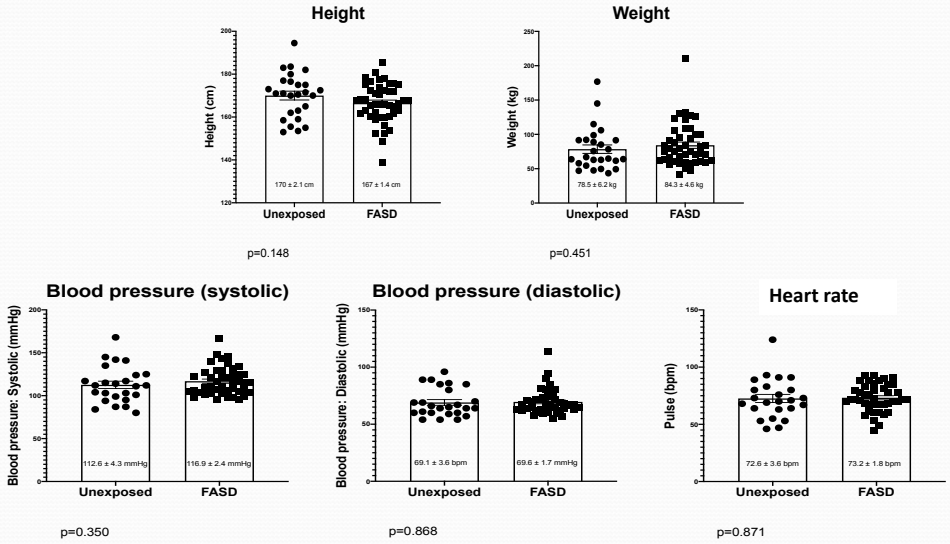
No differences between groups in height, weight, blood pressure, heart rate



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Physical Health Issues

Health survey question	Unexposed 🥂 %/n = yes	FASD %/n = yes
# days physical health not good over the past month	7.4 (n=12)	16.1 (n=29) ⌘
# days mental health not good over the past month	13.2 (n=13)	10.8 (n=30) ⌘
# hours of sleep/night on average	7.1 (n=25)	6.8 (n=44)
Eye problems	31% (n=26)	61% (n=46) ⌘
Hearing problems	20% (n=25)	53% (n=45) ⌘
Teeth problems	50% (n=26)	80% (n=46) ⌘
Childhood heart problems	0% (n=26)	11% (n=36) ⌘
High cholesterol	13% (n=24)	17% (n=42)

6

Physical Health Issues (cont'd)

Health survey question	Unexposed %/n = yes	FASD %/n = yes
Asthma	20% (n=26)	44% (n=45) ⌘
Epilepsy	4% (n=26)	24% (n=46) ⌘
Diagnosed with cancer	4% (n=26)	2% (n=43)
Digestive problems	20% (n=25)	68% (n=46) -
Kidney disease	0% (n=26)	5% (n=44) ⌘
Diabetes	0% (n=26)	7% (n=45) ⌘
Thyroid or parathyroid problems	0% (n=26)	14% (n=44) ⌘
Skin problems	50% (n=26)	32% (n=44)

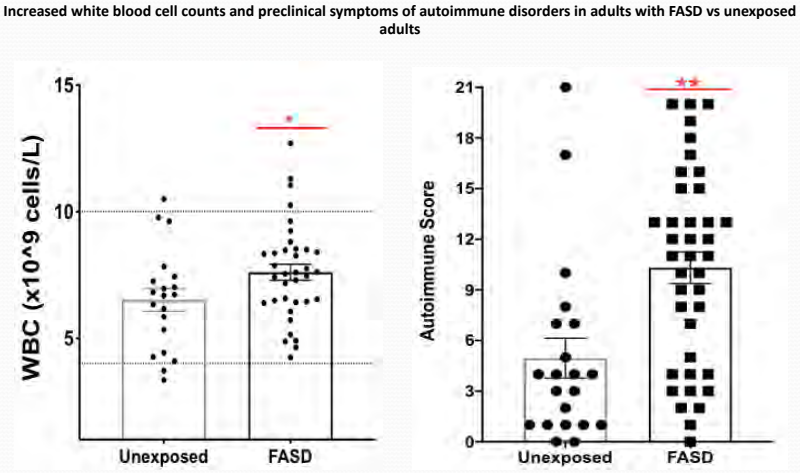
7

Mental Health Issues

Health survey question	Unexposed %/n = yes	FASD %/n = yes
ADHD	20% (n=25)	33% (n=42) ⌘
Depressive disorder	46% (n=26)	59% (n=44) ⌘
Bi-polar disorder	8% (n=24)	11% (n=46)
Anxiety disorder	50% (n=24)	58% (n=45)
Psychotic disorder or schizophrenia	0% (n=24)	4% (n=46) ⌘
>2 adverse childhood experiences	54% (n=26)	83% (n=46) ⌘

8

Adults with FASD exhibit adverse changes in immune function (increased WBC counts) and increased preclinical symptoms of autoimmune disorders than their unexposed counterparts



9

Pre-Post COVID-19 Study on adult cohort (ongoing)

- Re-contacting all participants already tested (total n=72) to examine impact of COVID-19 on mental health status, stress levels, and other related domains.
- Questionnaires selected from the NIH COVID-19-related resources and focus on Covid-related stress and anxiety, the impact of COVID-19 on work and finances, and assessment of barriers to overcoming self-isolation/accessing health care (with a focus on questions geared to people with disabilities).
- Beck Depression, Beck Anxiety, Perceived Stress Scale, Penn State Worry Questionnaires administered previously
- Open-ended questions from the "telling our stories in the age of COVID-19" questionnaire.
- Aiming for January/February completion

10

COVID-19 Considerations and future plans, Yr 4 and beyond

- We are well on our way to meeting our targets for most aspects of Aim 1, but may fall short in some areas due to impact of COVID-19 on our collaborators
- If we cannot resume recruitment and testing over the next few months, we will likely fall short of our targets for Aim 2
- With these possibilities in mind, we have begun to reach out to colleagues elsewhere who have access to FASD study populations, and who may be able to fill the gap for us if needed, or if not, to extend our subject pools for Aims 1 and 2
  - Mindful of the need to increase recruitment of Indigenous unexposed controls

11

COVID-19 Considerations and future plans Yr 4 and beyond

- **Dr. Natasha Reid -** Clinical Psychologist and Research Fellow, Child Health Research Centre, Faculty of Medicine, University of Queensland (UQ).
  - Affiliated with the research team of Dr. Karen Moritz, who is Director of this Centre.
  - Natasha is working with a diagnostic clinic at UQ- assessment services for treatment and management of children with FASD
    - Research to develop a diagnostic tool to examine possible biomarkers for alcohol exposure in pregnancy.
  - In collaboration with Natasha
    - Obtain blood spots + demographic and health information, cognitive, language, and behavioral assessments from children with FASD and matched controls
    - We already have a good working relationship with Dr. Reid through interactions over many years at RSA and other meetings

12

COVID-19 Considerations and future plans, Yr 4 and beyond

- **Dr. Kaitlyn McLachlan -** Assistant Professor in the Clinical Psychology program at the University of Guelph and a Research Lead for the Canada FASD Research Network (CanFASD)
  - We have had a previous successful collaboration with Dr. McLachlan to evaluate HPA function in children with FASD and associations among early life adversities, adverse outcomes, protective factors, and diurnal cortisol (McLachlan et al., Alcohol 53:9-18, 2016)
  - In collaboration with Kaitlyn, we are exploring the possibility of recruiting adults with FASD and appropriate unexposed controls to extend our Adult Study population
- **Dr. Catherine Lebel**, an Associate Professor at University of Calgary:
  - In collaboration with Catherine, we are exploring the possibility of recruiting adults with FASD and appropriate unexposed adults in Calgary, AB, to extend our Adult Study population

13

Deliverables:

- For RSA 2020, 2 posters and 3 symposia presentations – Cancelled
- Since 2017, a total of:
  - 2 manuscripts published, 1 in preparation
  - 6 Symposia presentation
  - 12 oral presentations
  - 6 poster presentations
- Cytokine assays and pre-processing completed for samples from Jeff Wozniak; analysis ongoing
- Pre-Post COVID-19 study underway

14

U01: Human Genetics
Tatiana Foroud
Leah Wetherill

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1

Aim 1

Develop a web portal with a novel, online consenting process to create a large CIFASD cohort of individuals with prenatal alcohol exposure for new studies.

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2

Aim 1

Participants from several countries

Diverse genetic ancestry
- ✓ 65% Caucasian
- ✓ 7% Native American/First Nation
- ✓ 8% African
- ✓ 20% Other/Mixed ancestry

51% Female

Age range 1-77, 64% <18 years (minor)

Most with minimal exposure (42.2%)

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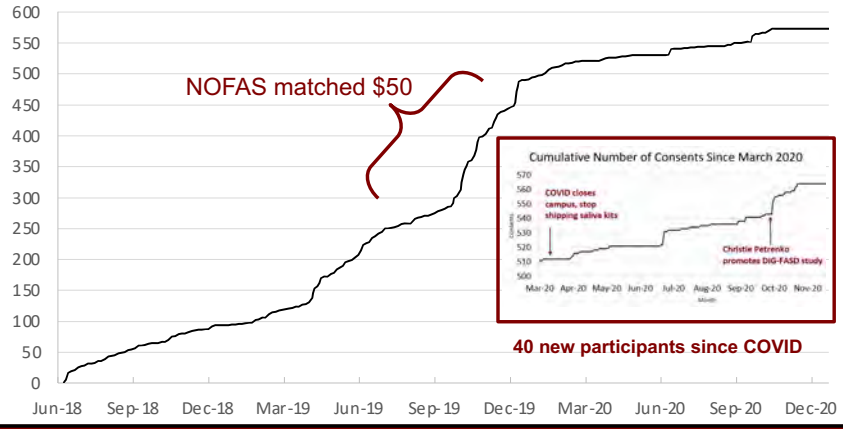
3

Aim 1

Cumulative # consents since inception



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4

Increasing Online Enrollment: Implementation of Suggestions

- Increase compensation for saliva to $30
  - $10 other components
- Consent videos currently in IRB pipeline
  - Feedback from Vancouver, CIFASD
  - 3 videos, ~2 minutes each, complete videos to consent
  - Simplify language and update graphics on flyers, website
- Shortened case-report forms
  - Decreases the total time

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5

Collaboration with CIFASD Projects

- **Mattson:** Brief Assessment of Individual Neurobehavior (BRAIN)
  - Consent and Assent Completed - IRB
  - Will produce similar video as Genetics Consent (waiting on IRB approval)
  - Will send email and link to previous participants
  - Will become part of DiG-FASD online flow
  - Data will be included in Central Repository upload
- **Coles/Weinberg:** Health questions
  - Questionnaire is in IRB pipeline for approval
  - Uses same questions to facilitate combining data
  - Will send email and link to previous participants
  - Will become part of DiG-FASD online flow
  - Data will be included in Central Repository upload

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6

Aim 2

Perform whole exome sequencing in a targeted set of the newly recruited online CIFASD cohort to compare individuals with (1) high probability of FAS/FASD features to (2) low probability.

- *Opportunity for analyses using a broader range of quantitative phenotypes (neurobehavior, facial features, etc) … but there are challenges*

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7

Whole Exome Sequencing (WES)

Phase I
- 273 exposed
  - 62 FAS
  - 111 FASD
  - 100 NOFAS

- Selection of 273 for WES (from CIFASD 2/3)
  - All seen by Ken Jones
  - All had prenatal alcohol exposure
- Initial analysis focused on comparison of dysmorphology extremes (FAS vs noFAS)
- Subset for analysis included:
  - 154 (African + Caucasian ancestry) children
  - Did not include children of other ancestry
  - Did not include Deferred by dysmorphologist
  - Initial results: *HTT, KIF2A, CRIPAK*

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8

Whole Exome Sequencing (WES)

Phase II
- 207 exposed
  - 76 FAS
  - 72 FASD
  - 59 TBD

- # from CIFASD 4 (n=129)
- # from DIG-FASD (n=78)

- Analysis: compare dysmorphology extremes (FAS vs noFAS)
- Challenge: Assessments not uniform
  - CIFASD 4 multiple sources of diagnosis:
    - Dysmorphologist
    - Dysmorphology severity score
    - Self report of previous diagnosis
  - DIG-FASD
    - Medical record review (genetic counselor) to identify features for FAS/noFAS
    - *small # with sufficient data*

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9

Analysis

- Reprocessed all WES data (Phase 1+2) together using GATK (VQSR variant filtering) (hg38)
- Annovar was used for variant annotation:
  - Retained single nucleotide variants (SNVs) that are predicted to change coding sequence
  - Retained SNVs with GnomAD minor allele frequency (MAF) <5% in EA, AA, and AMR samples
- Analysis of FAS vs noFAS includes 190 subjects
  - 78 FAS; 112 noFAS
  - To retain statistical power, cross-population analyses were done
  - Adjusted for 10 principal components and age, sex
  - Able to include individuals of other ancestries

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10

More Analyses of Previous Findings

- *CRIPAK* – not defined as a gene anymore, dropped
- *KIF2A* –one of the two variants was dropped
  - Had low quality mapping (highly variable quality across samples)
  - Now had an InDel in the region where the variants used to be
- *HTT* – 2.63×10^{-5} for FAS vs no FAS
  - Includes 17 SNVs
  - Higher burden increases risk for FAS
  - Consistent with previous result

	noFAS	FAS	%FAS
nonGC	75	28	27.2
GC	37	50	57.5

Follow up of *HTT* in animal models
- Scott Parnell: Htt knockout mice
- Johann Eberhart: Htt zebrafish in pipeline

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11

Next Steps for Genetic Analysis

- Facial phenotypes
  - Mike: dysmorphology index from facial signature (control ---- FAS)
  - Mike: sub-indices for specific facial regions
  - Chris: dysmorphology score from 2D photos (current) + 3D images (previous phases) converted to 2D
  - Ganz: lip/philtrum quantitative score from Morpheus Q
- Neurobehavioral phenotypes
  - Sarah: limited to different assessments across previous phases, reduces sample sizes for analyses
  - Sarah: BRAIN provides uniform measures, potential to increase sample size

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12

Whole Exome Sequencing (WES)

Phase I
- 273 exposed
  - 62 FAS
  - 111 FASD
  - 100 NOFAS

WES complete; data processed

Phase II
- 207 exposed
  - 76 FAS
  - 72 FASD
  - 59 TBD

WES complete; data processed

Phase III
- 132 exposed
  - 49 FAS
  - 31 FASD
  - 52 TBD

The plan…

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13

Question for the Group

- Sample size is always an issue in analysis. Genetic results are not robust with small sample sizes.
- How do we best use the resources of this project?
  - Incorporate additional assessments from other projects into online DIG-FASD protocol?
  - When will more facial phenotypes be available for analysis with existing WES sample?
  - Perform WES on another group of samples to increase sample size?

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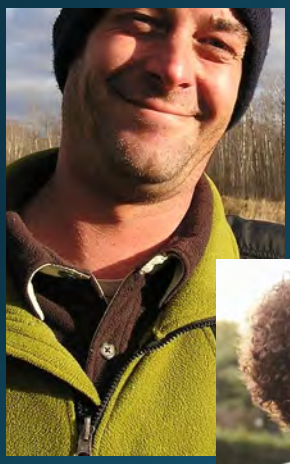
14



Fetal Alcohol Spectrum Disorders in Adults: Health and Neurobehavior: December 2020

NIH/NIAAA #: U01AA026108

Claire D. Coles, PHD
Emory University School of Medicine

Therese Grant, PHD
University of Washington

And Edward P. Riley, PhD,
in collaboration with Joanne Weinberg, PhD

1

Update: December 2020

- Status of Data Collection:
  - Both Atlanta and Seattle are collecting data in person as of November 1, 2020.
  - Both sites continue Remote data collection for all activities that can be carried out this way.
    - Tier 1 :Activities were mostly Remote already
    - Tier 2: Questionnaires done remotely
    - COVID: Questionnaires
- In-person data collection resuming for:
  - Lab work (blood/urine/saliva), photographs, *dysmorphology*, NIH Toolbox, supplemental studies). NIH Toolbox cannot be done in Seattle at present.

2

Supplements Update: December 2020

- COVID Supplement
  - COVID-19 Supplement received with goal of identifying impact of pandemic on individuals with FASD .
  - Activities will include COVID-Specific Questionnaires to assess social, economic and psychological impact.
  - Antibody testing as part of Tier 2-Atlanta only
  - National Death Index (NDI) used to identify increased mortality in sample.
  - All procedures have been approved and being implemented.
- Diversity Supplement (to Gaby Ritfeld, MD, PHD)
  - Focus on children (ages 5-17) of alcohol-affected adults
  - Evaluate parenting skills and child emotional/behavioral outcomes.
  - All procedures approved and being implemented

3

Update: December 2020

- Challenges
  - Delays in collection of Tier 2 in-person data. COVID safety precautions are limiting rate of data collection
  - Participants continue to be anxious about direct data collection
  - Staff is growing less anxious about direct data collection
  - Increase time and costs to carry out protocols
  - Vancouver collaborators not yet able to resume activities.
- Products
  - Insulin paper written and submitted for publication (Kable).
  - Presentation to PROOF Alliance meeting.
  - Collaborated with Indiana team on health questionnaire.

4

Data analysis: Cognitive outcomes in midlife.

- NIH Toolbox Used to measure "fluid" intelligence in midlife.
- Tests used:
  - Dimension Change Card Sort (DCDS)
  - Flanker Test of Executive Functioning, inhibitory Control and attention
  - Picture Sequence Memory Test of Episodic Memory
  - List Sorting Working Memory Task
  - Pattern Comparison Processing Speed Test
- Tests can be summed into a Cognitive Fluid Composite Standard Score
- Multivariate analysis (N=115) using Alcohol Group, Site, Sex and Age. Only Alcohol Group and Site are significant factors. Sample is too small to sort out dose/severity questions at this time.

5

Results

Adult Study Results: Standard Scores

	Alcohol		Control		Stat	p
	Atlanta (n=38)	Seattle (n=40)	Atlanta (n=26)	Seattle (n=9)		
DCCS Task	86.0 (20.0)	91.8 (17.4)	98.6 (17.2)	112.4 (21.2)	EtOH: $F_{(1,113)}$= 15.81 Site: $F_{(1,113)}$=5.57 ExS: $F_{(1,113)}$=0.9	.000 .019 NS

Measures Executive Functioning. Ability to Switch Cognitive Set.

Dimensional Change Card Sort (DCCS)

Tap picture that matches on either color or shape.

6

Results

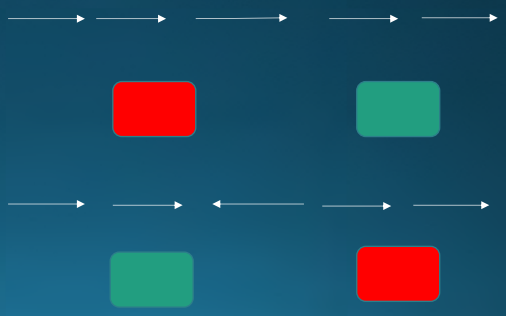
Adult Study Results: Standard Scores

	Alcohol		Control		Stat	p
	Atlanta (n=38)	Seattle (n=40)	Atlanta (n=26)	Seattle (n=9)		
Flanker Task	75.4 (13.2)	81.2 (12.9)	80.8 (14.9)	102.7 (21.2)	EtOH: $F_{(1,113)}$= 17.93 Site: $F_{(1,113)}$=18.92 ExS: $F_{(1,113)}$=6.37	.000 .000 .013

Measures Executive Functioning, Attention, Impulse Control.

Flanker Task:

Goal is to tap the L or R box depending where the middle arrow points



7

Results

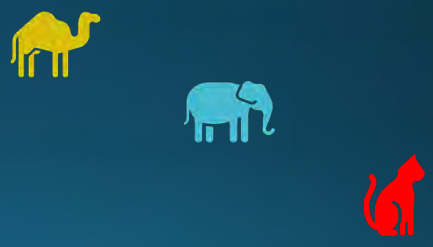
Adult Study Results: Standard Scores

	Alcohol		Control		Stat	p
	Atlanta (n=38)	Seattle (n=40)	Atlanta (n=26)	Seattle (n=9)		
List Sorting	82.9 (16.2)	87.4 (18.29)	88.5 (14.3)	107.9 (15.5)	EtOH: $F_{(1,113)}$= 12.4 Site: $F_{(1,113)}$=10.39 ExS: $F_{(1,113)}$=4.06	.001 .002 .046

Measures Working Memory

List Sorting

Goal is to remember pictures presented one by one and name them in size order from smallest to largest.



Correct: "cat", "camel", "elephant"

8

Results

Adult Study Results: Standard Scores

	Alcohol		Control		Stat	p
	Atlanta (n=38)	Seattle (n=40)	Atlanta (n=26)	Seattle (n=9)		
List Sorting	85.3 (21.1)	87.4 (16.7)	86.1 (26.5)	120.8 (18.6)	EtOH:$F_{(1,113)}$ =13.43 Site: $F_{(1,113)}$=15.43 ExS: $F_{(1,113)}$=12.13	.000 .000 .001

Measures: Processing Speed

(*Note that only Seattle Controls are different*)

Pattern Comparison Processing Speed

Goal is to decide if 2 pictures are the same or different.

Touch Yes if the same; No if different

Yes

No

9

Results

Adult Study Results: Standard Scores

	Alcohol		Control		Stat	p
	Atlanta (n=38)	Seattle (n=40)	Atlanta (n=26)	Seattle (n=9)		
Picture Sequence	91.9 (16.3)	96.85 (16.9)	96.5 (15.6)	107.2 (12.1)	EtOH:$F_{(1,113)}$= 4.26 Site: $F_{(1,113)}$=4.72 ExS: $F_{(1,113)}$=0.66	.038 .032 NS

Measures : Episodic Memory

(*Note: All scores in Average range.*)

Picture Sequence Memory

Goal is to remember pictures presented one by one and arrange them in correct order.

10

Results

Adult Study Results: Age Corrected Standard Scores

Cognitive Fluid Composite

Summary of five Subtest

Standard Scores available with and without Age Correction. These are Age Corrected.

	Alcohol		Control		Stat	p
	Atlanta (n=38)	Seattle (n=40)	Atlanta (n=26)	Seattle (n=9)		
Cognitive Composite	77.3 (17.3)	83.6 (17.9)	85.4 (18.5)	114.1 (19.8)	EtOH:$F_{(1,113)}$= 22.7 Site: $F_{(1,113)}$=18.82 ExS: $F_{(1,113)}$=7.75	. 000 .000 .006

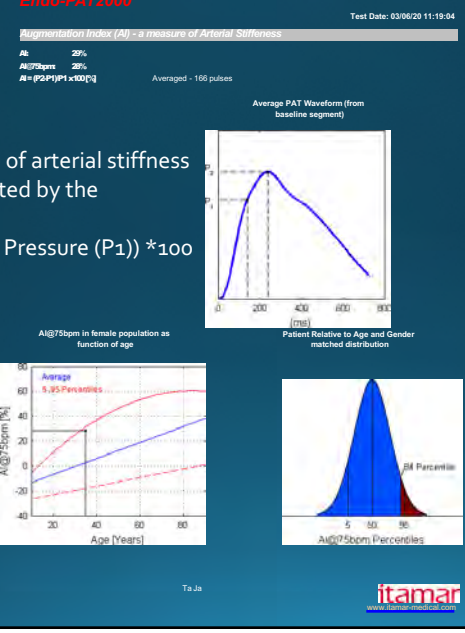
Seattle Control group is skewing results. However, SDs are large perhaps reflecting the effects of severity of exposure.

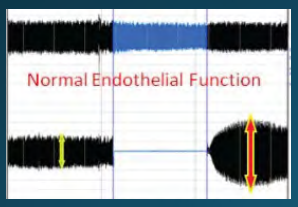
Results correlate with Years of School. And weight.

11

Augmentation Index (AI)-Arterial Stiffness

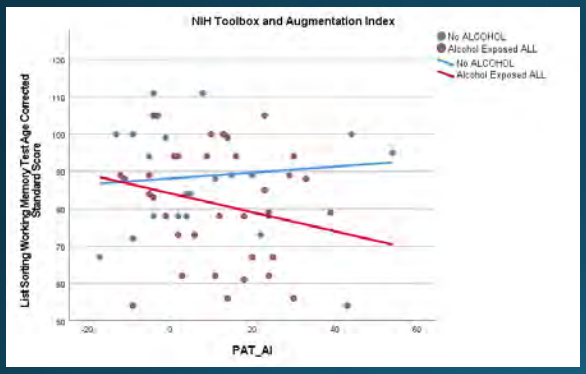
Augmentation index (AI) is a measure of arterial stiffness expressed as a percentage. It is computed by the following formula:
(Augmentation Pressure (P2-P1)/Pulse Pressure (P1)) *100





12

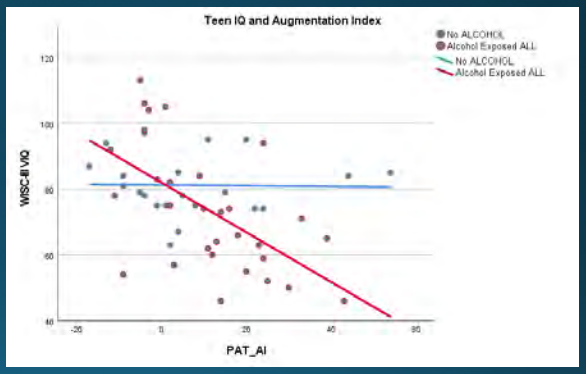
Cognitive Functioning and Arterial Stiffness Atlanta Site only (N=57)



Working Memory

No Alcohol: r (n=21) = .115 (95% CI: -.208- .415)

Alcohol-Exposed: r (n= 36) = -.235 (95% CI: -.513- -.087)



Verbal IQ

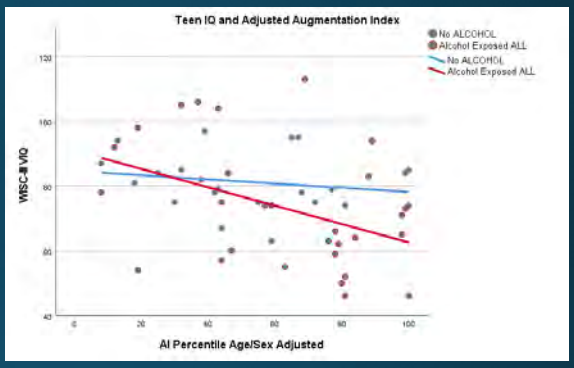
No Alcohol: r (n=21) = -.022 (95% CI: -.362- .324)

Alcohol-Exposed: r (n=30) = -.583 (95% CI: -.772- -.300)***

13

Possible Implications

- There may be a relationship between arterial stiffness and intellectual functioning that is affected by PAE.
- This may be present early in life. There is a relationship with WISC-III scores from Adolescence but not clear if both are related to a 3rd factor.
- If there is a relationship with vascular problems, we might expect acceleration with aging as arterial stiffness increases with age in typical population. This would suggest that early cognitive decline may be expected as a result of PAE.



No Alcohol: r (n=21) = -.201 (95% CI: -.509- .153)

Alcohol-Exposed: r (n=30) = -.411 (95% CI: -.661- -.078)*

14

Plans

Process Goals

- Continue to enlarge samples working within the restraints of Safety protocols.
- Carry out goals of supplemental projects.
- Continue collaboration with other sites, particularly Vancouver.

Analysis Goals

- When samples are large enough, examine outcomes *vis a vis* severity of exposure.
- Develop models to evaluate relative effects of PAE and environmental factors.

CIFASD 5 Goals

- Adult Health issues opening new area for research.
- Changing the paradigms of previous research in this area.
- Lifespan issues remain to be explored.

15

NIH National Institute on Alcohol Abuse and Alcoholism
NIH...Turning Discovery Into Health®

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Image Analysis of Neurofacial Effects of Prenatal Alcohol Exposure

CIFASD 2020

Michael Suttie
Alison Noble
Chris Nellaker
Ralf Haeusler
Zeyu Fu

CIFASD | Collaborative Initiative on Fetal Alcohol Spectrum Disorders

1

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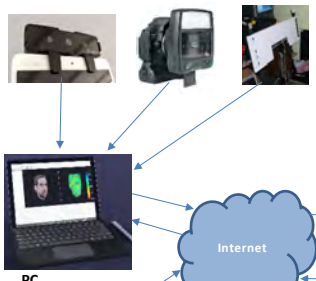
REST API – Cloud Based Processing



Automated PFL
Control-FAS Classification
Secondary Feature Assessment
FASD Risk (requires further cognitive data)

2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FaceScreen Live Demo

3


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iPhone App Video Demo

4

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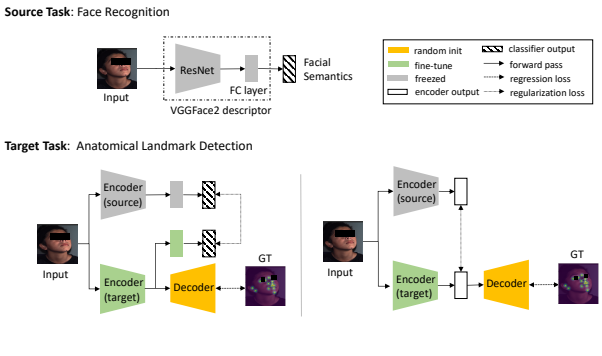
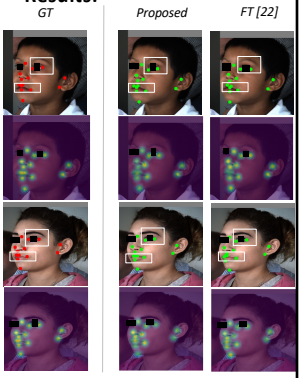
Cross-task Representation Learning for Anatomical Landmark Detection

➢ **Proposed Framework:**



➢ **Results:**



➢ An end-to-end CNN based heatmap regression approach for automatically localizing anatomical landmarks in 2D facial images.

➢ The proposed framework reused the knowledge from a source facial recognition model for learning the landmark detector.

➢ It can potentially provide an automated alternative to the manual anthropometric placement.

(Fu et al, MICCAI-MLMI 2020)

5

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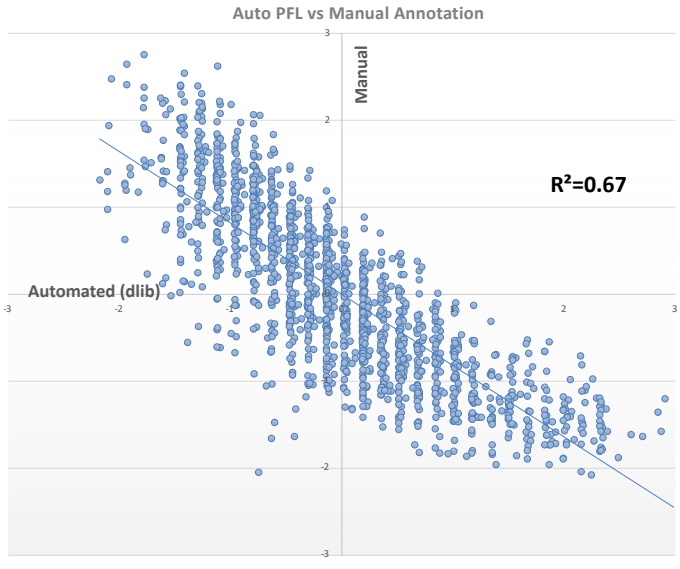

6

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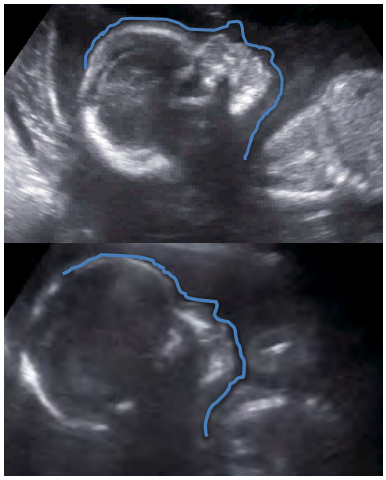
Ultrasound – Profile Extraction



- Failed on profile
- Looking to use more sophisticated approach

7

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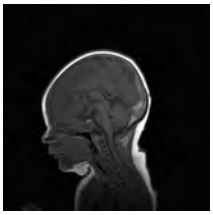
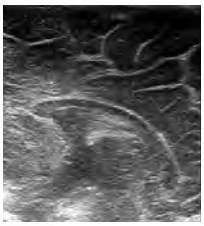
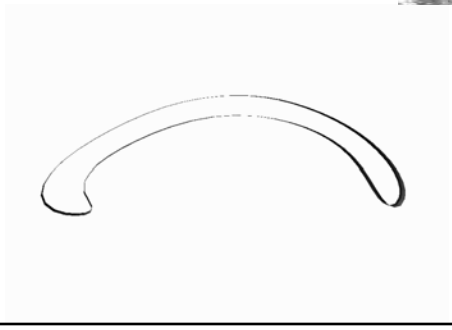
Transfontanelle Ultrasound vs MRI



VS





- N=32,
- Capture within 1 week
- Alcohol-exposed/combined exposure
- Promising preliminary results
- Control data required

8

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Future Plans Y4 Y5

- **API and APP completion** (Y4), security in place for distribution in Y5
  - Automated landmarking pipeline included.
  - Automated PFL validation from different camera modalities
  - Make available for collaborators (Ganz)

- *PASS dataset: Concurrent Smoking & PAE finalise and submit to Paediatrics*
- *Clinical validation comparing 4-digit to 3D automated tools*
  - *To include CIFASD4 3D data from Jeff Wozniak (and any other NEW data) + UK data from Dr Raja Mukherjee*

- *Ukraine ultrasound data:*
  - *Rethink strategy for automated recognition of brain differences*

- *2D image analysis: Chris Nellaker*
  - *Utilising digFAS images*

- *CIFASD5 groundwork*

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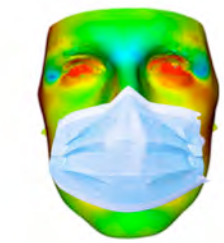
Nuffield Department of Women's and Reproductive Health, University of Oxford

UNIVERSITY OF OXFORD

Covid-19 Impact



- UK still has intermittent lockdowns
- University buildings are part-open although full access still not granted
- Integration of new team members challenging
- Utilise budgets effectively to make up for lost time
  - New post
  - Use external consultancy for final API/App deployment

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Nuffield Department of Women's and Reproductive Health, University of Oxford

UNIVERSITY OF OXFORD

Publications Since July

Cross-Task Knowledge Distillation for Anatomical Landmark Detection. Z Fu, J Jiao, M Suttie, A Noble.

MICCAI-MLMI 2020 Accepted Aug 2020

Fetal Alcohol Spectrum Disorders – an overview of current evidence and activities in the UK. L Schölin, R Mukherjee, N Aiton, C Blackburn, S Brown, K Fleming, P Gard, H Howlett, M Plant, A Price, J Shield, L Smith, M Suttie, DC Zammitt, PA Cook.

Submitted Nov 2020 to Archives of Diseases Childhood

Regularized Transfer Learning for Anatomical Landmark Detection in Fetal Alcohol Syndrome. Z Fu, J Jiao, M Suttie, A Noble.

Immanent submission to the IEEE Journal of Biomedical and Health Informatics

Facial Dysmorphism of Concurrent Smoking and Prenatal Alcohol Exposure in Infants using 3D Image Analysis. M Suttie, H Odendaal, H Nolan, L Brink, C Cluver, A Kirsten, S Parnell, L Wetherill, T Foroud, P Hammond and the CIFASD

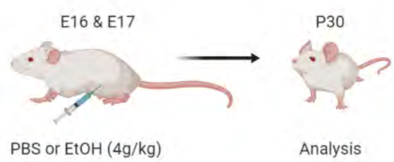
In preparation

11

CD-1 outbred mouse

ETOH I.P. at 2.0 g/kg weight for embryonic day 16 and 17

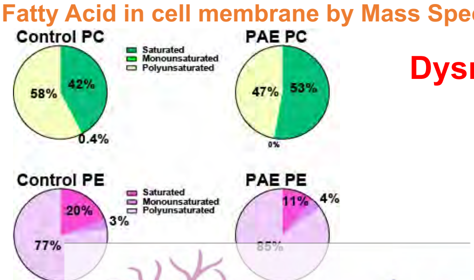
Neurobehavior battery at 1 month old



Motor skill learning deficit
Cognitive inflexibility
Increased anxiety
Normal locomotion

1

Fatty Acid in cell membrane by Mass Spec

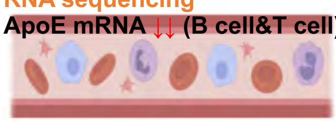


Dysregulated Lipidome

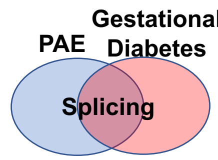
UH2

RNA sequencing

ApoE mRNA ↓↓ (B cell&T cell)



ApoE protein ↓↓ (Fasted only)



R01

ApoE protein ↓↓ (Fasted only)

Normal Blood Glucose
Normal Body Weight

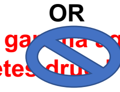
Changes in Fatty Acid related Microbiome

Single Cell RNA sequencing
Fatty Acid biogenesis related gene expressions (Mohammad et al., 2020)

17 amino acid pep[...]f human APOE

OR

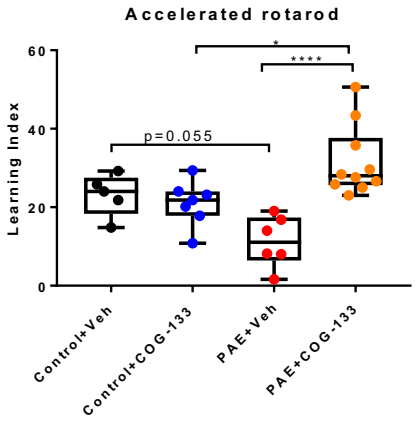
PPAR ga[...]gonist (Type2 diabetes dru[...]ioglitazone)



F31 (Amy Hwang)

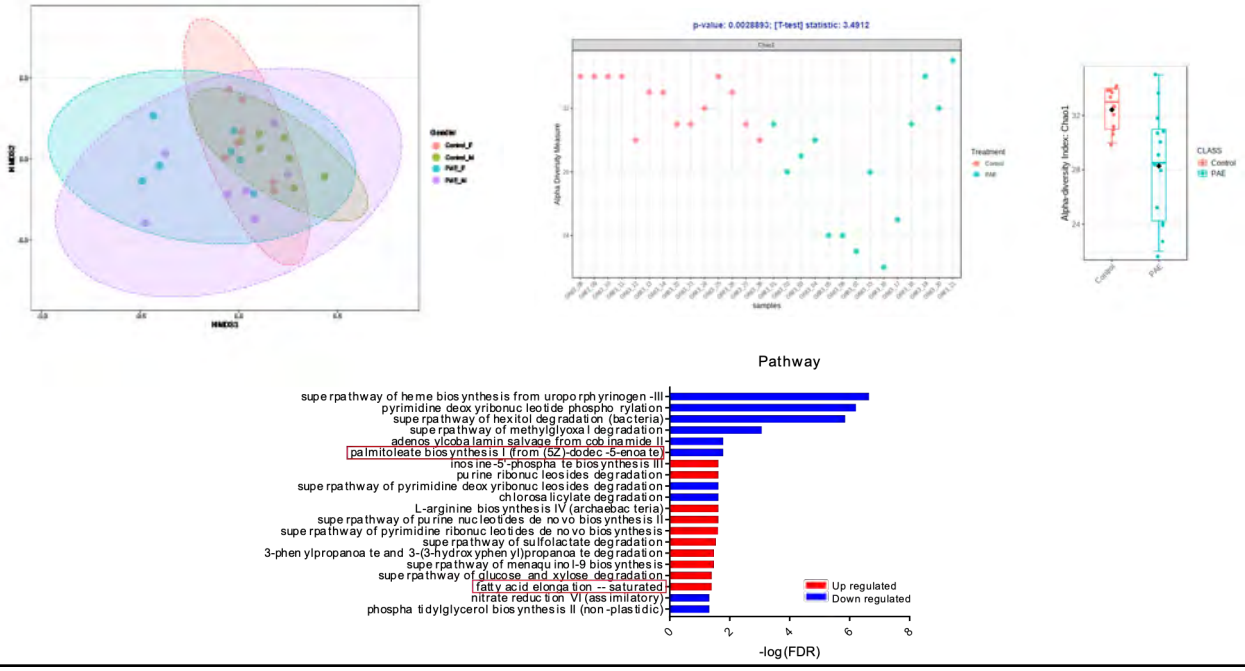
2

COG-133 (ApoE short peptide) improves learning deficit in PAE mice



3

Microbiome data



4

Neurogenetics Division at Children's National (Chief: Andrea Gropman, MD) will open FASD clinic to serve for greater Washington DC to Baltimore area

Alcohol problem is highly prevalent in minority community
Neurobehavior, Imaging
Human iPS cells will be generated from patients who have susceptible genomic loci
Test the effects of alcohol in mini human tissues (human organoid) made from those iPS cells.

5

UH2 update

Sandra Mooney

Nutrition Research Institute of UNC Chapel Hill

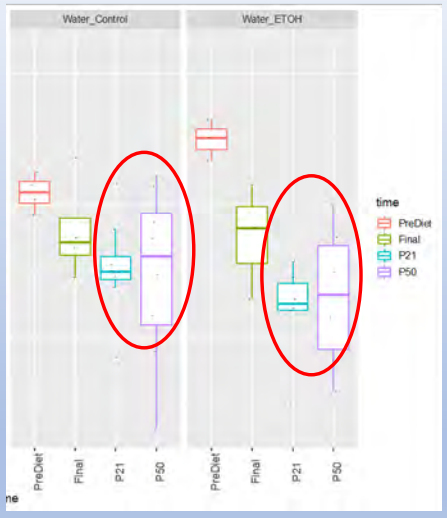
1

Prenatal Alcohol Exposure

- In rats, PAE:
  - Alters fecal microbiome of dam and offspring – reduces alpha diversity (lower diversity is associated with higher levels of pro-inflammatory cytokines)
  - Changes the plasma cytokine signature in offspring in late adolescence [**same animals** as microbiome]
    - BLOOD ALCOHOL CONCENTRATION ~60 mg/dl prior to conception through birth
  - Alters cognitive ability and functional connectivity in offspring
    - BLOOD ALCOHOL CONCENTRATION ~30 mg/dl from ~gastrulation through birth

2

Microbiome Alpha Diversity in Dam and Pups

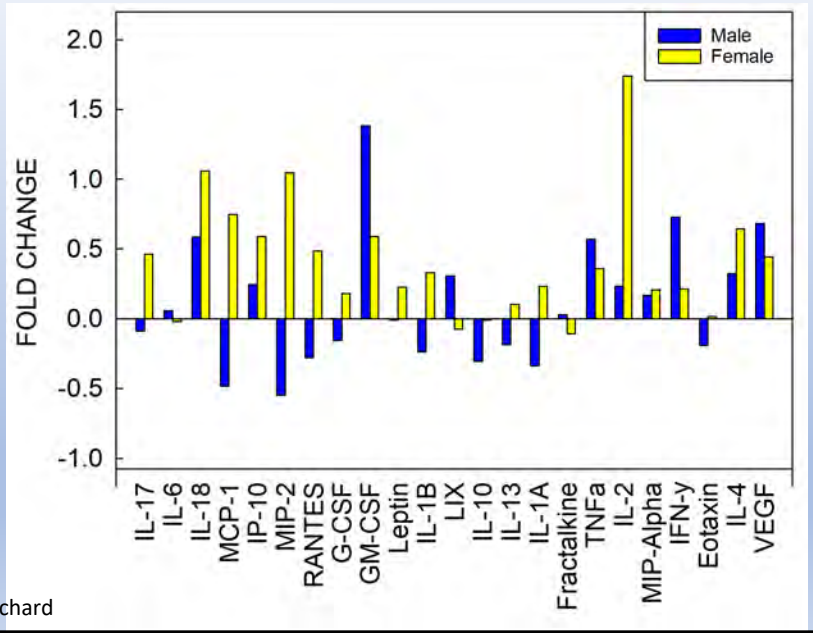


Lower alpha diversity has been linked with increases in pro-inflammatory cytokines

w. Tom Blanchard

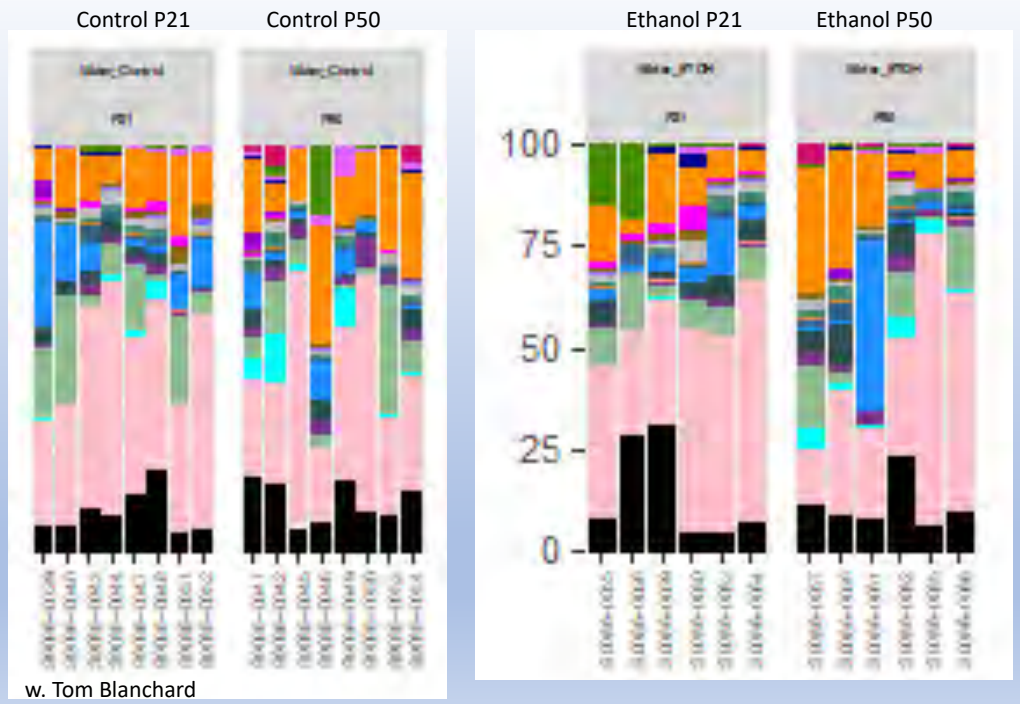
3

P50, plasma cytokines in PAE relative to Control



w. Tom Blanchard

4

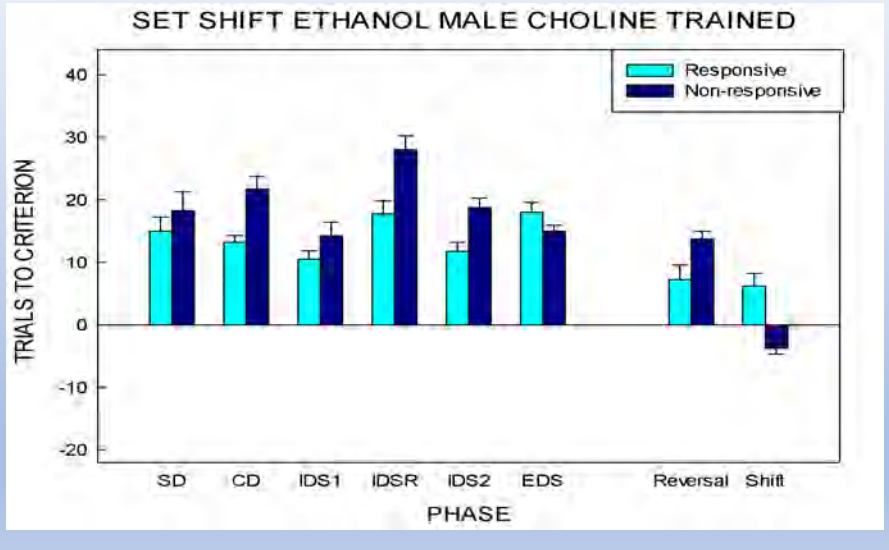


5

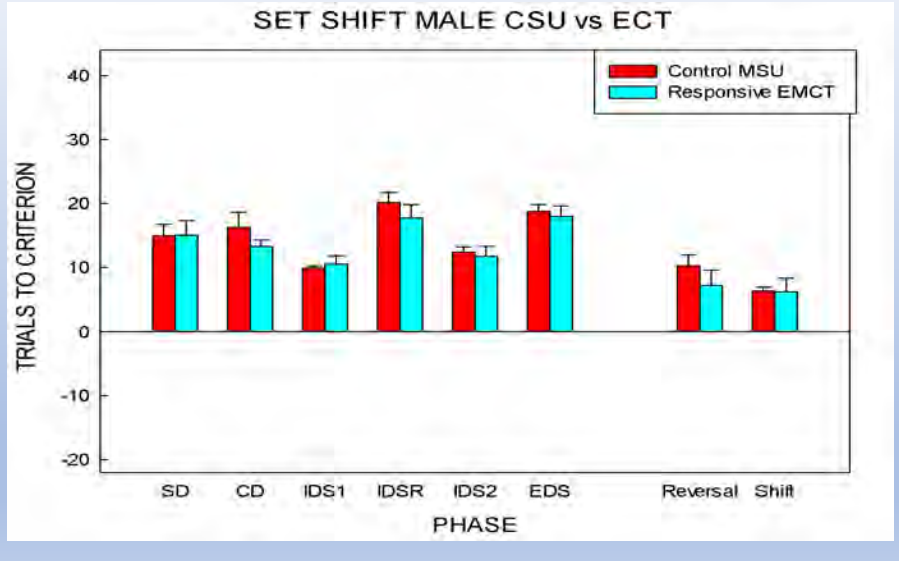
Rat behavior: Learning

	FEMALE Control	FEMALE PAE		MALE Control	MALE PAE
No Intervention	66.80 (5.91)	86.00 (5.00)		73.25 (9.42)	80.33 (11.32)
Intervention 1	67.40 (2.93)	**65.50 (1.50)**		94.25 (12.33)	82.50 (15.50)
Intervention 2	68.71 (4.17)	90.33 (12.91)		74.20 (5.23)	**72.75 (7.45)**

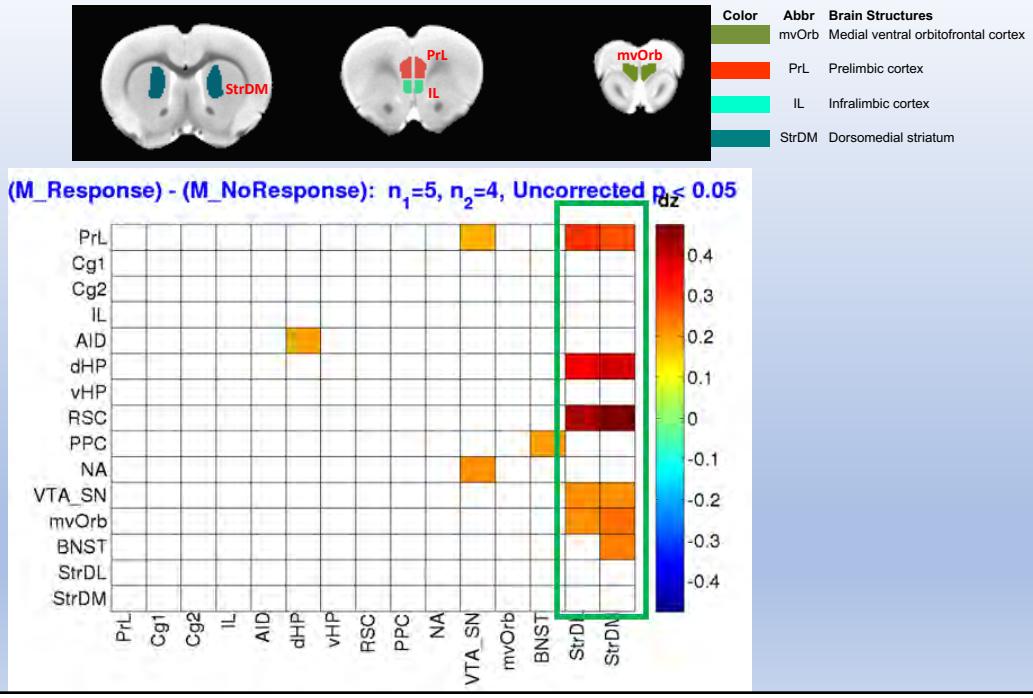
6


SET SHIFT ETHANOL MALE CHOLINE TRAINED
Responsive
Non-responsive
TRIALS TO CRITERION
40
30
20
10
0
-10
-20
SD
CD
IDS1
IDSR
IDS2
EDS
Reversal
Shift
PHASE

7


SET SHIFT MALE CSU vs ECT
Control MSU
Responsive EMCT
TRIALS TO CRITERION
40
30
20
10
0
-10
-20
SD
CD
IDS1
IDSR
IDS2
EDS
Reversal
Shift
PHASE

8



9

What's next

- Fecal microbiome assay
- Bioinformatics to look for drivers of between-group differences
- Bioinformatics to determine if there's an association between microbiome and behavior outcomes
- Bioinformatics to determine if there's an association between microbiome and response to treatments

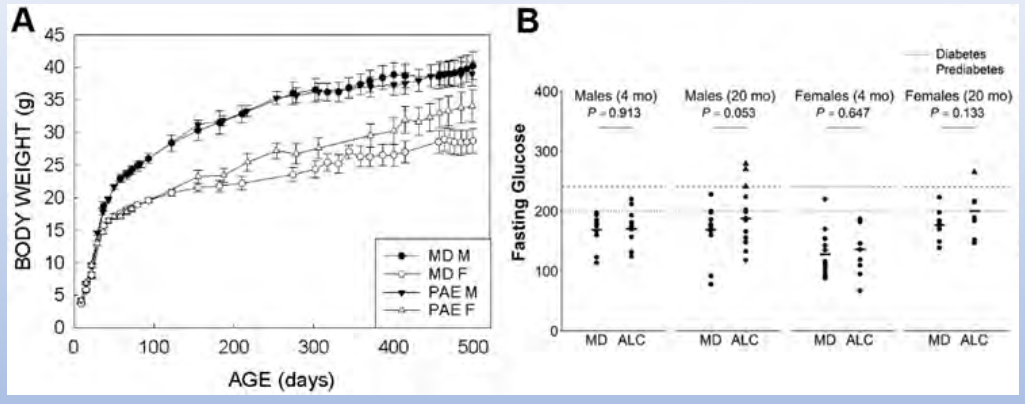
- Could potentially be an informative biomarker for degree of affectedness and/or ability to respond to Tx

10

Prenatal Alcohol Exposure (w. Susan Smith)

- In mice, PAE:
  - Alters the levels of microbial-derived products in the maternal plasma… and in the fetal liver and brain [resubmission under review at Sci Reports]
  - Increases body weight gain in female offspring after ~7 months of age
  - Increases the chance offspring will show evidence of pre-diabetes or diabetes
  - Reduces lifespan, particularly in male offspring
  - Impairs memory
    - BLOOD ALCOHOL CONCENTRATION ~200 mg/dl from neurulation through end of gestation

11

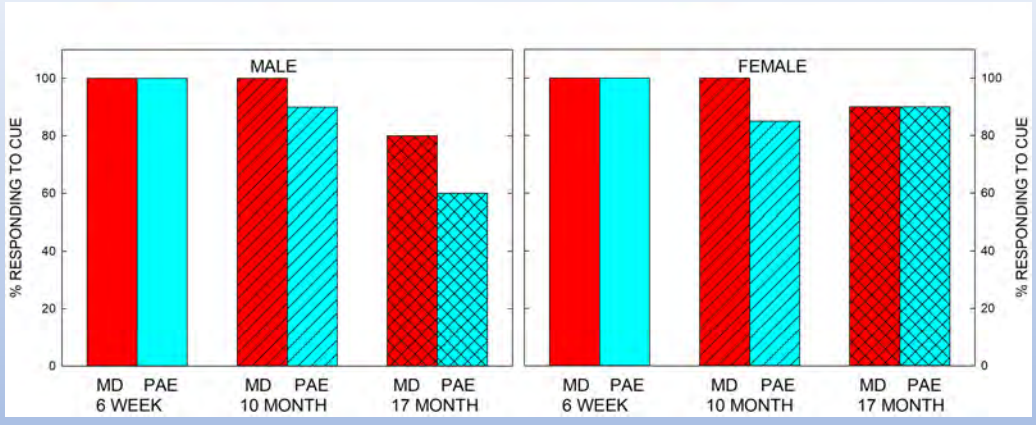


We also found increased mortality in PAE males compared with control males and with PAE females

w. Susan Smith

12

Fear conditioning - % animals that remember what the cue means



At 24 mo, ~60% females respond to cue

w. Susan Smith

13

What's next

- Recently received grant from NRI to assay cecal microbiome and use bioinformatics to analyze data and integrate with existing metabolome and transcriptome datasets
- Ongoing study examining outcomes in offspring of dams treated with choline during EtOH exposure – health, behavior, -omics
- Ongoing study examining PAE in an Alzheimer's Disease model
- We collect various tissues for later analyses
- With Phil May we're looking at metabolome in maternal blood spots to determine if there's a microbial-derived signature there too
- Useful models to drill into mechanisms underlying PAE – aging dynamic

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Deliverables

- Directly relevant: Blanchard microbiome paper is in draft form. Will take some work
- Related: Virdee et al. (plasma microbial-derived products) paper was revised & is under re-review
- Rat cognition paper was recently accepted
- Received internal funding to assay mouse microbiome

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