Neurotoxicology and Teratology 61 (2017) 138–164

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera

41st Anniversary Annual Meeting of the Developmental Neurotoxicology Society Held in Conjunction with the 57th Annual Meeting of the Teratology Society Grand Hyatt Hotel, Denver CO June 24–28, 2017

2017 Richard Butcher New Investigator Award, Supported by San Diego Instruments

Jenna Sprowles

Cincinnati Children's Research Foundation and University of Cincinnati College of Medicine.

Perinatal antidepressant exposure influences spatial learning and memory, acoustic startle response, anxiety, and locomotor activity in adult Sprague-Dawley rats

2017 Patricia Rodier Mid-Career Award

Sonia Minnes

Case Western Reserve University

Project Newborn: What We Have Learned from 20 Years of Research on Prenatal Cocaine Exposure

DNTS Conference Awards

Steven Boomhower – **Supported by Battelle**

Auburn University

Adolescent methylmercury exposure: effects on behavioral flexibility, delay discounting, fixed-ratio performance, and gene expression in the prefrontal cortex

Katherine Hatcher

University of Illinois at Urbana-Champaign

Transgenerational effects of di-(2-ethylhexyl) phthalate on behavior and hippocampal gene expression in male and female mice

Gloria Lee

Florida State University.

Neurobehavioral and neuroanatomical consequences of cell-type specific inactivation of dopamine D2 receptors in the mouse brain

Yingying Xu

Cincinnati Children's Hospital Medical Center

Low-level mercury exposure from fish consumption: Associations with childhood neurodevelopment

Katie O'Shaughnessy

Oak Ridge Institute for Science and Education and US Environmental Protection Agency.

Transient Maternal Hypothyroidism Alters Neural Progenitors Resulting in Abnormal Brain Development

Emily Pitzer

Cincinnati Children's Research Foundation and University of Cincinnati College of Medicine.

Developmental deltamethrin exposure causes adult learning and memory deficits

DNTS 2017 Program

Saturday, June 24, 2017

8:00 AM–12:00 Noon	**Teratology Society Education Course Session I** **Renal Development: Embryology, Renal Abnormalities and Teratogens, and Clinical Management and Treatment** *(Separate Registration Required)*	**Aspen Ballroom**
8:00 AM–4:30 PM	**Research Society on Alcoholism (RSA)** **Fetal Alcohol Spectrum Disorders Study Group** *(Separate Registration Required - a limited number of free advance registrations will be provided)*	**Hyatt Regency**
12:00 Noon–5:00 PM	**DNTS Registration**	**Colorado Ballroom B Foyer**
1:00 PM–2:00 PM	**DNTS Public Affairs Committee Meeting**	**Mt. Wilson**

http://dx.doi.org/10.1016/j.ntt.2017.04.004

Available online 27 April 2017
0892-0362/

1:30 PM–5:00 PM	**Teratology Society Education Course Session II** **Epigenetics: A Primer** *(Separate Registration Required)*	**Aspen Ballroom**
2:00 PM–3:00 PM	**DNTS Publications Committee Meeting**	**Mt. Wilson**
3:30 PM–6:00 PM	**DNTS Council Meeting**	**Mt. Wilson**

Please note: Committee meeting schedules may be modified to accommodate for optional RSA/FASD-SG sessions once that schedule is announced.

Sunday, June 25, 2017

7:30 AM–8:15 AM	**Morning Coffee and Pastries** (Joint with the Teratology Society)	**Aspen Foyer**
8:00 AM–5:00 PM	**DNTS Registration**	**Colorado Ballroom B Foyer**
8:15 AM–9:00 AM	**Josef Warkany Lecture** (joint with the Teratology Society) DNTS 01: **Eliminating Congenital Zika Syndrome: Lessons Learned from Rubella Elimination** *Chairperson: Sonja A. Rasmussen, Centers for Disease Control and Prevention* *Lecturer: José F. Cordero, University of Georgia*	**Aspen Ballroom**
9:00 AM–9:15 AM	**DNTS President's Welcome**	**Colorado Ballroom B**
9:15 AM–11:30 AM	**DNTS Symposium** **What's Right and Wrong with Our Mice (and our Worms, and our Flies, and our Cells, and our…)** *Chairpersons: Gregg D. Stanwood, Florida State University College of Medicine and Christine Curran, Northern Kentucky University*	**Colorado Ballroom B**
9:15 AM–9:20 AM	Introduction: Rigor and Reproducibility in Neurotoxicity and Neurobehavioral Studies *Gregg Stanwood, Florida State University*	
9:20 AM–9:45 AM	DNTS 02: Reproducibility through rigor and transparency – the CSR perspective *Jana Drgonova, Center for Scientific Review, National Institutes of Health*	
9:45 AM–10:10 AM	DNTS 03: 101 Ways to Mess Up a Mouse Study: The Rocky Road to Rigor and Reproducibility *Christine Curran, Northern Kentucky University*	
10:10 AM–10:35 AM	DNTS 04: Reducing the Wiggle Room in Data Generated from *C. elegans* *Vanessa Fitsanakis, King University*	
10:35 AM–11:00 AM	DNTS 05: Translational Studies on the Role of Developmental Pyrethroid Exposure in ADHD: From Cells to Zebrafish to Mice to Humans and Back Again *Jason Richardson, Northeast Ohio Medical University*	
11:00 AM–11:30 AM	Discussion	
10:00 AM–10:30 AM	**Spouse and Guest Meet-and-Greet** (Open to Teratology Society, DNTS, and OTIS Spouses and Guests)	**Mt. Wilson**
11:30 AM–1:00 PM	**Lunch on Your Own**	
1:00 PM–3:00 PM	**Platform Session 1** *Chairperson: Paul Eubig, University of Illinois at Urbana-Champaign*	**Colorado Ballroom B**
1:00 PM–1:20 PM	DNTS 06: Associations between Early Life Exposure to Traffic Related Air Pollution and Symptoms of Depression and Anxiety at Age 12 Years *Kimberly Yolton, Jane Khoury, Cole Brokamp, Rachel Severs, Christopher Wolfe, Zana Percy, Jeff Burkle, Kim Cecil, Grace LeMasters, Patrick Ryan, Cincinnati Children's Hospital Medical Center and University of Cincinnati*	
1:20 PM–1:40 PM	DNTS 07: Transgenerational effects of di-(2-ethylhexyl) phthalate on behavior and hippocampal gene expression in male and female mice *Katherine M. Hatcher, Jari Willing, Catheryne Chiang, Saniya Rattan, Janice M. Juraska, Jodi A. Flaws, Megan M. Mahoney, University of Illinois at Urbana-Champaign*	
1:40 PM–2:00 PM	DNTS 08: Transient Maternal Hypothyroidism Alters Neural Progenitors Resulting in Abnormal Brain Development *Katherine O'Shaughnessy, Susan Thomas, Jermaine Ford, Richard Ford, Mary Gilbert, Oak Ridge Institute for Science and Education and US EPA*	
2:00 PM–2:20 PM	DNTS 09: Maternal overnutrition and trichloroethylene co-exposure augments neurotoxicity in offspring in an autoimmune-prone mouse model *Sarah Blossom, Jakeira Davis, Oleksandra Pavliv, Kathleen Gilbert, Frank Simmen, University of Arkansas for Medical Sciences and Arkansas Children's Research Institute*	
2:20 PM–2:40 PM	DNTS 10: Prenatal and postnatal tobacco and cannabis exposure: joint and bidirectional associations with child behavior problems *Rina Eiden, Junru Zhao, Meghan Casey, Shannon Shisler, Pamela Schuetze, State University of New York at Buffalo and Buffalo State College*	
2:40 PM–3:00 PM	DNTS 11: Determining origins of increased obesity risk in children with FASD: Is a hyperphagic feeding phenotype the result of abnormal metabolic requirements or a reward system dysfunction? *Robyn Amos-Kroohs, David Nelson, Jeffrey Wozniak, Chi-Liang Eric Yen, Susan Smith, University of*	

	North Carolina Nutrition Research Institute, University of Wisconsin-Madison, Madison, and University of Minnesota	
3:00 PM–3:30 PM	**Patricia Rodier Mid-Career Award for Research and Mentoring**	**Aspen Ballroom**
	DNTS 12: **Project Newborn: What We Have Learned from 20 Years of Research on Prenatal Cocaine Exposure**	
	(Joint with the Teratology Society)	
	Chairpersons: Janee Gelineau-van Waes, Creighton University School of Medicine and Patricia A. Janulewicz, Boston University	
	Lecturer: Sonia Minnes, Case Western Reserve University	
3:30 PM–6:15 PM	**DNTS Symposium**	**Colorado Ballroom B**
	Current Perspectives on Cognitive Effects Following Developmental Methylmercury Exposure	
	Chairpersons: Carol Starkey (ORISE Research Participant at US EPA) and Deborah Segal (US EPA, National Center for Environmental Assessment)	
3:30 PM–4:00 PM	DNTS 13: Impact of early life methylmercury exposure on child neurodevelopment	
	Susan Korrick, Harvard Medical School	
4:00 PM–4:30 PM	DNTS 14: Assessment of Methyl Mercury and Fish Oil Modulation of Neurodevelopment in Developing a Risk/Benefit Model of Fish Consumption	
	Gary Ginsberg, Connecticut Dept. of Public Health	
4:30 PM-4:45 PM	Break - Aspen Foyer	
4:45 PM–5:15 PM	DNTS 15: Determination of individual variation in methylmercury (MeHg) metabolism and elimination status (MerMES) in humans	
	Matthew Rand, University of Rochester	
5:15 PM–5:45 PM	DNTS 16: Developmental Neurotoxicity of Methylmercury in Animal Models: A Lifespan Approach with Emphasis on Executive Functions	
	Christopher Newland, Auburn University	
5:45 PM–6:15 PM	DNTS 17: Windows of Vulnerability to Low Levels of MeHg in the Rat Hippocampus	
	Katie Sokolowski, Rutgers University Alumni	
7:00 PM–8:30 PM	**Welcome Reception, Graduate Student and Postdoctoral Fellow Research Showcase and Exhibits Attended**	**Mt. Sopris**
	(Joint with the Teratology Society)	

Monday, June 26, 2017.

7:30 AM–8:00 AM	**Morning Coffee and Pastries**	**Aspen Foyer**
	(Joint with the Teratology Society)	
8:00 AM–5:00 PM	**DNTS Registration**	**Colorado Ballroom B Foyer**
8:00 AM–9:00 AM	**Keynote Address**	**Aspen Ballroom**
	DNTS 18: **Cannabis in Colorado: The Impact of Legalization on Children and Families**	
	(Joint with the Teratology Society)	
	Chairpersons: Alan M. Hoberman, Charles River Laboratories and Gregg D. Stanwood, Florida State University	
	Speaker: Larry I. Wolk, Colorado Department of Public Health and Environment	
9:15 AM–12:00 Noon	**RSA/FASD-SG, Teratology Society, OTIS, and DNTS Exchange Symposium**	**Aspen Ballroom**
	Evaluation of Fetal Risk in the Context of Multiple Co-Exposures	
	Chairpersons: Ludmila Bakhireva, University of New Mexico and Jeffrey R. Wozniak, University of Minnesota	
9:15 AM–9:25 AM	Introduction: Methodological Challenges of Evaluating the Effect of Multiple Exposures	
	Ludmila Bakhireva, University of New Mexico	
9:25 AM–9:50 AM	DNTS 19: Defining the Human Exposome	
	Cynthia F. Bearer, University of Maryland	
9:50 AM–10:15 AM	DNTS 20: PK/PD Modelling for Multiple Exposures in Pregnancy	
	Donald R. Mattison, Risk Sciences International	
10:15 AM–10:40 AM	Networking Break—Aspen Foyer	
10:40 AM–11:05 AM	DNTS 21: Alcohol and Nicotine-Induced Epigenetic Changes (miRNAs)	
	Rajesh C. Miranda, Texas A&M Health Sciences Center	
11:05 AM–11:30 AM	DNTS 22: Epigenetic Changes Induced by Prenatal Nicotine and Cocaine Exposure	
	Pradeep Bhide, Florida State University	
11:30 AM–11:35 AM	Concluding Remarks	
	Jeffrey R. Wozniak, University of Minnesota	
11:35 AM–12 Noon	Panel Discussion	
12:00 Noon–1:30 PM	**Lunch on your own**	
12:00 Noon–1:30 PM	**NTT Editorial Board Luncheon**	**Torreys Peak**
	(For Board Members Only)	

1:30 PM–3:10 PM	**DNTS Symposium**	**Colorado Ballroom B**
	Prenatal Electronic Cigarette Use: Mechanisms, Characteristics, and Outcomes	
	Chairperson: Gale A. Richardson, University of Pittsburgh School of Medicine	
1:30 PM–1:35 PM	Introduction	
	Gale A. Richardson, University of Pittsburgh School of Medicine	
1:35 PM–1:55 PM	DNTS 23: Effects of Prenatal Nicotine Exposure on Adolescent Dopamine Systems	
	Frances Leslie, University of California at Irvine School of Medicine	
1:55 PM–2:15 PM	DNTS 24: Electronic Cigarette Use in Pregnancy: Patient and Provider Perspectives	
	Katrina Mark, University of Maryland School of Medicine	
2:15 PM–2:35 PM	DNTS 25: Perceptions and Use of Electronic Cigarettes during Pregnancy: Implications for Infant Outcomes	
	Laura Stroud, Brown Medical School	
2:35 PM–2:55 PM	DNTS 26: Pathways from Prenatal Tobacco Exposure to Electronic Cigarette Use	
	Natacha M. DeGenna, University of Pittsburgh School of Medicine	
2:55 PM–3:10 PM	Discussion	
3:15 PM–4:15 PM	**Elsevier Distinguished Lecturer**	**Colorado Ballroom B**
	DNTS 27: **Parental Stress and Epigenetic Programming of the Developing Brain**	
	Chairperson: Gregg D. Stanwood, Florida State University	
	Lecturer: Tracy Bale, University of Pennsylvania	
4:15 PM–5:30 PM	**DNTS Business Meeting and Awards**	**Colorado Ballroom B**
5:30 PM–7:30 PM	**Poster Session and Exhibits**	**Mt. Sopris**
	(Joint with the Teratology Society and OTIS)	

DNTS P01: Adolescent methylmercury exposure: effects on behavioral flexibility, delay discounting, fixed-ratio performance, and gene expression in the prefrontal cortex. Steven R. Boomhower, M. Christopher Newland, *Auburn University, Auburn, AL, USA*

DNTS P02: Prenatal thyroid hormone insufficiency diminishes short-term object recognition memory in Long-Evans rats. Megan Sieg [1], Catherine Townes [1], Rekha Balachandran [1], Mary Gilbert [2], Paul Eubig [1]. *[1] Department of Comparative Biosciences, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA [2] U.S. Environmental Protection Agency, National Health and Environmental Effects Research Laboratory, Toxicity Assessment Division, Research Triangle Park, N, USA*

DNTS P03: Potential Systematic Evaluation Frameworks of Mechanistic Data for Developmental Neurotoxicity Outcomes. Laura M. Carlson [1], William Mundy [2], Elaine M. Faustman [3], Deborah A. Cory-Slechta [4], Christina Sobin [5], Frances Champagne [6], Sue Makris [7], Andrew Kraft [7]. *[1] National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Durham, NC, USA [2] National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Durham, NC, USA [3] School of Public Health, Institute for Risk Analysis and Risk Communication, University of Washington, Seattle, WA, USA [4] Department of Environmental Medicine, University of Rochester Medical School, Rochester, NY, USA [5] University of Texas El Paso, El Paso, TX, USA [6] Department of Psychology, Columbia University, New York, NY, USA [7] National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington D.C., USA*

DNTS P04: The role of chemical speciation for manganese-induced developmental neurotoxicity through disrupting cross-talking pathways and its implication for manganese in neurodegeneration. Raul Hernandez [1], Montserrat Carrascal [2], Joaquin Abian [2], Bernhard Michalke [3], Marcelo Farina [4], David Park [5], Yasmilde González [5], Cristina Suñol [6]. *[1] Federal University of São Paulo, Diadema, Canada [2] CSIC/UAB Proteomics Laboratory, Institut d'Investigacions Biomèdiques de Barcelona, IIBB-CSIC, IDIBAPS, Barcelona, Spain [3] Helmholtz Zentrum München GmbH, German Research Center for Environmental Health, Research Unit Analytical BioGeoChemistry, Neuherberg, Germany [4] Departamento de Bioquímica, Centro de Ciências Biológicas, Campus Universitário, Trindade, Bloco C. Universidade Federal de Santa Catarina, Florianópolis, Brazil [5] Cellular and Molecular Medicine. Faculty of Medicine. University of Ottawa, Ottawa, Canada [6] Department of Neurochemistry and Neuropharmacology. Institut d'Investigacions Biomèdiques de Barcelona, IIBB-CSIC, IDIBAPS, CIBERESP, Barcelona, Spain*

DNTS P05: The behavioral and cognitive effects of chronic taurine exposure in C57BL/6 J mice: a dose-response study. Yislain Villalona, Jamie Weimer, Lisa Massie, Katelyn Dunn, Junessa Lanada, Cecile Marczinski, Christine Curran. *Northern Kentucky University, Highland Heights, KY, USA.*

DNTS P06: Developmental deltamethrin exposure causes adult learning and memory deficits. Emily Pitzer [1,2], Rebecca Bailey [1,2], Michael Williams [1,2], Charles Vorhees [1,2]. *[1] University Of Cincinnati College of Medicine, Cincinnati, OH, USA [2] Division of Neurology, Cincinnati Children's Research Foundation, Cincinnati, OH, USA*

DNTS P07: Does High Quality Maternal Care Ameliorate the Effects of Prenatal Stress? Leah Grande [1], Curt Sandman [2], Laura Glynn [2,3], Elysia Davis [1]. *[1] University of Denver, Denver, CO, USA [2] University of California Irvine, Irvine, CA, USA [3] Chapman University, Orange, CA, USA*

DNTS P08: Exposure to Traumatic Events in Childhood Shapes Stress Physiology during Pregnancy: Implications for the Intergenerational Transmission of Risk. Danielle Swales [1], Stephanie Stout [1], Laura Glynn [2], Curt Sandman [2], Deborah Wing [3], Elysia Davis [1]. *[1] Department of Psychology, University of Denver, Denver, CO, USA [2] Department of Psychology, Chapman University, Orange, CA, USA [3] Obstetrics and Gynecology, University of California, Irvine, Irvine, CA, USA*

DNTS P09: Identifying Predictors of Intimate Partner Violence during Pregnancy to Deter the Intergenerational Transmission of Maternal and Fetal Risk. Victoria Atzl, BS [1], Angela Narayan, PhD [1], Luisa Rivera, MPH [2], Alexandra Ballinger, BS [3], Melanie Thomas, MS, MD [3], Alicia Lieberman, PhD [3]. *[1] University of Denver, Denver, CO, USA [2] Emory University, Atlanta, GA, USA [3] University of California, San Francisco, San Francisco, CA, USA*

DNTS P10: Predictors of Substance Use Disorders among Emerging Adults with Prenatal Cocaine Exposure. Sonia Minnes [1,2], Meeyoung Min [1,2], June-Yung Kim [1,2], Sun Kyung Kim [1,2], Paul Weishampel [1,2], Lynn Singer [1,3]. *[1] Case Western Reserve University, Cleveland, OH, USA [2] Mandel School of Applied Social Science, Cleveland, OH, USA [3] School of Medicine, Cleveland, OH, USA*

DNTS P11: Prenatal and postnatal tobacco and cannabis exposure: Effects on focused attention in infancy. Rina Eiden [1], Shannon Shisler [1], Pamela Schuetze [2]. *State University of New York, Buffalo, NY, USA [2] Buffalo State College, Buffalo, NY, USA*

DNTS P12: Placental CRH predicts risk of preterm imminent delivery: Implications for the timing of betamethasone administration. Leah Grande* [1], Danielle Swales* [1], Michelle Edelmann [1,4], Curt Sandman [2], Laura Glynn [2,3], Deborah Wing [2], Elysia Davis [1] (Note: *First and second authors

contributed equally). [1] *University of Denver, Denver, CO, USA* [2] *University of California Irvine, Irvine, CA, USA* [3] *Chapman University, Orange, CA, USA* [4] *University of Colorado Anschutz Medical Campus, Aurora, CO, USA*

DNTS P13: Associations of maternal prenatal stress with measures of cognition in 4.5-month-old infants.
Francheska M. Merced-Nieves [1,2], Salma Musaad [4], Andrea Aguiar [2,3], Kelsey L.C. Dzwilewski [1,2], Susan A. Korrick [5,6], Susan L. Schantz [1,2,3]. [1] *Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana, IL, USA* [2] *Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, IL, USA* [3] *Department of Comparative Biosciences, University of Illinois at Urbana-Champaign, Urbana, IL, USA* [4] *Deparment of Human Development and Family Studies, University of Illinois at Urbana-Champaign, Urbana, IL, USA* [5] *Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA* [6] *Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA*

DNTS P14: Associations of adolescent exposure to Polychlorinated Biphenyls or Polybrominated Diphenyl Ethers with cognitive flexibility in children of sports anglers. Supida Monaikul [5], Joseph Gardiner [3], Natawut Monaikul [2], Andrea Aguiar [1], Paul Kostyniak [4], Susan Schantz [1]. [1] *University of Illinois, Urbana-Champaign, Urbana, IL, USA* [2] *University of Illinois at Chicago, Chicago, IL, USA* [3] *Michigan State University, East Lansing, MI, USA* [4] *University of Buffalo, Buffalo, NY, USA* [5] *Experimur, Chicago, IL, USA*

DNTS P15: Altered Cocaine-induced Sensitization in Middle-aged Rats Following Gestational Exposure to Cocaine and/or Nicotine. Sonya K. Sobrian, Carlana Ramlochansingh, Jewel Wright, Daniella Kuhn. *Howard University College of Medicine, Washington, DC, USA*

DNTS P16: An Assessment of Spatial Learning and Memory using the Morris Water Maze Following Adolescent Nicotine Exposure in Adult Long-Evans Rats. Evan Youker, Korinna Sherman, Greg Butcher, Laura Pickens. *Thiel College, Greenville, PA, USA*

DNTS P17: Developmental Exposure to Mild Variable Stress: Adult Offspring Performance in Trace Fear Conditioning after Prenatal and Postnatal Stress. Jason Franklin, Virginia Moser, Wendy Oshiro, Tracey Beasley, Kathy McDaniel, David Herr. *U.S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC, USA*

DNTS P18: Learning and memory deficits from neonatal methamphetamine in Sprague-Dawley rats are not ameliorated by blockade of reactive oxygen species. Michael Williams, Sarah Jablonski, Charles Vorhees. *Division of Neurology, Cincinnati Children's Research Foundation, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA*

DNTS P19: Thyroid Hormone Insufficiency Induced by Perchlorate in the Pregnant Rat Results in a Cortical Heterotopia in the Brains of Offspring. Mary Gilbert [1], Spring Stephanie [1,2], Jermaine Ford [1], Richard Ford [1,2], Susan Thomas [1,2], Katherine O'Shaughnessy [1,2], Carmen Wood [1]. [1] *US EPA, Research Triangle Park, NC, USA* [2] *ORISE, Oak Ridge, TN, USA*

DNTS P20: Neurobehavioral and neuroanatomical consequences of cell-type specific inactivation of dopamine D2 receptors in the mouse brain. Gloria Lee [1], Devon L. Graham [1], Lisa R. Anderson [1], Taylor S. Trammell [1], Marcelo Rubinstein [2], Gregg Stanwood [1]. [1] *Biomedical Sciences and Center for Brain Repair, Florida State University College of Medicine, Tallahassee, USA* [2] *Instituto de Investigaciones en Ingeniería Genética y Biología Molecular, Consejo Nacional de Investigaciones Científicas y Técnicas, Buneos Aires, Argentina*

DNTS P21: Delineating the role of GLP-1R in various aspects of cocaine reward. Devon Graham [1], Michael Campos [2], Heather Durai [2], Anders Fink-Jensen [3], Aurelio Galli [2], Gregg Stanwood [1]. [1] *Florida State University College of Medicine, Tallahassee, FL, USA* [2] *Vanderbilt University, Nashville, TN, USA* [3] *University of Copenhagen, Copenhagen, Denmark*

7:30 PM–10:00 PM	**Teratology Society and MARTA Student Career Event** (Open to Teratology Society, DNTS, and OTIS Students and Postdoctoral Fellows)	**Crystal Peak C**

Tuesday, June 27, 2017

8:00 AM–5:00 PM	**DNTS Registration**	**Colorado Ballroom B Foyer**
7:30 AM–8:00 AM	**Morning Coffee and Pastries** (Joint with the Teratology Society)	**Aspen Foyer**
8:00 AM–9:00 AM	**Platform Session 2** *Chairperson: Rina Eiden, State University of New York at Buffalo*	**Colorado Ballroom B**
8:00 AM–8:20 AM	DNTS 28: Prenatal Cocaine Exposure and Trajectories of Externalizing Behavior Problems from Age 4 to 12 *Meeyoung Min, Sonia Minnes, Hyunyong Park, June-Yung Kim, Lynn Singer, Case Western Reserve University and Sungshin Women's University*	
8:20 AM–8:40 AM	DNTS 29: Circadian Disruption Affects Initial Learning but not Cognitive Flexibility In an Automated Set-Shifting Task in Adult Long-Evans Rats *Rekha Balachandran, Audrey Robertson, Megan Mahoney, Paul Eubig, University of Illinois Urbana Champaign*	
8:40 AM–9:00 AM	DNTS 30: Latrophilin-3: A new model of ADHD-like behavior in a rat knockout model *Charles Vorhees, Jillian Hufgard, Jenna Sprowles, Gary Gudelsky, Michael Williams, Cincinnati Children's Research Foundation and University of Cincinnati*	
9:05 AM–12:30 PM	**Public Affairs Symposium** **The Toxicology of Tobacco Smoke and E-Cigarette Use during Pregnancy** (Joint with the Teratology Society) *Chairpersons: Ludmila Bakhireva, University of New Mexico and John M. Rogers, US Environmental Protection Agency*	**Aspen Ballroom**
9:05 AM–9:15 AM	Introduction	
9:15 AM–9:55 AM	DNTS 31: Tobacco as a Reproductive and Developmental Toxicant *John M. Rogers, US Environmental Protection Agency*	

9:55 AM–10:35 AM	DNTS 32: *E*-Cigarettes: What Are They, What Do They Do, and What Are Potential Impacts on Pregnancy Outcomes? *Alison Breland, Virginia Commonwealth University*	
10:35 AM–10:50 AM	Break	
10:50 AM–11:30 AM	DNTS 33: The Role of Nicotine in the Effects of Maternal Smoking during Pregnancy on Lung Development and Childhood Respiratory Disease *Virender K. Rehan, University of California–Los Angeles*	
11:30 AM–12:10 PM	DNTS 34: Neurodevelopmental Toxicity of Tobacco Smoke and Nicotine *Edward D. Levin, Duke University*	
12:10 PM–12:30 PM	Discussion	
12:30 PM–2:00 PM	**Lunch on Your Own**	
2:00 PM–3:00 PM	**Platform Session 3** *Chairperson: Mary Gilbert, US EPA*	**Colorado Ballroom B**
2:00 PM–2:20 PM	DNTS 35: Effects of Manganese Body Burden on Fine Motor Skills in Children Aged 6–14 Years *Lonnie Sears, Lindsay Tompkins, Carol Hanchette, Barbara Polivka, Kristina Zierold, University of Louisville*	
2:20 PM–2:40 PM	DNTS 36: Low-level mercury exposure from fish consumption: Associations with childhood neurodevelopment *Yingying Xu, Kim Dietrich, Jane Khoury, Heidi Sucharew, Aimin Chen, Kim Yolton, Cincinnati Children's Hospital Medical Center and University of Cincinnati*	
2:40 PM–3:00 PM	DNTS 37: Polychlorinated Biphenyl Mixture Evaluations: A Case Study for Neurotoxicity *Laura M. Carlson, Prachi Pradeep, Jeff Gift, Chris Gennings, Grace Patlewicz, Geniece Lehmann, U.S. Environmental Protection Agency, Icahn School of Medicine at Mount Sinai, and Oak Ridge Institute for Science and Education*	
3:05 PM–5:30 PM	**Marijuana and Child Development Symposium** (Joint with the Teratology Society and OTIS) *Chairpersons: Diana Dow-Edwards, SUNY/Downstate Medical Center and Susan* L. *Makris, US Environmental Protection Agency*	**Aspen Ballroom**
3:05 PM–3:10 PM	Introduction *Diana Dow-Edwards, SUNY/Health Science Center*	
3:10 PM–3:35 PM	DNTS 38: Dynamic Changes in Endocannabinoid Signaling During Adolescence: Implications for Substance Use and Psychopathology *BJ Casey, Yale University*	
3:35 PM–4:00 PM	DNTS 39: Counseling Women About Prenatal Marijuana Use: Weeding through the Data *Torri D. Metz, University of Colorado–Denver*	
4:00 PM–4:15 PM	Break	
4:15 PM–4:40 PM	DNTS 40: Cannabis and the Adolescent Brain: What Does the Evidence Say? *Joanna Jacobus, University of California–San Diego*	
4:40 PM–5:05 PM	DNTS 41: Cannabinoids for Treatment of Pediatric Epilepsy: The Hype and the Evidence *Amy R. Brooks-Kayal, University of Colorado–Denver*	
5:05 PM–5:30 PM	DNTS 42: Cannabis Policy: Challenges and Future Directions *Susan R.B. Weiss, National Institute on Drug Abuse*	
6:30 PM–9:30 PM	**DNTS Social Event**	

Wednesday, June 28, 2017

7:45 AM–8:00 AM	**Morning Coffee and Pastries** (Joint with the Teratology Society)	**Aspen Foyer**
8:00 AM–9:30 AM	**Platform Session 4** *Chairperson: Devon Graham, Florida State University*	**Colorado Ballroom B**
8:00 AM–8:30 AM	DNTS 43: **Richard Butcher New Investigator Award:** Perinatal antidepressant exposure influences spatial learning and memory, acoustic startle response, anxiety, and locomotor activity in adult Sprague-Dawley rats *Jenna Sprowles, Cincinnati Children's Research Foundation and University of Cincinnati College of Medicine*	
8:30 AM–8:50 AM	DNTS 44: Prenatal exposure to tobacco smoke extract and some of its constituents in rats cause persisting neurobehavioral effects in the offspring *Edward Levin, Marty Cauley, Brandon Hall, Yael Abreu-Villaça, Shaqif Junaid, Hannah White, Abtin Kiany, Duke University*	
8:50 AM–9:30 AM	DNTS 45: **Special Lecture:** Interaction: Considering the Social World in Developmental Neurotoxicology *Joseph Grzywacz, Florida State University*	
9:35 AM–12:30 PM	**An Update on the Zika Virus Symposium** (Joint with the Teratology Society) *Chairpersons: José F. Cordero, University of Georgia and Sonja A. Rasmussen, Centers for Disease Control and Prevention*	**Aspen Ballroom**

9:35 AM–9:50 AM	Introduction *Chairpersons: José F. Cordero, University of Georgia and Sonja A. Rasmussen, Centers for Disease Control and Prevention*	
9:50 AM–10:25 AM	DNTS 46: The Zika Epidemic: An Update from the CDC *Margaret Honein, Centers for Disease Control and Prevention*	
10:25 AM–11:00 AM	DNTS 47: Neurobehavioral Aspects of Zika Virus *Vanessa Van der Linden, Association for Assistance of Disabled Children*	
11:00 AM–11:30 AM	Warkany Tea (see below)	
11:30 AM–12:05 PM	DNTS 48: Zika Infection: From Basic Science to Treatment *Alysson Renato Muotri, University of California–San Diego*	
12:05 PM–12:30 PM	Panel Discussion	
11:00 AM–11:30 AM	**Warkany Tea** (Joint with the Teratology Society)	**Aspen Foyer**
12:30 PM	**DNTS 2017 Adjourned**	

Oral Presentations

DNTS 01

Eliminating Congenital Zika Syndrome: Lessons Learned from Rubella Elimination (TS Josef Warkany Lecture)

José F. Cordero

University of Georgia, Athens, GA, USA

Emergence of rubella in the 1950s marked the first recognized teratogenic infection and raised concerns that other infections in pregnancy may affect the developing fetus. Although other teratogenic infectious agents have been identified, Zika is the first recognized vector-borne teratogenic infection. Lessons learned by the emergence of congenital rubella syndrome offer opportunities to address Zika teratogenesis. Unlike other vector-borne diseases, Zika, also transmitted through, person to person sexual contact, and possibly through blood transfusion raises new questions about its transmission biology and how its genome differs from other flaviviruses with exclusive mosquito transmission. The Zika mechanism of teratogenesis has not been fully elucidated, but its neurotropism, cell apoptosis, and subsequent brain disruption appears to be one route. On-going surveillance of birth defects must focus on examining the spectrum of Zika teratogenesis. Understanding the mechanisms of teratogenesis and virus transmission is an urgent matter to inform development of drugs and biological to prevent infections as well as effective vaccine development. Given the severity of Zika teratogenesis, a focus for vaccine development should be on identifying a highly effective vaccine for the population and in specific for women of childbearing age that can prevent Zika infection. While a vaccine and Zika control becomes a reality, prevention of Zika infection among women of reproductive age has become a major global health issue. The need for effective and accessible planning programs in Zika endemic areas where nearly half of pregnancies are unintended has become a major priority. In a similar fashion, Zika emergence has brought vector control efforts to new level of urgency, particularly in the development of novel approaches for controlling and eliminating Aedes mosquito species. In summary, Zika emergence represents a call for the best of team science to understand the biology of Zika infection, develop novel vector control, treatment strategies, innovative approaches for prevention, and eventual elimination of this challenging teratogen.

DNTS 02

Reproducibility through rigor and transparency – the CSR perspective

Jana Drgonova

Neurotoxicology and Alcohol Study Section (NAL), Center for Scientific Review, NIH, Bethesda, MD, USA

To support the highest quality science and public accountability in the conduct of biomedical research, the NIH has updated review criteria for research grant and mentored career development applications. The goal of these Rigor and Transparency efforts is to emphasize four areas that may need more explicit attention by applicants and reviewers: 1) Scientific Premise, which reflects the quality of data upon which the hypothesis is based. This includes both the preliminary data, and referenced publications, and sufficient evaluation of their strengths and weaknesses needs to be supplied. Scientific premise is addressed in review as part of the Significance criterion. 2) Scientific Rigor is the strict application of the scientific method to ensure robust, reproducible and unbiased experimental design, methodology, analysis, interpretation and reporting of results. Sufficient information needs to be provided for the study to be assessed and reproduced. 3) Consideration of Relevant Biological Variables that are critical factors affecting the outcomes (for example: sex, age, source, weight, genetic strain). Consideration of sex as a biological variable (SABV) is required for all studies involving human subjects or vertebrate animals. SABV and Scientific Rigor are assessed in review as part of the Approach criterion. 4) Authentication of Key Biological and/or Chemical Resources, which can influence the research outcome and which may differ between laboratories or change over time, is needed to ensure validity and reproducibility of the results. However, the inadequacy of the authentication plan does not affect the overall impact score, as these issues can be resolved before the project is funded. Close attention to the four areas of Rigor and Transparency during the review process should ensure that NIH is funding the best and most rigorous science.

DNTS 03

101 Ways to Mess Up a Mouse Study: The Rocky Road to Rigor and Reproducibility

Christine Perdan Curran [1], Amy Ashworth [1], Molly Griffith [2], Jocelyn Fowler [1], Helen Garber [1], Amber Evans [1], Rikki Floyd [1], Cellestine Kamau-Cheggeh [1], Emily Altenhofen [1], Ashton Samuels [1], Yislain Villalona[1], Katelyn Dunn[1], Junessa Lanada[1]

[1] Northern Kentucky University, Highland Heights, KY, USA [2] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Ever since Crabbe et al. (1999) reported differential results from identically designed studies conducted in three separate laboratories, we've recognized that factors outside of the investigator's control can confound the results of rodent behavior studies. More recently, Sorge et al. (2014) reported that mice showed a differential stress response when exposed to male odors v. female odors, raising concerns about factors under direct control of the investigator. In our own studies, we have documented behavioral changes caused by the timing of cage changes, odors from disinfectants, construction noise, exposure to rat odor. We identified substrain differences between C57BL6/J and C57BL6/N in three of the most commonly used neurobehavior tests – Morris water maze, rotarod and fear conditioning. Inbred mouse strains offer the advantages of reduced genetic variability and potentially behavioral variability. This can enhance studies of knockout and knock-in mice and more quickly identify gene function. Unfortunately, inbreeding also increases the incidence and prevalence of deleterious traits such as malocclusions, alopecia, and microphthalmia. The presence of unrecognized passenger mutations can also confound the interpretation of results. Genetic drift is another major

factor that is often unrecognized when maintaining colonies of genetically modified mice. Examples of significant changes affecting behavioral studies include a subpopulation (B6JOlaHsd) with a mutation in the alpha synuclein gene (*Snca*) and a mutation in the cytoplasmic FMR1 interacting protein 2 gene *Cyfip* found in B6N mice that results in an attenuated response to cocaine and methamphetamine. These and other examples will be discussed with the goal of moving toward a consensus on best practices in the conduct and reporting of neurobehavioral rodent studies. Supported by ES020053 and GM103436.

DNTS 04

Reducing the Wiggle Room in Data Generated from *C. elegans*

Vanessa Fitsanakis

King University, Bristol, TN, USA

C. elegans are an attractive model organism for numerous reasons, among one of more important of which is the fact that they exist as hermaphrodites. While this characteristic can potentially minimize the natural genetic variability, it does not eliminate it completely. Failure to recognize the importance of fertilization of hermaphrodites by *C. elegans* males can complicate studies built around the assumption that all future generations share the same genetic background. But potential genetic heterogeneity is not the only variable that should be considered when using these worms. Due to their short life span (approximately 22–24 days at 20 °C), temperature sensitivity (optimal growth and development from 18-22 °C), and the ability to enter a dauer stage, these organisms are much more sensitive to small changes in these parameters than other model organisms. Our lab has found that subtle changes in humidity, temperature, genetic background, and amount of bacteria on feeding plates can lead to changes in reproduction time or increase mortality, both of which may adversely affect the timing of later experiments. When specific endpoints are assessed, these environmental differences may result in variation between data generated on different days (interexperimental variation). For example, behavioral assay data from our lab indicate that control worms (N2 strain) compared to transgenic strains show differences in baseline movement profiles, lethality profiles, and uptake of the fluorescent dye TMRE, used to assess mitochondrial membrane potential. Data from other labs also indicate that the introduction of green fluorescent protein as a marker for endogenous protein expression can also differ based on the original strain used for the genetic cross. While differences attributable to strain/genetic background or environmental variations leading to "data wiggle" are not completely unanticipated, this has not always been appreciated by toxicologists who are new to using *C. elegans*.

DNTS 05

Translational Studies on the Role of Developmental Pyrethroid Exposure in ADHD: From Cells to Zebrafish to Mice to Humans and Back Again

Jason Richardson

Northeast Ohio Medical University, Rootstown, OH, USA

Attention-deficit hyperactivity disorder (ADHD) is a clinically heterogeneous disorder characterized by core features of impulsivity, hyperactivity, and attention deficits, which is estimated to affect 8–12% of school-aged children worldwide. While ADHD is a complex disorder with significant genetic contributions, no single gene has been linked to a significant percentage of cases, suggesting that environmental factors or gene-environment interactions may contribute to the etiology of ADHD. Several environmental factors have been identified as potential risk factors for ADHD, including prenatal exposure to alcohol, tobacco, and lead. However, studies of environmental risk factors for ADHD have been hindered by the difficulties of quantifying environmental exposures in humans along with the impossibility of conducting experimental exposures of humans due to ethical considerations. Here, I will describe our collaborative work incorporating multiple models to determine mechanisms by which pyrethroids alter the developing nervous system, the development of alternative animal models to increase throughput of our work and the translation of our findings to human epidemiological studies. Data generated demonstrate that developmental exposure of mice to the pyrethroid pesticide deltamethrin produces neurochemical and behavioral dysfunction similar to that observed in ADHD patients. Cell culture models allowed for the identification of mechanism. Studies with zebrafish reveal the ability to transfer the mouse model into zebrafish, which will allow for higher throughput screening of additional pyrethroids and take advantage of genetic tools. Finally, epidemiological data reveal that elevated urinary pyrethroid metabolite levels in children increases risk of ADHD diagnosis in children 2.3-fold and that the specific behavioral effects observed in children are similar to that observed in mice. Together, the data presented frame a multi-disciplinary and collaborative framework for pursuing translational research into the developmental neurotoxicity of pyrethroid pesticides and neurodevelopmental disorders. Supported in part by NIEHS R01ES015991, ES015991-S4, and P30ES005022.

DNTS 06.

Associations between Early Life Exposure to Traffic Related Air Pollution and Symptoms of Depression and Anxiety at Age 12 Years

Kimberly Yolton [1], Jane Khoury [1], Cole Brokamp [1], Rachel Severs [1], Christopher Wolfe [1], Zana Percy [2], Jeff Burkle [2], Kim Cecil [1], Grace LeMasters [2], Patrick Ryan [1]

[1] Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA [2] University of Cincinnati, Cincinnati, OH, USA

Air pollution has been associated with increased depression, anxiety, and risk of suicide in adults, but associations with mental health outcomes in children have not been studied. We examined the association between early life exposure to traffic related air pollution (TRAP) and internalizing symptoms of depression and anxiety at age 12 years in an established epidemiologic cohort study. Within the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), we calculated early life exposure to TRAP at 6 months (6 m) in 334 children using a previously developed and validated land use regression model. At age 12 years (12y), we assessed internalizing symptoms by parent report with the Behavior Assessment System for Children-2 (BASC2), and by child report with the Child Depression Inventory-II (CDI-II) short form and the Spence Children's Anxiety Scale (SCAS). Mothers completed the Beck Depression Inventory-II (BDI-II) and the Parenting Relationship Questionnaire (PRQ). Covariates retained in final regression models included child sex and race, child cotinine at age 12y, maternal depression, and PRQ scales. Child blood lead level at age 12y and early life cotinine measures; maternal age at delivery, education, and marital status; and household income were not significant covariates and were not included in final models. In multivariable analyses of child self-reported internalizing symptoms, early life TRAP exposure was not significantly associated with parent-reported child internalizing symptoms on the BASC2. In contrast, early life TRAP exposure was significantly associated with child-reported depression on the CDI-II ($\beta = 13.20$, se = 3.75, $p = 0.005$) and anxiety on the SCAS ($\beta = 7.31$, se = 3.05, $p = 0.02$). TRAP exposure at 12y was not significantly associated with either parent or child reported symptoms. Early life TRAP exposure was positively associated with self-reported, but not parent-reported, depression and anxiety symptoms in children assessed at age 12 years. These findings suggest that the negative impact of TRAP on mental health outcomes that has been reported among adults may also be present during childhood. *Funding: Funding for this project came from the National Institutes of Environmental Health Sciences (NIEHS) R01 ES019890, R01 ES11170, R01 ES019890, P30 ES006069, T32 ES10957.*

DNTS 07

Transgenerational effects of di-(2-ethylhexyl) phthalate on behavior and hippocampal gene expression in male and female mice

Katherine M. Hatcher [1,3], Jari Willing [2,3], Catheryne Chiang [1], Saniya Rattan [1], Janice M. Juraska [2,3], Jodi A. Flaws [1], Megan M. Mahoney [1,3]

[1] *Department of Comparative Biosciences, University of Illinois at Urbana-Champaign, Urbana, IL, USA* [2] *Department of Psychology, University of Illinois at Urbana-Champaign, Champaign, IL, USA* [3] *Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana, IL, USA*

Phthalates, including di-(2-ethylhexyl) phthalate (DEHP), are a class of industrial plasticizers commonly found in polyvinyl chloride plastic products, including food packaging, cosmetics, medical devices, and children's toys. DEHP, one of the most commonly used phthalates, exhibits endocrine-disrupting characteristics and exposure leads to reproductive and behavioral abnormalities. Direct exposure to DEHP is capable of modifying behavior, potentially by disrupting gene expression in the brain. Interestingly, increasing evidence indicates that DEHP can alter the reproductive system, behavior, and neural gene expression three or more generations following exposure. However, the extent of these transgenerational effects remain widely unexplored. Here, we modeled transgenerational exposure by orally dosing pregnant CD-1 mice daily with either tocopherol-stripped corn oil (vehicle control) or concentrations of DEHP (20 or 200 μg/kg/day; 500 or 750 mg/kg/day) from gestational day 10.5 until birth to produce the F1 generation. Female offspring from the F1 and then F2 generations were bred with untreated, unrelated males to produce the F3 generation, yielding the first generation not exposed to DEHP. The elevated plus maze and Morris water maze were used to assess anxiety-like behavior and spatial memory, respectively, in F3 intact adult males and females. Following behavior testing, brains were collected and bilateral hippocampal tissue punches were taken for gene expression analyses using quantitative PCR. For analysis of hippocampal gene expression, we selected two genes relevant to anxiety-like behavior, glucocorticoid receptor (GR) and estrogen receptor 2 (ESR2), and one gene relevant to epigenetic inheritance, DNA methyltransferase 3a (Dnmt3a). Behavioral tests revealed that transgenerational DEHP exposure decreases anxiety-like behavior in the elevated plus maze for females but not males. DEHP exposure did not affect spatial memory. Preliminary gene expression data indicate that transgenerational DEHP exposure modifies GR and Dnmt3a gene expression in the hippocampus of males but not females; however, these data are not statistically significant. Together, these data add to the growing body of evidence showing that transgenerational DEHP exposure can modify behavior and brain gene expression. Funding: National Institute Health grant [P01 ES022848 and Environmental Protection Agency grant [RD-83459301].

DNTS 08

Transient Maternal Hypothyroidism Alters Neural Progenitors Resulting in Abnormal Brain Development

Katherine O'Shaughnessy [1,2], Susan Thomas [2], Jermaine Ford [2], Richard Ford [1,2], Mary Gilbert [2].

[1] *Oak Ridge Institute for Science and Education, Oak Ridge, TN, USA* [2] *US EPA, Research Triangle Park, NC, USA*

Heterotopias are a birth defect of the brain and have varying etiologies in humans. They are characterized as clusters of mislocalized neurons and are associated with disorders such as autism, epilepsy, and learning disabilities. We have previously characterized the robust penetrance of a cortical heterotopia in a rat model, induced by low/moderate levels of thyroid hormone (TH) disruption during neurodevelopment. This structural abnormality is highly reproducible, and its severity is dose-dependent; however, little is known about the cellular and molecular alterations that link decreased TH to this phenotype. To elucidate the mechanisms of this adverse development we first determined the precise period of TH sensitivity. Our ongoing work has demonstrated that prenatal TH insufficiency is necessary for heterotopia formation. Therefore, we treated pregnant rats with a moderate dose (10 ppm) of propylthiouracil (PTU) to induce hypothyroidism at four distinct gestational windows. The presence and size of the heterotopia was quantified, in addition to serum and brain TH levels across multiple developmental stages. We show that five days of PTU treatment during the perinatal period (GD19-PN2) is both sufficient and necessary for heterotopia formation. Beginning in the early postnatal brain, we find that mature neurons begin to collect in the periventricular space of treated animals. Quantitative gene expression analyses of this region show significant changes in a suite of genes, including downregulation of *Spred1*, a negative regulator of Ras–MAPK–ERK signaling. Others have shown that transient downregulation of *Spred1* in the mouse brain results in a heterotopia by increasing stem cell self-renewal and progenitor proliferation in the ventricular zone. Consistent with these findings, we also see upregulation of *Pax6*, a marker of radial glial progenitors. We then show abnormalities in radial glial morphology and organization within the hypothyroid brain, which suggests that abnormal cell migration may underlie heterotopia formation. These data indicate that acute TH disruption induces a cortical malformation, and provides a potential functional role between hypothyroidism and dysregulation of neural progenitors in the developing brain. *This work does not reflect EPA policy.*

DNTS 09

Maternal overnutrition and trichloroethylene co-exposure augments neurotoxicity in offspring in an autoimmune-prone mouse model.

Sarah Blossom [2], Jakeira Davis [1], Oleksandra Pavliv [2], Kathleen Gilbert [2], Frank Simmen [1].

[1] *Universitiy of Arkansas for Medical Sciences, Little Rock, AR, USA* [2] *Arkansas Children's Research Institute, Little Rock, AR, USA.*

Neuroinflammation and impaired glutathione redox balance and methyl metabolism are associated with neurotoxicity. Oxidative stress and inflammation are increased with developmental exposure to the industrial solvent and environmental pollutant, trichloroethylene (TCE) in autoimmune prone MRL+/+ mice. Maternal obesity/ovenutrition can also promote neuroinflammation. We hypothesized that maternal overnutrition would augment these effects in offspring of TCE exposed mice. Four weeks pre- mating, mice were exposed to vehicle or an environmentally-relevant dose of TCE (0.05 μg/ml ~16 μg/kg/day). The dams in both groups were fed either standard diet (17% kcal derived from fat or obesogenic diet (45% kcal derived from fat). The pups were exposed in utero and throughout lactation. The exposure continued directly for 7 weeks post weaning. At 10 weeks of age, mice were switched to standard diet and water until 20 weeks of age in order to see if the effects persisted after exposure cessation. Brains were harvested from offspring and subjected to HPLC or qRT-PCR for the evaluation of redox/methyl metabolites, inflammatory factors, and enzymes involved in DNA methylation. Brain reactive antibodies were evaluated in sera by western blotting. The results showed a significant decrease in the ratio of reduced to oxidized glutathione by 34%, 49%, and 53%; obesogenic diet alone, TCE alone, and TCE/obesogenic diet (co- exposure) compared to controls, respectively. Methyl metabolites and DNA methyltransferases were also decreased in all exposure groups relative to control indicating DNA hypomethylation. This effect was most evident with co-exposure. There was a significant decrease in chemokine, CCL3 and neurotrophin, BDNF, involved in synaptic transmission, neuroplasticity, and memory. Interestingly, maternal overnutriton alone was sufficient to enhance brain-reactive antibodies. The results demonstrated neurotoxic effects with TCE and obesogenic diet co-exposure and suggest that nutritional intervention may reduce risk of neurotoxicity in the context of environmental toxicant exposure.

DNTS 10

Prenatal and postnatal tobacco and cannabis exposure: joint and bidirectional associations with child behavior problems

Rina Eiden [1], Junru Zhao [1], Meghan Casey [1], Shannon Shisler [1], Pamela Schuetze [2]

[1] *State University of New York, Buffalo, NY, USA* [2] *Buffalo State College, Buffalo, NY, USA*

Large numbers of women use both tobacco and cannabis during pregnancy but the joint effects of both substances are poorly understood. We examined joint effects of prenatal exposure to both substances, potential bidirectional associations between substance use and child behavior problems, and gender differences. The sample consisted of 251 women recruited in the first trimester of pregnancy and assessed once in each trimester. Based on maternal reports and biomarkers, 103 exposed to both tobacco and cannabis, 75 to tobacco only, and 73 in the control group. Mothers and children were assessed postnatally at 2, 9, 16, 24, and 36 months of child ages. Infant salivary cotinine (2 to 24 months) and maternal reports of postnatal tobacco and cannabis use (2 to 36 months) were obtained. Maternal reports of child behavior problems were measured at 24 and 36 months. We hypothesized potential bidirectional associations between child behavior problems and maternal postnatal substance use. Results were partially supportive of this hypothesis, and there were some gender specific effects. Results indicated prospective, bidirectional associations between behavior problems at 2 years and maternal postnatal marijuana use. Higher maternal marijuana use across the infant toddler period was predictive of higher behavior problems at 2 years, which in turn was prospectively predictive of higher maternal marijuana use a year later, even after accounting for within time associations and stability in marijuana use across time. An additional predictive pathway from postnatal infant/toddler tobacco exposure to higher behavior problems at 2 years was significant for girls but not boys. Analyses of group differences with prenatal exposure groups also indicated stronger associations for girls compared to boys. Tobacco exposed girls had higher anxiety/depression, emotion regulation problems, withdrawal/depression, and overall internalizing behavior problems compared to the other two groups, and were reported to have higher attention and sleep problems compared to the control group. Results highlight the importance of considering joint effects of tobacco and cannabis, point to bidirectional effects between maternal substance use and child behavior problems, add to the literature on gender differences in tobacco and cannabis exposure, and indicate generally stronger exposure effects for girls.

DNTS 11

Determining origins of increased obesity risk in children with FASD: Is a hyperphagic feeding phenotype the result of abnormal metabolic requirements or a reward system dysfunction?

Robyn Amos-Kroohs [1], David Nelson [2], Jeffrey Wozniak [3], Chi-Liang Eric Yen [2], Susan Smith [1].

[1] University of North Carolina Nutrition Research Institute, Kannapolis, NC, USA [2] University of Wisconsin-Madison, Madison, WI, USA [3] University of Minnesota, Minneapolis, MN, USA

Fetal Alcohol Spectrum Disorder (FASD) is the largest preventable neurodevelopmental disability. Although prenatal alcohol exposure (PAE) is associated with reduced growth trajectories, recent studies suggest that children with FASD may have increased obesity risk as they enter adolescence. In published survey results, we document disordered feeding behavior in these children. In comparison with typically developing children, we find that impaired satiety was common ($p < 0.001$): 23% were never full/satisfied, 29% constantly snacked, 27% ate too quickly, and 24% concealed food. Caregivers restrict food access to prevent overeating and children with FASD ate the equivalent of an additional meal/snack daily (4.9/d vs. 3.9/d; $p < 0.001$). To investigate whether this obesity risk was the result of a PAE-related metabolic disorder or related to the hyperphagic behavior, we developed a novel mouse model of gestational binge alcohol exposure. Pregnant C57Bl/6 J females were gavaged with 3 g/kg alcohol (ETOH) daily from gestational day 12.5 to 17.5 in two half doses, two hours apart. Maltodextrin (MD) and medium chain triglycerides (MCT) served as isocaloric nutritional controls. Sham (H2O) treatment controlled for gavage stress. Although ETOH pups were initially smaller than all other groups, weanling MCT, MD, and ETOH pups gained significantly more weight than did H2O offspring, regardless of sex. ETOH males had significantly increased adiposity compared with MD males ($p < 0.05$), but did not differ from other groups. Other metabolic assays, including glucose tolerance, were not significant except comparisons between added calorie groups (MD, MCT, and ETOH) and H2O controls. These data suggest that the previously reported effects of moderate PAE upon animal offspring metabolism reflect the contribution of added gestational calories, rather than the effects of alcohol itself. Interestingly, the ETOH offspring did not exhibit the specific hyperphagic phenotype in feeding behavior we documented in children with FASD. We believe this suggests an environmental influence on neurological mechanisms damaged by PAE such as behavioral regulation and the dopaminergic reward system. Future studies in affected children will focus on diet choice and food reward in the context of an obesogenic environment using a revised survey, biomarker analyses, and then associated with existing fMRI data.

DNTS 12

Patricia Rodier Mid-Career Award for Research and Mentoring - **Project Newborn: What We Have Learned from 20 Years of Research on Prenatal Cocaine Exposure**

Sonia Minnes

Case Western Reserve University, Cleveland, OH, USA

DNTS 13

Impact of early life methylmercury exposure on child neurodevelopment.

Susan Korrick

Brigham and Women's Hospital, Boston, MA, USA Harvard Medical School, Boston, MA, USA Harvard T.H. Chan School of Public Health, Boston, MA, USA

Methylmercury (MeHg) is a known developmental neurotoxicant. Studies initiated decades ago among populations in the Seychelles, New Zealand and Faroe Islands with MeHg exposures due to heavy fish or marine mammal consumption, established the basis for concerns about MeHg neurotoxicity in the general population. However, at common lower-level exposures, MeHg has not been consistently associated with adverse neurodevelopment. This presentation will review epidemiologic studies assessing the impact of low-level early life MeHg exposure on child neurodevelopment and identify factors that may contribute to inconsistent findings. Findings support a number of possible sources of variability in observed associations such as exposure timing (exposures during pre-natal development are generally more adverse than postnatal exposures) and the neurodevelopmental domain being measured with memory, verbal/language skills, and visual motor functions likely more sensitive to MeHg than other skills. This literature also demonstrates the potential for individual differences (for example, sex, genetics) and co-occurring exposures (for example, PCBs) to modify susceptibility to MeHg's neurotoxicity. One of the more pervasive and incompletely resolved issues impacting this research is how best to address the potential for confounding by nutrition. Because fish consumption is the primary route of MeHg exposure for most populations, disentangling the potential adverse impacts of MeHg from the likely nutritional benefits of fish is a challenge and one that likely contributes substantial uncertainty to findings from observational epidemiologic research. Indeed, a number of studies have reported associations of MeHg with better neurodevelopment, a paradoxical finding attributed to negative confounding by nutrition. Recent research among populations for which rice, rather than fish, is the predominant route of MeHg exposure, shows promise as a context for assessing MeHg's impacts independent of

dietary benefits. These challenges reflect the complexities of studying health risks associated with food contaminants, especially foods such as fish with high nutritional value. They also highlight the importance of understanding low-level MeHg's potential contribution to adverse neurodevelopment to better inform guidelines for exposure remediation, including remediation via dietary recommendations.

DNTS 14

Assessment of Methyl Mercury and Fish Oil Effect on Neurodevelopment in Developing A Risk/Benefit Model of Fish Consumption

Gary Ginsberg

Connecticut Department of Public Health, Hartford, CT, USA

The developmental neurotoxicity of methyl mercury has been demonstrated in human populations with evidence of effects on cognitive function in the Faroe Islands cohort used to derive a reference dose (RfD) by USEPA. While that RfD is useful for risk assessment in general, when it comes to fish consumption sole reliance on risk-based approaches can lead to an underappreciation of the benefits associated with fish oils and other nutrients. Epidemiology studies have generally shown fish consumption during pregnancy to have neurodevelopmental benefits in spite of the intake of methyl mercury. Therefore, the goal of this research has been to develop a quantitative risk/benefit model that evaluates the adverse effect of methylmercury and the beneficial effect of omega-3 fatty acids (O-3FA) on neurodevelopment from fish consumption of particular species. This project developed slope factors for the effects of these fish constituents on neurodevelopment based upon evidence of prenatal exposure having impacts on visual recognition memory (VRM), an early life indicator of IQ. Initial modeling estimates have been refined by calibrating to epidemiological data and comparing to risk and benefit slope factors derived by the World Health Organization and US FDA. This modeling approach has enabled the evaluation of both locally caught and market purchased fish species based upon datasets describing the O-3 FA and mercury content of these species. The implications of such an approach for fish consumption advisories are that: 1) provides a tool to evaluate the health effects of fish consumption in addition to the mercury RfD (risk only approach); 2) it provides an evidence-based rationale for advising greater fish consumption in those cases where in spite of the presence of mercury, the modeling predicts a clear benefit; 3) it allows for ready comparison of risks and benefits across seafood choices; and 4) it provides a framework for evaluating fish that can be improved as new toxicology/epidemiology data are gathered for these and other fish constituents. Key uncertainties include the lack of quantitative information on other fish contaminants (e.g., PCBs) or nutrients (e.g., selenium) that may affect neurodevelopment.

DNTS 15

Determination of individual variation in methylmercury (MeHg) metabolism and elimination status (MerMES) in humans

Matthew Rand [3], Samuel Caito [3], Alex Grier [1], Steven Gill [1], Edwin VanWijngaarden [1], Tanzy Love [1], Thomas Scrimale [1], Gene Watson [1], Tracy Punshon [2], Brian Jackson [2]

[1] University of Rochester, Rochester, NY, USA [2] Dartmouth College, Hanover, NH, USA [3] Department of Environmental Medicine, University of Rochester, Rochester, NY, USA

Characterizing potential neurotoxic effects of methylmercury (MeHg) that accompany fish consumption remains a priority public health issue. Variable outcomes seen among populations and between individuals experiencing similar levels of MeHg exposure has complicated formulation of fish advisories. Establishing Hg body burden, e.g. via Hg in hair or blood, is critical for determining associations of neurotoxic endpoints with MeHg exposure. The major determinant of the Hg body burden is the slow elimination rate of MeHg ($k_{el} \sim 0.014\ day^{-1}$ or $t_{1/2} \sim 50$ days). In both controlled studies and in cases of accidental poisonings, MeHg elimination rate among individuals can vary widely ($t_{1/2}$ = 35 to > 150 days). Mechanisms that control MeHg elimination from the human body remain poorly understood. Nonetheless, microbial demethylation of MeHg by gut flora is thought to enhance excretion as inorganic Hg (I-Hg) via the feces. We seek to characterize the extent to which individuals vary in MeHg metabolism and elimination to shed light on factors controlling MeHg body burden. Using a recently improved method of longitudinal Hg analysis in a single hair using laser ablation-ICP-MS (Rand et al. 2016, Tox Sci 149:385), we measured MeHg elimination rates for 37 individuals (ages 21–69) following the consumption of just three fish meals. We also determined the MeHg demethylation status for each individual through Hg speciation in feces. Elimination rates were found to vary more than two-fold (k_{el} = 0.0246–0.0112 day^{-1}; $t_{1/2}$ = 28–62 days). No significant correlations with age, gender or BMI were seen in this small cohort. However, within-subject variation in elimination rate was evident, notably in cases where subjects were prescribed antibiotic midway through the elimination period. Faster elimination rates were seen to positively associate with %I-Hg in feces, suggesting that demethylation plays a role in MeHg excretion. We show the existence of a wide range of variation in MeHg metabolism and elimination status (MerMES) on an individual basis. Our findings point to the gut microbiome as source of variation in MeHg demethylation and elimination. Future investigations will focus on determining MerMES of the most vulnerable populations, i.e. pregnant women and young children.

DNTS 16

A Lifespan Approach to Methylmercury Neurotoxicity with Emphasis on Executive Functions

M. Christopher Newland, Steven R. Boomhower

Auburn University, Auburn, AL, USA

Behavioral studies in laboratory animals provide an experimental link between neurobiological effects of neurotoxicants and epidemiological results derived from exposed populations. We have taken a lifespan approach to the study of methylmercury's behavioral toxicity. In this context we have examined potential protective factors, including the fish nutrients DHA and selenium, environmental enrichment and the HDAC inhibitor sodium butyrate. In rats, gestational exposure to methylmercury disrupts behavioral flexibility as detected and replicated in discrimination reversal tasks and in the transition from high- to low-rate responding. These effects are related to disrupted impact of reinforcing events, enhanced sensitivity to dopamine agonists, diminished sensitivity to the GABA agonist pentobarbital, and accelerated aging. Similar experiments with C57Bl/6 mice have revealed less sensitivity to gestational exposure, suggesting an unknown genetic contribution to its neurotoxicity. Adolescent exposure disrupts choice and produces a biphasic dose-effect relation on impulsivity, as measured by a delayed discounting task. Selenium, but not DHA, protects against adult-onset, but not gestational, exposure. These studies point to the prenatal period as being especially sensitive but we still lack enough information to form a firm conclusion about adolescent-onset exposure. The behavioral endpoints affected by developmental exposure can be viewed as animal models of executive function, suggesting that these functions, which are distinct from the IQ measures commonly used, might be sensitive indicators in human populations.

DNTS 17

Windows of Vulnerability to Low Levels of MeHg in the Rat Hippocampus

Katie Sokolowski, Maryann Obiorah, Anthony Falluel-Morel, Elizabeth McCandlish, Helene Sisti, Brian Buckley, Tracey Shors, Emanuel DiCicco-Bloom

Rutgers University, Piscataway, NJ, USA

Humans are exposed to methylmercury (MeHg) through diet, and historical poisonings have demonstrated that the developing brain is particularly vulnerable. At chronic low levels of exposures in fish-eating communities, epidemiological studies have raised concern for the developing brain with respect to behavioral outcomes such as learning and memory. In turn, research investigations have focused on a brain region that is critical for learning and memory, the hippocampus, which is a particularly sensitive target of MeHg since new neuron generation (neurogenesis) occurs throughout life. Our model uses a single subcutaneous injection of 0.6 mcg/gbw MeHg in postnatal day (P7) 7, P14, and P21 rats to understand the vulnerability across late in utero, prepubescent, and adolescent humans, respectively. Peak hippocampal concentrations of Hg were at P7, P14, and P21 were within range of Seychelle Island fetal temporal/hippocampal tissues (240 ppb, Lapham et al. 1995). When exposed at P7, the hippocampus exhibited increased apoptosis of neural stem cells as measured by decreased BrdU and an increase in Sox2 + and Nestin + neural stem cells that co-labeled with caspase-3 at 24 h. The acute decreases in P7 neural stem cells lead to decreases in later stem cells as well as total neuron numbers at P21 and a functional deficit in memory as detected with the Morris water maze. To define developmental vulnerability to MeHg in prepubescent (P14) and adolescent (P21) rats, BrdU and caspase-3 was examined 24 h after exposure. There were no adverse effects on neurogenesis at P14 or P21 after low exposures of MeHg (0.6 mcg/gbw), though P14 neurogenesis was impacted following higher exposure (5 mcg/gbw). These observations suggest that vulnerability to MeHg diminishes with age, and reflect changes in cell and tissue resistance rather than mercury transport across the blood brain barrier.

DNTS 18

Cannabis in Colorado: The Impact of Legalization on Children and Families

Larry I. Wolk

University of Colorado, Denver, CO, USA, Rocky Vista University, Parker, CO, USA and Rocky Mountain Youth Clinics, Denver, CO, USA

On January 1, 2014, Colorado became the first state in the nation to make legal recreational marijuana available for adult use. As a result, Colorado has had to carefully examine potential population health and safety impacts as well as the role of public health in response to legalization. The presentation will highlight our emerging and evolving public health framework for legalized recreational marijuana, including the coexistence of such with a longer standing legalized medical marijuana program. Preliminary data will be presented to offer insight into the impact of legalized cannabis on children and families, including health and safety behaviors and outcomes. Additionally, challenges to both policy and data interpretation will be presented.

DNTS 19

Defining the Human Exposome

Cynthia F. Bearer

University of Maryland School of Medicine, Baltimore, MD, USA

Introduction: The purpose of this talk is to describe the human exposome, discuss measurement of the exposome, and the complexity of the analysis of the exposome. Methods: The methodology for determining the human exposome will be discussed, as well as possible biological matrices and early biomarkers of exposure. Several longitudinal studies will be described. Results: The results of several studies will be presented, demonstrating the complexity of the exposome. Results will show that many chemicals can be found in umbilical cord blood, implying complex exposure to the fetus; the fetus is not sterile but contains a microbiome which is part of the exposome; that the exposome changes with time, and timing of exposure impacts health outcomes; the exposome may be an unrecognized confounder when dealing with human studies linking exposure to one chemical to a health outcome. Conclusion: Studies may need to incorporate exposome analysis to determine the impact of single chemical exposure to outcome. The microbiome may be an important part of the total exposome.

DNTS 20

PK/PD Modelling for Multiple Exposures in Pregnancy

Donald R. Mattison

Risk Sciences International, Ottawa, ON, Canada

During pregnancy women are exposed to multiple chemicals, including; medications, life-style, occupational and residential exposures. These exposures can interact, altering pharmacokinetics (PK); absorption, distribution, metabolism, and elimination. Additionally, pharmacodynamics (PD) can be altered; changing toxicity. This review will describe physiological changes of pregnancy, multiple medications used and substances abused during pregnancy. These complex exposures occur in a setting of changes in PK/PD which can alter the consequences of the exposures. Physiological Changes: Pregnancy is a dynamic state in which the functions of the mother, placenta, and fetus are changing. Maternal body composition, cardiovascular, renal, gastrointestinal, and pulmonary function adapt to pregnancy. At the cellular level pregnancy alters phase 1 (oxidative) and phase 2 (conjugative) enzymes as well as transport proteins changing gut absorption and renal elimination and tubular reabsorption. These adaptations lead to changes in PK (absorption, distribution, metabolism, and elimination) and PD (modifying responses to medications and their metabolites). Not only do these changes influence our approaches to therapeutics they influence the consequences of mixtures of abused drugs. Exposure to Mixtures: Just as clinicians often use several medications to treat diseases in pregnancy, self-medication with mixtures of abused substances can occur. Many women are treated with more than one prescription medication during pregnancy. Similarly, tobacco and many different abused substances are used together. Mixture PK/PD: Chemicals can act together so the overall level of toxicity is altered in one of three ways; chemicals with common modes of action typically can be modeled with dose or concentration additivity, those with independent modes of action can be modeled with response or effect additivity. A third type of joint action are those with interactions (synergism, antagonism, or potentiation), resulting from toxicokinetic, metabolic, or toxicodynamic interactions. Alterations in PK/PD occur in concert with physiological changes during pregnancy. These changes in PK/PD can influence the possible outcomes of exposure to, or treatment with mixtures. Summary: Understanding the consequences of multiple exposures across pregnancy presents critical challenges for clinicians; whether the focus is on appropriate therapeutic interventions or understanding the risks of abused medications.

DNTS 21

Alcohol and Nicotine-Induced Epigenetic Changes (miRNAs)

Rakesh C. Miranda

Texas A&M Health Science Center, Bryan, TX, USA

Tobacco use is common among individuals with Alcohol Use Disorders (AUDs), and several studies have shown that nicotine, an important psychoactive component of tobacco, can increase craving and tolerance for alcohol. Consequently, despite long term evidence for teratogenicity, smoking and alcohol consumption often co-occur during pregnancy. In a recent study to develop a biomarker-based algorithm to predict infant

outcomes associated with heavy maternal alcohol consumption, we found that a history of maternal smoking was an important predictor for adverse birth outcomes due to maternal alcohol consumption. We hypothesized that microRNAs (miRNAs), small non-protein-coding translation-regulatory RNAs that constitute an important layer of epigenetic regulation in all cells and tissues, would be a common target of both alcohol and nicotine. We previously found evidence in ex vivo mouse models for fetal neural stem cells (NSCs) and zebrafish models for embryonic development, that miRNAs mediated some of the teratogenic effects of ethanol. Nicotine and nicotinic receptor agonists also targeted ethanol-sensitive miRNAs. However, surprisingly, in NSCs the effects of nicotinic receptor activation were antagonistic to ethanol for both assessed miRNAs and miRNA-regulated genes. The implications of this antagonistic relationship between two teratogens will be discussed in the context of biochemical studies into the roles of teratogen-sensitive miRNAs in fetal NSC growth and maturation.

DNTS 22

Epigenetic Changes Induced by Prenatal Nicotine and Cocaine Exposure

Deirdre M. McCarthy, Pradeep G. Bhide

Florida State University, Tallahassee, FL, USA

Prenatal exposure to drugs of abuse can produce changes in the structure and function of the brain, some of which can last a lifetime. Recent evidence suggests that epigenetic modification of DNA and histones is one of the mechanisms mediating the effects of such environmental agents. We examined the anatomical, molecular, and behavioral changes associated with prenatal exposure to cocaine and prenatal or paternal exposure to nicotine in mouse models. Prenatal cocaine exposure produced a significant increase in signaling via the brain derived neurotrophic factor (BDNF)-TrkB pathway in the frontal cortex, which contributed to reversal learning deficits. The increase in BDNF expression was associated with epigenetic modification of histones in the promoter regions of the *bdnf* gene. Prenatal nicotine exposure produced significant changes in the neuroanatomical and neurotransmitter phenotypes as well as behavioral changes such as deficits in working memory and attention. Paternal nicotine exposure also produced significant deficits in attention. Interestingly, cocaine and nicotine not only produced epigenetic changes in somatic cells (in the brain) but also in germ cells. For example, prenatal cocaine exposure produced significant alterations in global DNA methylation and histone acetylation in the *bdnf* promoter region in spermatozoa. Paternal nicotine exposure produced significant changes in global DNA methylation as well as DNA methylation in promoter regions of dopamine receptor genes in the spermatozoa. Thus, our data show that cocaine and nicotine produce epigenetic modification of the DNA and histones in somatic and germ cells, and that the epigenetic changes in the germ cells likely contribute to transgenerational transmission of drug-induced behavioral and molecular phenotypes from one generation to the next.

DNTS 23

Gestational nicotine sex-dependently alters adolescent dopamine system development

Frances Leslie, Jennifer Dwyer, Shahrdad Lotfipour, James Belluzzi

University of California, Irvine, Irvine, CA, USA

Despite public health initiatives, many women continue to smoke or use e-cigarettes during pregnancy. Since maternal smoking has been linked to persistent, gender-dependent neurobehavioral deficits in the offspring, many physicians now recommend the nicotine patch as a safer alternative to tobacco use during pregnancy. However, as we presently show, sustained exposure to low doses of nicotine during fetal development, similar to that seen clinically with the nicotine patch, produces substantial changes in developing dopamine systems of adolescent offspring. Briefly, pregnant dams were implanted on gestational day 4 with an osmotic mini-pump that delivered either saline (GS) or nicotine (3 mg/kg/day) (GN) for two weeks. At birth, pups were cross-fostered with treatment naive dams, to avoid confounding withdrawal effects on maternal behavior. The pups were handled daily. At postnatal day 32 or 33, representative of adolescence in the rodent, they were sacrificed for biochemical assays or were behaviorally tested. GN treatment had both sex-dependent and -independent effects on corticolimbic dopamine systems, altering catechol-*O*-methyl transferase (COMT)-dependent dopamine turnover in males and transporter-dependent turnover in both males and females. GN altered striatal dopamine transporter (DAT) binding in females only, who also showed enhanced cocaine-induced locomotor activity. GN also enhanced ventral striatal D2-like receptor expression and G-protein coupling, while altering the roles of D2 and D3 receptors in cocaine-induced locomotion. These data show that low-dose prenatal nicotine treatment sex-dependently alters corticolimbic and striatal dopamine system development, which may underlie clinical deficits seen in adolescents exposed to tobacco or nicotine replacement therapy in utero.

DNTS 24

Electronic Cigarette Use in Pregnancy: Patient and Provider Perspectives

Katrina Mark [1], Brooke Farquhar [1], Victoria Coleman-Cowger [3], Mishka Terplan [2]

[1] *University of Maryland School of Medicine, Baltimore, MD, USA* [2] *Virginia Commonwealth University, Richmond, VA, USA* [3] *Battelle Research Institute, Baltimore, MD, USA*

It is well known that smoking cigarettes can cause long-term health consequences. Regulations have been enacted requiring tobacco products to use warning labels, and restrictions have been placed on advertising. Electronic cigarettes are often advertised as “tobacco free” and, as of yet, do not have as strict regulations regarding labeling and marketing. They are often touted as safer than traditional cigarettes given that their delivery systems allow for nicotine consumption without the combustion byproducts. Although not specifically advertised toward pregnant women, this implicit idea that e-cigarettes are “safer” may be appealing to women trying to engage in harm reduction during pregnancy. However, most of these products do contain nicotine, which has deleterious effects in pregnancy. This study was designed to investigate the misconceptions about the safety of electronic cigarettes in pregnancy. A survey of 316 pregnant women found that 57% of all respondents believed that e-cigarettes contain nicotine, 61% that e-cigarettes can be addictive, and 43% that e-cigarettes are less harmful to a fetus than traditional cigarettes. Although $< 1\%$ reported current daily use, 14% reported lifetime use. Among those who had used electronic cigarettes, the most common reasons given for use of e-cigarettes were the perception of less harm than traditional cigarettes (74%) and help with smoking cessation (72%). Work by others has shown that providers also have deficient knowledge and counseling practices. In a separate survey, approximately 40% of 252 obstetric providers admit to never screening patients for e-cigarette use, 29% believe that electronic cigarettes are safer in pregnancy, and 14% believe there is no potential harm of use during pregnancy. Misconceptions about e-cigarettes are common among pregnant women and providers, possibly motivating use that poses potential maternal and child health risks. Screening and education regarding e-cigarettes should be included in prenatal care. Future research in this area is necessary, including research examining pregnancy outcomes among women who use e-cigarettes.

DNTS 25

Perceptions and Use of Electronic Cigarettes during Pregnancy: Implications for Infant Outcomes

Laura Stroud [1,2], Tessa Kehoe [1], Meaghan McCallum [1], George Papandonatos [2], Margaret Bublitz [1], Lori Scott-Sheldon [1,2]

[1] *Brown Medical School, Providence, RI, USA* [2] *School of Public Health, Providence, RI, USA*

Electronic cigarette (e-cigarette) awareness, interest, and use have increased dramatically since their introduction to the US market in the mid-2000s. There has also been a proliferation of available flavors for e-cigarettes, with unknown health consequences. E-cigarettes are often marketed and perceived by users as a safe alternative to conventional cigarettes. Yet, little is known regarding perceptions, preferences, and use of e-cigarettes and flavorings during pregnancy, when use may adversely impact both the mother and fetus. The current research presents data from two studies: (1) Study 1, a brief telephone survey of 1356 pregnant women, and (2) Study 2, an in-depth interview of 58 pregnant women. In Study 1, 1356 low-income pregnant women (64% minorities, M_{age} = 27) completed a brief telephone survey between 2012 and 2016. Four percent (n = 51) endorsed the use of e-cigarettes during or in the three months prior to pregnancy. Compared to controls (i.e., pregnant women not using tobacco), e-cigarette users were less likely to be a racial/ethnic minority, and more likely to report depression symptoms and alcohol and marijuana use ($ps \leq 0.06$). Compared to pregnant cigarette smokers, e-cigarette users were more educated and reported a higher income ($ps \leq 0.05$). In Study 2, 58 pregnant women (55% tobacco users, 69% minorities, M_{age} = 27) completed a comprehensive interview regarding preferences, perceptions, and use of e-cigarettes and flavorings in 2015–2016. Rates of lifetime and pregnancy use were 41% and 7%, respectively. The most common reasons for e-cigarette use among tobacco users were: (a) to help quit smoking cigarettes (72%), (b) to replace cigarettes (63%), and (c) to help reduce or cut back the amount smoked (59%). Pregnant mothers perceived sweet-flavored (i.e., fruit, chocolate, candy) e-cigarettes as less harmful than tobacco-flavored e-cigarettes ($ps \leq 0.08$) and held more positive perceptions (liking, attractiveness, interest) of e-cigarettes flavored with menthol/mint, fruit, candy, chocolate, and alcohol vs. tobacco-flavored e-cigarettes ($ps \leq 0.04$). Results highlight the growing prevalence of e-cigarettes and positive perceptions of sweet-flavored e-cigarettes in this highly vulnerable population. Implications for pregnant women and infants will be discussed.

DNTS 26

Pathways from prenatal exposures to tobacco and cannabis to adult electronic cigarette use

Natacha De Genna [1], Lidush Goldschmidt [2], Gale Richardson [1], Nancy Day [1], Marie Cornelius [1]

[1] *University of Pittsburgh School of Medicine, Pittsburgh, PA, USA* [2] *University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA, USA*

Abstract

The best predictor of electronic cigarette use is current or recent combustible cigarette use. Moreover, prenatal exposures to maternal cigarette and cannabis use are associated with combustible cigarette use and tobacco dependence in adolescent and adult offspring. Thus, we hypothesized that prenatal exposures to tobacco and cannabis would be linked to adult electronic cigarette use via early adolescent cigarette use. Telephone interviews were conducted with 413 young adults from 3 prenatal cohorts with trimester-specific data on prenatal exposures to tobacco, alcohol and cannabis. The offspring were 22–33 years old (M = 29.7, SD = 3.4), 60% female and 40% male, 60% Black and 40% White. Participants reported current and past use of electronic cigarettes and other substances. The main outcome variable was offspring use of an electronic cigarette more than once (17% of the sample). The exposures were quantity and frequency of cigarette, alcohol, and cannabis use by their mothers during the first trimester, summarized as average cigarettes, drinks, and joints per day. Covariates included maternal race and offspring age, sex, and educational attainment. Using logistic regression and structural equation modeling, we examined the effects of gestational exposures on adult electronic cigarette use via early cigarette use (by age 14). There was a significant indirect effect of prenatal exposure to tobacco and cannabis on electronic cigarette use, thus supporting the hypothesis. These results suggest that there is a pathway from prenatal exposures to combustible tobacco and cannabis to adult electronic cigarette use via early combustible cigarette use in offspring.

DNTS 27

Parental Stress and Epigenetic Programming of the Developing Brain

Tracy L. Bale

University of Pennsylvania, Philadelphia, PA

Parental lifetime exposures to perturbations such as stress, infection, malnutrition, and advanced age have been linked with an increased risk for offspring disease, including a strong association with neurodevelopmental disorders. While maternal insults during pregnancy can directly impact somatic cells and fetal development, the mechanisms by which lifelong parental experiences can alter germ cell programming and affect offspring brain development are just beginning to be examined. Surprisingly few animal models have been developed to study mechanisms of preconception perturbations. This session will discuss preclinical research that has begun to define the windows of vulnerability for both transgenerational and intergenerational programming and the epigenetic mechanisms involved. We have developed mouse models of both paternal and maternal life stress in which adult mice are exposed to chronic stress prior to breeding, including early pregnancy maternal stress as a sensitive window of fetal development. In our mouse model of early prenatal stress (EPS), stress exposure during the first week of gestation imparts long-term developmental programming deficits in male, but not female, offspring resulting in hypersensitivity to stress, cognitive impairments, and alterations in metabolic programming. The placenta, a fetally-derived organ reflecting fetal sex chromosome complement, acts as an arbitrator between the mother and fetus, providing necessary factors for early fetal neurodevelopment. Thus, sex differences in placental function may dramatically influence sex bias in vulnerability to prenatal insults. We identified the X-linked, stress sensitive, nutrient sensor O-linked-*N*-acetylglucosamine (OGT) as a placental biomarker of prenatal stress. Placental-specific reduction of OGT recapitulates the developmental and metabolic impairments associated with our EPS model. We found that OGT determines genome-wide sex differences in H3K27me3 and gene expression in placental trophoblasts. Our studies have currently focused on demonstrating the prenatal resilience for females that is programmed by the high levels of this transcriptionally repressive histone mark. In paternal transmission of life stress experience, our mouse model of paternal stress produces offspring with hypothalamic-pituitary-adrenal (HPA) stress axis dysregulation. Paternal sperm examined for changes in miRNA content established 9 specific miRNA that were significantly increased in stressed sperm. To test the relevance and potential mRNA targets of these miRNAs, we synthesized and injected the 9 miRNAs into single cell zygotes and found that the resulting offspring recapitulated the stress phenotype found from paternal stress sires. In addition, we have now completed single cell amplification from injected zygotes using Fluidigm technology and ascertained the stored maternal mRNAs that are targets of these sperm miRNAs and thus affecting post-fertilization development that results in a reprogrammed brain that is stress hypo-responsive. We hypothesize that the epididymal epithelial cells secreting miRNA-containing exosomes are involved in the sperm programming, and our current studies are targeting these cells to rescue this paternal transmission. Overall, these results demonstrate that parental life experience can induce germ cell epigenetic reprogramming and impact offspring development, and may therefore offer novel insight into factors influencing sex-specific disease risk. Identification of the specific miRNA in germ cells or histone modifications in the placenta may point to unique biomarkers that could identify at-risk populations.

DNTS 28

Prenatal Cocaine Exposure and Trajectories of Externalizing Behavior Problems from Age 4 to 12

Meeyoung Min [1], Sonia Minnes [1], Hyunyong Park [2], June-Yung Kim [1], Lynn Singer [1]

[1] Case Western Reserve University, Cleveland, OH, USA [2] Sungshin Women's University, Seoul, Republic of Korea

Objective: Prenatal cocaine exposure (PCE) is linked with greater externalizing behavior. The purpose of the present study is 1) to identify developmental trajectories of externalizing problems, 2) to examine whether trajectories differ by PCE and other environmental and biological correlates, and 3) to investigate how trajectories are associated with adolescent substance use and sexual behavior.

Methods: Adolescents (N = 394; 203 PCE, 191 NCE; 206 girls, 188 boys), primarily African-American and of low socioeconomic status, were prospectively enrolled in a longitudinal study at birth. Externalizing problems were assessed with the Child Behavior Checklist (CBCL) at 4, 6, 9, 10, 11, and 12 (98% retention). Substance use, via self-report and biologic assays, and early (before age 15) sexual intercourse were assessed at age 15.

Results: Latent class growth model (LCGM) indicated that a four-class model represented the best fit to the data for externalizing behavioral problems (BIC = − 7247, entropy = 0.91, smallest group = 14%), supporting heterogeneity in developmental trajectories of behavioral problems across ages 4–12. The four externalizing behavior trajectory groups were: 1) accelerated risk group (14%); 2) low-decreasing group (32%); 3) moderate-decreasing group (32%); and 4) elevated-chronic group (22%).

Multinomial regression analyses indicated that, compared to the low-decreasing group, PCE was associated with increased odds of being in the accelerated risk group (OR = 2.86, 95% CI = 1.06–7.70); biological mothers' psychological distress (OR = 4.54, 95% CI = 1.67–12.38) and boys (OR = 2.21, 95% CI = 1.16–4.23) were associated with increased odds of being in elevated chronic group. Overall trajectory differences were found in adolescent tobacco and marijuana use and early sexual behavior. Controlling for race, sex, and violence exposure assessed at age 12, the accelerated risk group (45.8%, 42.3%, 53.8%) and elevated-chronic group (48.5%, 39.8%, 40.9%) were more likely to use tobacco and marijuana and to be engaged in early sexual intercourse than low-decreasing group (16.6%, 19.0%, 22.3%) or moderate-decreasing group (29.5%, 28.7%, 27.3%), all *p*'s

< 0.05.

Conclusions: PCE distinguished developmental trajectory that was related to adolescent substance use and sexual behavior. Maternal psychological distress was also a key antecedent predicting trajectory membership. Continued studies into adulthood will elucidate how the identified developmental trajectories may relate to social and vocational adjustment.

DNTS 29

Circadian Disruption Affects Initial Learning but not Cognitive Flexibility In an Automated Set-Shifting Task in Adult Long-Evans Rats

Rekha Balachandran [1], Audrey Robertson [1], Megan Mahoney [1,2], Paul Eubig [1,2].

[1] Department of Comparative Biosciences, College of Veterinary Medicine, University of Illinois Urbana Champaign, Urbana, IL, USA [2] Neuroscience Program, University of Illinois Urbana Champaign, Urbana, IL, USA.

Circadian disruption is caused by misalignment of innate rhythms to external cues such as light, sleep and food intake. Chronic circadian disruption negatively affects both physiology and cognition. We investigated the effects of circadian disruption on cognition in a rodent model. Adult Long-Evans rat were tested on an automated operant behavior task for 3 months under 12:12 h light: dark cycle, with testing occurring either 4 h after lights-on or lights-off. This resulted in day-tested rats realigning their activity patterns to become diurnal, whereas night-tested rats remained nocturnal. Rats then transitioned to an automated set-shifting (SS) task to assess cognitive flexibility, the ability to adapt to changing situational demands. We hypothesized that circadian disruption would result in the day-tested rats being slower to adapt to task transitions as compared to the night-tested rats. Contrary to our hypothesis, night-tested rats took longer to reach criterion performance in the visual-cue detection stage of the SS task compared to daytested rats. However, there were not differences between the two conditions in subsequent transitions to an egocentric-cue based phase or a reversal phase. We speculate that nighttested rats experienced a form of circadian disruption when they were exposed to ambient light during the testing procedure, and that this form of circadian disruption impaired initial task acquisition, but not actual cognitive flexibility, to a greater extent than testing during the day.

DNTS 30

Latrophilin-3: A new model of ADHD-like behavior in a rat knockout model

Charles Vorhees [1], Jillian Hufgard [1], Jenna Sprowles [1], Gary Gudelsky [2], Michael Williams [1]

[1] Cincinnati Children's Research Foundation, Cincinnati, USA [2] University of Cincinnati, Cincinnati, OH, USA

Attention deficit hyperactivity disorder (ADHD) affects 5–12% of children. Recently, an orphan receptor, latrophilin-3 (*LPHN3)*, was linked to ADHD and treatment response to psychostimulants. LPHN3 is a Ca-independent cell-adhesion G protein coupled receptor (GPCR); its extracellular domain binds to FLRT3, and its intracellular domain contains a Gq_{11} binding site. Although ancient, the function of this protein is unknown. Using CRISPR/Cas9 genome editing, we deleted exon-3 in Sprague-Dawley rats. Once established, we then used only heterozygous (HET) x HET crossings to create litters for testing. We Used 1 male and 1 female per genotype per litter from 20 different litters for behavior. 48 h home-cage activity showed that knock-out (KO) rats were hyperactive for the first 2 h. They then habituated to wildtype (WT) rat levels. The KO rats became hyperactive again during the dark cycle and this carried over into the next light cycle before gradually declining to WT levels. The nocturnal hyperactivity became larger the second night. KO females also had increased open time in an elevated zero maze. KO rats were hyper-responsive to acoustic and tactile startle stimuli with the largest effect being to the acoustic stimulus. Regional monoamine levels of dopamine (DA) and 5-HT were unchanged, however, norepinephrine (NE) was reduced in prefrontal cortex in KO rats. Amphetamine-stimulated DA release in the nucleus accumbens was also increased in KO rats (N = 5/group). Brain slice electrophysiological recordings of field EPSPs showed a trend toward increased induction of hippocampal long-term potentiation (LTP) in the perforant pathway in KO rats (N = 2/group). This model shows some ADHD-like features and warrants further investigation. (Supported by R21 MH101609 and T32 ES007051).

DNTS 31

Tobacco as a Reproductive and Developmental Toxicant

John M. Rogers

Toxicity Assessment Division, NHEERL, ORD, US EPA, Research Triangle Park, NC, USA.

Maternal cigarette smoking has long been known to result in effects on offspring including lower birthweight and neurobehavioral effects. Continuing studies have expanded the list of adverse outcomes in offspring to include sudden infant death syndrome, impaired lung function, and components of the metabolic syndrome including obesity and diabetes that manifest in late childhood or adolescence. Paternal smoking has been linked to increased risk of childhood cancers. Exposure to second-hand smoke during pregnancy has also been associated with adverse birth outcomes. Epigenetic analyses of cord blood and placentae from smoking mothers and tissues of offspring have demonstrated consistent alterations of DNA methylation of genes known to be involved in development and xenobiotic metabolism. Paternal tobacco smoking has been associated with

epigenetic changes in sperm and in offspring. Alterations to the epigenome in offspring of smoking parents may be permanent or at least persistent for many years. There is now concern that "third-hand smoke" (residue left on surfaces in areas where people smoke) is also a significant health risk. This presentation will discuss the current state of the science in terms of effects on development and reproduction caused by or associated with tobacco use and the potential role of epigenomic changes in the etiology of these effects. *[This presentation does not reflect US EPA policy.]*

DNTS 32

***E*-Cigarettes: What Are They, What Do They Do, and What Are Potential Impacts on Pregnancy Outcomes?**

Alison Breland

Virginia Commonwealth University, Richmond, VA, USA

Electronic cigarettes (ECIGs) are a class of products that have a variety of names. Most ECIGs consist of a battery, an electrical heater, and a liquid that is aerosolized for users to inhale. The liquid and the aerosol contains solvents, flavorants, and the dependence-producing drug nicotine. ECIG use among adults and in particular, adolescents, has increased rapidly in recent years. For example, among high school students in the US, ECIG use in the past 30 days is now higher than past 30-day cigarette use. Currently, little research shows that ECIGs are effective smoking cessation aids, and most ECIG users are "dual users" (that is, they use both cigarettes and ECIGs). Research on ECIGs indicates that some ECIGs can deliver as much nicotine, or more nicotine, than a combustible cigarette. However, there is much variation in nicotine delivery, depending on device type and user behavior. As nicotine is dependence-producing, can harm a developing brain, and can harm a developing fetus, there are concerns about the nicotine delivery associated with ECIGs. Nicotine crosses the placenta and in utero exposure may explain disorders such as hyperactivity, cognitive impairment, anxiety and sensitivity to nicotine and other stimulant drugs. ECIGs do not deliver carbon monoxide (known to be harmful to a fetus) but the aerosol does contain other toxicants; the effects in humans are largely unknown. Recent data collected in an ongoing project on pregnant ECIG users will be presented, and the current regulatory environment for ECIGs will be discussed.

DNTS 33

The Role of Nicotine in the Effects of Maternal Smoking during Pregnancy on Lung Development and Childhood Respiratory Disease

Virender K. Rehan

Harbor-UCLA Medical Center, David Geffen School of Medicine at UCLA, Torrance, CA, USA

There is extensive epidemiologic and experimental evidence from both animal and human studies that demonstrates detrimental long-term pulmonary outcomes in the offspring of mothers who smoke during pregnancy. Although the molecular mechanisms underlying these associations remain incompletely understood, recent data clearly demonstrate that nicotine directly and specifically disrupts epithelial-mesenchymal interactions that are essential for normal lung development. Specifically, nicotine alters the normal differentiation of mesenchymal cells in the developing lung by stimulating the Wnt pathway, inhibiting PPARγ signaling, resulting in the myogenic hyperresponsive phenotype of the airway smooth muscle cells. Interestingly, these effects are sex-specific, with the molecular and functional effects on airway smooth muscle cells seen exclusively in males. The mechanistic basis for the sex-specific effects of nicotine on airway smooth muscle cells is under intense investigation and it is likely to be due to the differential nicotine-induced expression and activation of certain developmentally relevant signal transduction pathways in male airway smooth muscle cells. Importantly, it has been shown that by altering specific developmental signaling pathways necessary for fetal lung development, the perinatal nicotine exposure-related chronic lung disease risk is not restricted only to the nicotine-exposed offspring, but is also transmitted transgenerationally to the progeny of the subsequent non-exposed offspring. This transgenerational transmission seem to be determined by nicotine-induced epigenetic changes in the gonadal germline. Even more importantly, PPARγ agonists, which are potent Wnt antagonists, can inhibit and/or reverse these effects. The comprehensive cell-molecular-epigenetic approach adopted to understand the pathogenesis of nicotine-induced chronic lung disease and its transgenerational transmission paves the way for studying molecular mechanisms underlying transgenerational effects of a host of other environmental toxin/exposures. *Grant Support: HL27137; HD71731; TRDRP: 23RT-0018.*

DNTS 34

Neurodevelopmental Toxicity of Tobacco Smoke and Nicotine

Edward D. Levin

Duke University Medical Center, Durham, NC, USA

Tobacco smoking during pregnancy has long been known to adversely impact children's development. In addition to the well-known birth weight deficit there are a variety of persisting neurobehavioral impairments. Epidemiological studies have found learning impairments and increased incidence of attention deficit hyperactivity disorder (ADHD) syndrome to be significantly associated with maternal tobacco smoking. Many experimental rodent studies have demonstrated that gestational nicotine exposure at primary smoking doses cause cognitive, sensorimotor and emotional dysfunction in the offspring. In a series of studies, we have shown in rats that gestational nicotine exposure causes memory impairment. Even at a ten-fold lower 0.2 mg/kg/day average nicotine dose mimicking exposure resulting from second hand smoke caused persisting cognitive dysfunction. Nicotine is not alone among chemicals in tobacco that cause developmental neurobehavioral toxicity. We found that developmental exposure to a complex mixture of tobacco smoke extract (TSE) taken from mechanically smoke cigarettes given with the same low 0.2 mg/kg/day nicotine dose level caused greater neurobehavioral consequences than this dose of nicotine alone. In a study of the critical developmental windows of exposure, we found that late gestational TSE exposure caused more pervasive neurobehavioral impairment than early gestational exposure, which also had effects. Even preconception TSE exposure to the dam caused neurobehavioral effects in the offspring. Prenatal nicotine potentiated the adverse neurobehavioral effects of other developmental toxicant exposure such as early postnatal exposure to the organophosphate pesticide chlorpyrifos. Finally, it should be noted that prenatal nicotine exposure has complex sex differences in behavioral response. Collaborative studies with Drs. Theodore Slotkin and Frederic Seidler showed that gestational nicotine exposure impaired cholinergic, serotonergic, dopaminergic and noradrenergic systems. These neurochemical effects can help with the discovery of the interactive adverse outcome pathway for developmental neurotoxicity of tobacco smoke. *This research was supported by the NIEHS Superfund Research Program (ES010356), the March of Dimes and the Children's Environmental Health and Prevention Center sponsored by the National Institutes of Health (Grant ES022831) and the U.S. Environmental Protection Agency (EPA) (Grant 83543701). EPA support does not signify that the contents reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.*

DNTS 35

Effects of Manganese Body Burden on Fine Motor Skills in Children Aged 6–14 Years.

Lonnie Sears [1], Lindsay Tompkins [2], Carol Hanchette [3], Barbara Polivka [4], Kristina Zierold [2]

[1] University of Louisville Department of Pediatrics, Louisville, KY, USA [2] University of Louisville School of Public Health and Information Sciences, Louisville, KY, USA [3] University of Louisville Department of Geology and Geosciences, Louisville, KY, USA [4] University of Louisville School of Nursing,

Louisville, KY, USA

Manganese (Mn) is an essential micronutrient although high levels of exposure to the metal through inhalation or ingestion has been shown to be neurotoxic. Parkinson-like effects are seen with high exposure suggesting involvement of the basal ganglia. Based on the evidence of the neurotoxic effects of Mn on motor skills, we analyzed data for motor skills from 69 children, aged 6 to 14 years, as part of a larger study of the effects of coal ash exposure on children's development. Subjects completed the Beery-Buktenica Test of Visual Motor Integration (VMI), the Purdue Pegboard, and the Behavior Assessment Research System finger tapping tasks. Neuropsychological data were compared to Mn levels in toenails and fingernails collected from the children. Nail samples were analyzed with Proton Induced X-ray Emission (PIXE). Results indicated that 20.3% (N = 14) of the sample had Mn toenail/fingernail levels ranging from 2.3 to 7.0 ppm. Compared to children with no detected Mn in their toenails/fingernails (N = 55) using Fischer's exact tests, children with Mn performed more poorly on the VMI (p = 0.027) however the high Mn level group, in contrast, performed better on the Purdue Pegboard task (dominant hand, p = 0.01). Finger tapping scores for both hands were not significantly different between groups. Results suggest that Mn body burden can be detected in toenail/fingernail samples using PIXE and that exposure to Mn increases risk for visual-motor integration impairments in children, possibly through effects on frontal-striatal brain circuits. In agreement with past research, however, the relationship appears complex based on inconsistent findings across fine motor tests with contrasting findings on the pegboard task. Mn levels in our study were similar to a previous study of exposed children suggesting Mn body burden above 2.0 ppm may impact brain function. Limitations of the study include the small sample size and the likelihood that subjects were exposed to multiple heavy metals which may also contribute to study findings. The relationship of low levels of Mn exposure to neuropsychological function appears complex and further research is needed to identify factors accounting for the variability in current and past research.

DNTS 36

Low-level mercury exposure from fish consumption: Associations with childhood neurodevelopment.

Yingying Xu [1], Kim Dietrich [2], Jane Khoury [1], Heidi Sucharew [1], Aimin Chen [2], Kim Yolton [1].

[1] Cincinnati Children's Hospital Medical Center, Cincinnati, USA [2] University of Cincinnati, Cincinnati, OH, USA

There remains scientific uncertainty about the childhood neurodevelopmental consequences due to gestational women or the children themselves consuming fish containing low levels of Methylmercury (MeHg). We examined the effects of low-level prenatal and postnatal mercury exposure from fish consumption on childhood neurodevelopment outcomes in a longitudinal cohort. We assessed neurodevelopment among 344 children at 1–8 years using the using the Bayley Scales of Infant Development-II (1, 2, 3y), Wechsler Preschool and Primary Scales of Intelligence-III (5y), and Wechsler Intelligence Scales for Children-IV (8y). We measured whole blood total mercury in serial maternal samples during pregnancy, and in children's samples (cord, 1, 2, 3, 4, 5, 8y). We surveyed maternal and child fish consumption and estimated polyunsaturated fatty acids (PUFA) intake. We examined the associations between prenatal and postnatal mercury exposure and neurodevelopmental outcomes using regression and structural equation modeling (SEM), adjusting for potential confounders. The majority of mothers (86%) reported consuming fish during pregnancy, mostly consuming fish with low MeHg content. Child fish consumption also included small amounts with low MeHg content. The geometric mean of maternal blood mercury was 0.64 μg/L. Children's blood samples had lower levels (geometric mean range: 0.18–0.26 μg/L). Prenatal mercury level was associated with lower Bayley Psychomotor Development Index (PDI). For each doubling of average maternal mercury concentration during pregnancy, the PDI decreased by 1.48 point (p = 0.01). In the SEM model examining the joint effects of prenatal and postnatal mercury, each doubling of the true prenatal mercury exposure was associated with a 1.55 point decrease in child PDI scores (p = 0.03), and each doubling of child concurrent mercury was associated with a 0.83 point decrease in PDI (p = 0.10). We did not observe a consistent association between prenatal or postnatal mercury exposure and child cognitive outcomes. In this cohort of children with low mercury exposure from low fish consumption, we found minimal evidence of detrimental effects from prenatal or postnatal mercury exposure on child cognitive abilities. However, we found negative effects from both prenatal and postnatal mercury exposure on child motor abilities assessed at age 1 to 3 years, where prenatal exposure may have a higher contribution to these mild deficits.

DNTS 37

Polychlorinated Biphenyl Mixture Evaluations: A Case Study for Neurotoxicity

Laura M. Carlson [1], Prachi Pradeep [2,4], Jeff Gift [1], Chris Gennings [3], Grace Patlewicz [2], Geniece Lehmann [1]

[1] National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Durham, NC, USA [2] National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Durham, NC, USA [3] Environmental Medicine & Public Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA [4] Oak Ridge Institute for Science and Education, Oak Ridge, TN, USA

Approaches that consider the potential toxicity of the combined components of a mixture (whole mixture approach) are preferred over individual component approaches for risk assessment of chemical mixtures. When toxicological data for a specific mixture are not available, Environmental Protection Agency guidance recommends the use of toxicology data from a "sufficiently similar" mixture as an alternative. Sufficient similarity can be assessed using equivalence testing methodologies that compare the distance between benchmark dose (BMD) estimates for different mixtures. Polychlorinated biphenyls (PCBs) exist as 209 unique congeners exhibiting diverse activity and chemical properties depending on their degree and pattern of chlorination. Humans are exposed to mixtures of PCB congeners by multiple routes, including dietary and inhalation sources, and the mixtures present in these sources have generally not been evaluated in toxicological studies; toxicological data for commercial PCB mixtures, including Aroclors, are much more abundant. This work illustrates the potential utility of equivalence testing methodologies for predicting the toxicological similarity of environmental PCB mixtures found in contaminated fish or air to Aroclor mixtures for which BMD estimates have been derived from existing dose-response data for neurotoxicological effects in rodents. The reliability of equivalence testing can be maximized by including toxicological potency information for individual PCB congeners in the analysis. In vitro data have been used to estimate relative potencies for 87 PCB congeners thought to contribute to neurotoxicity through alterations in calcium homeostasis. We developed a quantitative structure activity relationship model using positional substitution patterns and degree of chlorination as fingerprint descriptors together with the available relative potency information. We used the model to predict relative potencies for the 122 untested congeners. Equivalence testing results which incorporate these relative potency values provide a clear example of the potential for this methodology to be used for human health risk assessment purposes. We can identify commercial PCB mixtures with sufficient similarity to environmental mixtures which will better inform toxicological comparisons to real-world human exposures. *The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.*

DNTS 38

Dynamic Changes in Endocannabinoid Signaling during Adolescence: Implications for Substance Abuse and Psychopathology

BJ Casey

Yale University, New Haven, CT, USA.

Anxiety and substance abuse disorders peak in incidence during adolescence, a developmental window marked by dynamic changes in gene expression, endocannabinoid signaling and frontolimbic circuitry. We tested whether genetic alterations in endocannabinoid signaling related to a common polymorphism in fatty acid amide hydrolase (FAAH), the primary catabolic enzyme that breaks down the endocannabinoid anadamide, would impact the development of frontolimbic circuitry implicated in anxiety and substance abuse disorders. Based on analysis of a pediatric imaging sample of over 1,000 3 to 21 year olds, we show effects of the FAAH genotype specific to frontolimbic connectivity that emerge by approximately 12 years of age and are paralleled by changes in anxiety related behavior and cannabis use. Using a knock-in mouse model of the FAAH polymorphism that controls for genetic and environmental backgrounds, we confirm phenotypic differences in frontoamygdala circuitry and anxiety-related behavior by postnatal day 45 when anadamide levels begin to decrease, and also, at postnatal day 75, but not before. These results, which converge across species and level of analysis, highlight the importance of the underlying developmental neurobiology in the emergence of genetic effects on brain circuitry and function. Moreover, the results have important implications for the identification of risk for disease and precise targeting of treatments to the biological state of the developing brain as a function of developmental changes in gene expression and neural circuit maturation.

DNTS 39

Counseling Women about Prenatal Marijuana Use: Weeding through the Data

Torri D. Metz [1,2]

[1]Denver Health Medical Center, Denver, CO, USA, [2]University of Colorado School of Medicine, Aurora, CO, USA

With increasing legalization of marijuana across the United States, there are concerns about an increasing perception of safety and possibly increased use among pregnant women. Despite a large volume of literature on this topic, there remain many unanswered questions related to the safety of marijuana use for the pregnant mother and fetus. This is predominantly a result of lack of adequate ascertainment of exposure to cannabis with biological sampling, and lack of adjustment for other socioeconomic factors and tobacco use which are known to be associated with the outcomes of interest. In addition, the potency of the cannabis products used today is much higher than when studies were completed in the 1980s and 1990s. The objectives of this lecture are to allow the participant to: describe the overall prevalence of marijuana use in pregnancy and reported reasons for use; counsel women regarding the risks of marijuana use during pregnancy and lactation to the mother and fetus based on current evidence; and access available on-line resources for practitioners and the public containing information about marijuana use in pregnancy.

DNTS 40

Cannabis and the Adolescent Brain: What Does the Evidence Say?

Joanna Jacobus, Susan Tapert

University of California–San Diego, San Diego, CA, USA

Marijuana use has become increasingly prevalent over the past decade and changing legal policies have aroused public concern about the potential for use to increase further among youth. Therefore, the need to understand its long-term effects on the developing adolescent brain has become increasingly important. Teens who engage in heavy marijuana use often show disadvantages in neurocognitive performance, macrostructural and microstructural brain development, and alterations in brain functioning. Neuroimaging and neurocognitive findings will be reviewed from several prospective cohort studies of adolescents and young adults (ages 15–22) conducted at the University of California–San Diego. Findings suggest that adolescent heavy alcohol and marijuana use may be linked to altered neurodevelopmental trajectories and compromised neural health, particularly in those reporting younger age of initiation. It remains unclear whether such disadvantages reflect pre-existing differences that lead to increased substances use and further changes in brain architecture and behavioral outcomes. Future work will focus on prospective investigations to help disentangle dose-dependent effects from pre-existing effects to understand how regular marijuana use influences neurodevelopmental trajectories.

DNTS 41

Cannabinoids for Treatment of Pediatric Epilepsy: The Hype and the Evidence

Amy Brooks-Kayal [1,2]

[1]University of Colorado, Aurora, CO, USA, [2]Children's Hospital Colorado, Aurora, CO, USA

This talk will discuss the current available data on the use of cannabidiol for the treatment of pediatric epilepsy. We will review the Children's Hospital Colorado experience with use of medical marijuana for pediatric epilepsy patients and the available medical evidence supporting the therapeutic use of cannabinoids in epilepsy. The current regulatory information and restrictions surrounding medical use of cannabinoids will be discussed, as will consideration of how to monitor and counsel patients who pursue medical cannabinoid use.

DNTS 42

Cannabis Policy: Challenges and Future Directions

Susan RB Weiss

National Institute on Drug Abuse, Bethesda, MD, USA

A majority of Americans now live in states that provide legal access to cannabis either recreationally or for therapeutic use. Recent national surveys show an increase in nonmedical cannabis use among adults and declining perception of harm associated with cannabis use by all age groups. The full public health impact of these changes in policies, behaviors, and attitudes is still unknown, but there is strong reason to think that individuals whose brains are actively developing may be particularly vulnerable to neurologic and psychiatric effects of cannabis. This includes not only children and adolescents but also those exposed during prenatal development. In 2015, approximately 3.4% of pregnant women reported past month use of cannabis, and some research suggests that this population is using cannabis to help control the nausea associated with pregnancy. The endocannabinoid system, which delta-9-tetrahydrocannabinol (THC) interacts with to produce its effects, is present from early in gestation and plays a significant role in the proper formation of synapses and neural circuitry; thus, any substance that interferes with this system—including THC as well as other cannabinoids in the marijuana plant and synthetic variants now being sold and consumed as “K2/Spice” or “herbal incense”—could influence how the fetal brain wires itself. “Morning sickness” is particularly associated with the first trimester of pregnancy, which also is the period of greatest risk for the damaging effects of drug exposure to the fetus. More research is urgently needed to clarify the neurodevelopmental impact of prenatal exposure to cannabis, especially the high-potency extracts increasingly common among some users. Establishing the effects of prenatal cannabis exposure is challenging for many reasons, including common co-use of alcohol, tobacco, and other drugs by pregnant women; individual differences in nutrition and prenatal care; possible confounding effects of mental illness; and possibly unreliable self-report data as a result of stigma

and/or legal concerns. Disentangling these various factors to better understand the short and long term impact of prenatal cannabis exposure, and the impact of policies governing its use and availability, will require a significant and sustained investment in research, which will be discussed in this presentation.

DNTS 43

Perinatal antidepressant exposure influences spatial learning and memory, acoustic startle response, anxiety, and locomotor activity in adult Sprague-Dawley rats

Jenna Sprowles [1], Jillian Hufgard [1,2], Arnold Gutierrez [1,2], Rebecca Bailey [1,2], Sarah Jablonski [1], Michael Williams [1,2], Charles Vorhees [1,2]

[1] Division of Neurology, Cincinnati Children's Research Foundation, Cincinnati, OH, USA [2] University of Cincinnati College of Medicine, Cincinnati, OH, USA

Most antidepressants (ADs) inhibit neurotransmitter reuptake. Selective serotonin (5-HT) reuptake inhibitors (SSRIs) act on the 5-HT transporter (SERT) while norepinephrine-dopamine reuptake inhibitors (NDRIs) act on the norepinephrine and dopamine transporters. The effects of this activity on early brain development are not well understood. During fetal life, the brain rapidly develops and monoamines play a key role, making the brain potentially vulnerable to insult from ADs. Epidemiological reports link SSRI use during pregnancy to increased risk of autism spectrum disorder (ASD) (Boukhris et al., 2016; Croen et al., 2011). A study in rats showed that exposure to the SSRI citalopram (CIT) from P11–20 resulted in learning and memory deficits (Schaefer et al., 2013), and we have shown behavioral alterations consistent with an ASD-like phenotype in adult rats after perinatal CIT exposure (Sprowles et al., 2016). The present study investigated effects of perinatal exposure to CIT, another SSRI, fluoxetine (FLX), and an NDRI, bupropion (BUP). Sprague-Dawley dams were randomly assigned to one of four groups: CIT (5 mg/kg), FLX (5 mg/kg), BUP (15 mg/kg), or saline (SAL); doses were by subcutaneous injection twice daily (6 h apart) from E6–21, and pups were dosed directly from P1–20. Beginning on P60, one male/female pair from each of 25 CIT, 23 FLX, 20 BUP, or 24 SAL litters were given one of a series of behavioral tests. Both SSRI-exposed groups displayed spatial learning impairments in the Morris and radial water mazes, increased anxiety-like behavior in marble burying, increased acoustic startle/PPI, open-field hypoactivity, and blunted locomotor activity in response to the stimulating effect of the NMDA-R antagonist MK-801. Rats exposed to BUP showed anxiety-like behavior in the elevated zero maze and increased open-field activity following (+)-amphetamine challenge. No changes in egocentric learning, social preference, or forced swim were seen in any group. These results reinforce concern about the use of ADs during pregnancy. Due to the common use of ADs during pregnancy, further investigation about how ADs impact brain development resulting in persistent detrimental neurobehavioral effects is needed. (Supported by NIH training grant T32 007051 and research grant DOD W81XWH-13-0306).

DNTS 44

Prenatal exposure to tobacco smoke extract and some of its constituents in rats cause persisting neurobehavioral effects in the offspring

Edward Levin, Marty Cauley, Brandon Hall, Yael Abreu-Villaça, Shaqif Junaid, Hannah White, Abtin Kiany

Duke University, Durham, NC, USA

Maternal tobacco smoking has long been known to adversely affect neurobehavioral function in the offspring. Even low dose exposure to environmental tobacco or second hand smoke during development has been associated with neurobehavioral dysfunction in children. We have shown in rats that developmental exposure to a tobacco smoke extract (TSE) complex mixture at doses modeling second hand smoke causes persisting neurobehavioral impairment in the offspring with more pervasive effects of TSE than the same dose of nicotine given alone. To examine critical developmental windows of exposure, we compared pre-mating, early gestation and late gestational exposure. Female Sprague-Dawley rats were continuously exposed (SC) via minipump to TSE at a dose delivering 0.2 mg/kg/day nicotine during 10 days prior to mating or for 10 days during the first or second halves of gestation. Male and female offspring were assessed with a battery of tests for locomotor activity, anxiety, fear and cognition during adolescence and adulthood. During adolescence, late gestational TSE exposure was shown to cause significant locomotor hyperactivity and more anxiety-like behavior in the elevated plus maze in adolescence. Interestingly, exposure to TSE solely prior to mating also produced some significant behavioral effects in the offspring, including decreased habituation of locomotor activity over an hour-long session during adolescence, locomotor hyperactivity selectively in adult males and reduction in radial-arm maze working memory errors. These results reinforce findings of persistent emotional and cognitive effects after developmental exposure of rats to TSE and that persistent neurobehavioral toxicity was seen after all of the developmental windows tested. Tobacco smoke with over 4000 compounds present the classic mixture problem. Currently, we are investigating the interactions of two principal neuroactive compounds in tobacco smoke, nicotine and the polyaromatic hydrocarbon benzo(a) pyrene (BaP). Initial results indicate that gestational exposure to nicotine and BaP both have lasting behavioral consequences. Gestational BaP exposure caused a significant increase in latency to eat in a novel environment, whereas gestational nicotine eliminated the normal sex difference. It is more than just nicotine in the tobacco smoke complex mixture that causes long-lasting neurobehavioral disruption after gestational exposure. *This research was supported by the National Institutes of Health (Grant ES022831) and the U.S. Environmental Protection Agency (EPA) (Grant 83,543,701). EPA support does not signify that the contents reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use.*

DNTS 45

Interaction: Considering the Social World in Developmental Neurotoxicology

Joseph G. Grzywacz

Department of Family and Child Sciences, Florida State University, Tallahassee, FL, USA

There is a notable gap in the history of the Developmental Neurotoxicology Society: the social world that is inseparable from the developing human organism. The demonstrated effects of Adverse Childhood Experiences (ACEs) highlight the salience of the social world – particularly the family – for infants' and children's developing neural architecture. Despite this reality, the social world is rarely considered in developmental neurotoxicology. The primary goal of this Special Lecture is to stimulate consideration of Developmental Social Neurotoxicology. To accomplish this goal, the lecture will integrate the concepts of “interaction” and “probabilitistic epigenetics” from Developmental Systems Theories of human development with principles from social neuroscience to achieve three primary aims; the lecture will: (1) Highlight the conceptual and practical realities requiring consideration of the social world, particularly the family, in developmental neurotoxicology; (2) Showcase empirical examples of “interaction” that motivate considerations of the social world in developmental neurotoxicology; and (3) Outline potential areas for transdisciplinary collaboration to advance the concept of Developmental Social Neurotoxicology.

DNTS 46

The Zika Epidemic: An Update from the CDC

Margaret Honein, Dana Meaney-Delman, Coleen Boyle
Centers for Disease Control and Prevention, Atlanta, GA, USA.

In April 2016, the US Centers for Disease Control and Prevention (CDC) determined that Zika virus (ZIKV) infection during pregnancy can cause fetal brain defects and is associated with other adverse pregnancy and birth outcomes. To respond to the public health threat of ZIKV, CDC initiated and coordinated activities to understand the spectrum of outcomes that might result from ZIKV infection during pregnancy and prevent ZIKV infection in pregnant women and women who might become pregnant. CDC continues to monitor ZIKV infection during pregnancy to inform and address unanswered questions through multiple activities, including: launching surveillance of ZIKV infection in pregnancy to monitor pregnant women, fetuses, and infants in the United States, the US territories, and Colombia (in collaboration with the Colombian Instituto Nacional de Salud); launching rapid, population-based, surveillance of birth defects potentially related to ZIKV in US states and territories; launching rapid, population-based surveys to collect key information on women of reproductive age and postpartum women in the US; producing scientific guidance and extensive messaging about ZIKV diagnosis, testing, and risks associated with ZIKV infection for pregnant women and their health care providers; describing congenital Zika syndrome and other adverse outcomes associated with ZIKV; and responding to local transmission of ZIKV in the US. The spectrum of adverse outcomes associated with ZIKV infection during pregnancy remains unclear. Evidence from surveillance systems suggests that symptomatic and asymptomatic infection during pregnancy can cause brain anomalies. The period of highest risk to the fetus and the long-term impact of maternal ZIKV infection on infants and children remain questions of critical importance. Additionally, it is unknown how long the virus might persist and be infectious in blood and semen. CDC is working rapidly to collect data to inform key questions and facilitate ZIKV prevention efforts. Preventing infections in pregnant women remains a CDC priority. CDC is leveraging partnerships with state and local health departments to support timely data collection and prevention efforts. Our knowledge of ZIKV and its consequences during pregnancy is continually evolving. This presentation will share current information and preliminary results from select investigations.

DNTS 47

Neurobehavioral Aspects of Zika Virus

Vanessa van der Linden
Association for Assistance of Disabled Children (AACD), Brazil, Recife, Pernambuco, Brazil

Congenital Zika Syndrome (CZS) has as a main characteristic the brain impairment, with microcephalus, however it is still little known about this entity and its clinical spectrum that includes newborns with normal head circumference. In addition to congenital microcephaly and craniofacial disproportion, a range of manifestations, including neurologic symptoms, limb contracture, including arthrogryposis, hearing and ocular abnormalities, and brain anomalies detected by neuroimaging have been reported among neonates who had been exposed to Zika virus *in uterus*. The neurologic findings of severely affected patients include irritability, hyperexcitability, hypertonia, and dysphagia with feeding problems and secondary respiratory complications. Regardless of the ophthalmologic impairment, more than a half of the patients with the CZS and severe microcephaly have presented poor interaction with the environment related to cortical impairment. Motor disabilities are constantly found in patients with the most severe form of the disease, with the presence of pyramidal and extrapyramidal signs, usually associated with dystonic movement. These motor changes are probably correlated with the neuroimaging and pathological changes described, with predominant neural involvement. Epilepsy is frequent, even in patients with normal head circumference at birth, predominating asymmetric spasms in cluster. The rare and unusual arthrogrypotic joints did not result from abnormalities of the joints themselves and are likely to be of neurogenic origin. The pattern of brain images abnormalities in congenital Zika syndrome has been fully described, brain calcification and disorder of cortical development are the most frequent findings. Cerebellar atrophy and malformations of the brainstem may also occur. The pattern of calcifications at the junction between cortical and subcortical white matter, in addition to the cortical developmental disorders predominantly on frontal regions confers highly suggestive pattern of ZIKV congenital infection. Unlike other congenital infections, several patients are developing hydrocephalus between 3 and 12 months. The pathophysiology of hydrocephalus in CZS is still unknown. The complete neurological picture requires the central nervous system maturation and it will only become clear after, at least 18 months, so to a better definition of congenital Zika syndrome we need a longer follow-up.

DNTS 48

Zika Infection: From Basic Science to Treatment

Alysson R. Muotri
University of California–San Diego, La Jolla, CA, USA.

The recent outbreak of the Zika virus (ZIKV) has been associated with the increase in newborns with congenital malformations in Brazil. In adults, other clinical manifestations have been reported. We have previously shown that the Brazilian ZIKV ($ZIKV^{BR}$) infect fetuses, causing intrauterine growth restriction (IUGR) and microcephaly in mice. Moreover, the virus infects human cortical progenitor cells leading to an increase in cell death by apoptosis. Finally, we observed that infection of human brain organoids resulted in a reduction in proliferative zones and disrupt cortical layers. Our results indicate that the $ZIKV^{BR}$ cross the placenta and impairs neurodevelopment, causing microcephaly by targeting cortical progenitor cells, in mouse models. Given the growing threat of the ZIKV spreading, researchers worldwide have focused on vaccine development. While immunization initiatives are important, there is a need to develop clinical strategies to treat ZIKV-infected individuals, including pregnant women for whom prevention of infection is no longer an option. Indeed, ZIKV infection during the first trimester confers the greatest risk of congenital microcephaly, thus highlighting the urgent need for treatment of infected mothers. In order to provide a potential treatment against the detrimental effects of ZIKV infection, we have tested the clinically-approved antiviral inhibitors, both in vitro on ZIKV-infected human neural progenitor cells (NPCs) and cerebral organoids and in vivo using animal models. Altogether, our results revealed potential treatments that are well tolerated in vivo and able to decrease ZIKV replication. Our data demonstrate that repurposing the US FDA-approved antiviral drugs is a timely therapeutic opportunity to counteract harmful impact of the ZIKV in exposed individuals, including pregnant women.

Poster Presentations

DNTS P01

Adolescent methylmercury exposure: effects on behavioral flexibility, delay discounting, fixed-ratio performance, and gene expression in the prefrontal cortex

Steven R. Boomhower, M. Christopher Newland
Auburn University, Auburn, AL, USA

Human exposure to methylmercury (MeHg) is a significant public-health concern worldwide. In rodent models, gestational MeHg exposure distorts dopamine neurotransmission and enhances the impact of reinforcement on responding. However, the neurobehavioral impact of MeHg during other periods of development, such as adolescence, has been underexplored. The adolescent brain continues to undergo dramatic neural

remodeling, so MeHg exposure during this time may result in long-lasting cognitive and behavioral effects. The present experiments were designed to assess the extent to which behavior underlying executive functions and prefrontal-cortex gene expression were susceptible to MeHg exposure in adolescence using a mouse model. Male C57BL/6 mice were exposed to 0, 0.3, or 3.0 ppm MeHg via drinking water (n = 12/group) from postnatal day (PND) 21 to 60, the murine adolescent period. Behavioral testing began on PND 90 and included autoshaping, delay discounting, reversal learning, an extradimensional shift, and modeling fixed-ratio performance that described reinforcer efficacy, the binding of reinforcers to previous responses, and motor function. Adolescent MeHg exposure increased trials-to-criterion following a spatial-discrimination reversal and spatial-to-visual discrimination, suggesting impaired behavioral flexibility. The lower dose of MeHg (0.3 ppm) reduced estimates of delay discounting, suggesting larger-later reinforcers were preferred to smaller-sooner ones, but mice that received the higher dose of MeHg (3 ppm) showed no change relative to control. The higher dose of MeHg (3 ppm) also reduced estimates of the impact of delayed reinforcement on responding, which may be a behavioral mechanism of adolescent MeHg exposure. Directional poly(A)$^+$ RNA sequencing revealed that fourteen genes primarily involved in neural plasticity (e.g., *Fos* and *Arc*), apoptosis (e.g., *Csrnp1* and *Dusp1*), and signal transduction (e.g., *Btg2*, *Trib1*, *Arl4d*, and *Junb*) in the mouse prefrontal cortex were significantly downregulated following adolescent MeHg exposure relative to controls (n = 7/group). In summary, the prefrontal cortex and choice appear to be susceptible to MeHg exposure, as evidenced in impaired choice and operant ("voluntary") behavior that co-occur with suppressed gene expression in the prefrontal cortex. These studies carry implications for public health and the neurobehavioral mechanisms that permit MeHg toxicity.

DNTS P02

Prenatal thyroid hormone insufficiency diminishes short-term object recognition memory in Long-Evans rats

Megan Sieg [1], Catherine Townes [1], Rekha Balachandran [1], Mary Gilbert [2], Paul Eubig [1].

[1] *Department of Comparative Biosciences, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, IL, USA* [2] *U.S. Environmental Protection Agency, National Health and Environmental Effects Research Laboratory, Toxicity Assessment Division, Research Triangle Park, NC, USA*

Children whose mothers are severely hypothyroid during pregnancy exhibit learning and memory deficits. Fortunately, overt maternal hypothyroidism is usually recognized and treated. Yet, many women who are subclinically hypothyroid (SCH) are asymptomatic and are therefore never diagnosed or treated. The prevalence of SCH is thought to be higher in pregnant women than in the general population, but little is known of the effects of maternal SCH on the neurobehavioral outcomes of children. To model maternal SCH, we exposed pregnant rat dams to a low dose of propylthiouracil (3 ppm in drinking water) from gestation day 6 through postnatal day 14, and pups were cross-fostered at postnatal day 2, resulting in four treatment groups: control, prenatal exposure, postnatal exposure, and perinatal exposure. Rats were tested on the novel-object recognition paradigm at 36–38 weeks of age to examine effects of maternal SCH on short-term memory. Rats were allowed to investigate two identical objects, and then, one hour later, they were allowed to explore one of the prior objects and one novel object for 3 min in order to assess short-term object recognition memory. Prenatal exposure to PTU resulted in decreased time and decreased percent time exploring the novel object, decreased total time exploring both objects, and fewer entries to the novel object in the first minute of exploration. Postnatal exposure did not affect any of the measures examined. These results indicate that the prenatal phase of development is the sensitive period for the role of thyroid hormone in the development of novel-object recognition memory in rats. Developmentally, this corresponds with the first third to half of pregnancy in humans, suggesting that human cohort studies examining maternal SCH during the early stages of pregnancy should consider examining similar memory processes in the children of affected mothers. *Does not reflect EPA policy.*

DNTS P03

Potential Systematic Evaluation Frameworks of Mechanistic Data for Developmental Neurotoxicity Outcomes

Laura M. Carlson [1], William Mundy [2], Elaine M. Faustman [3], Deborah A. Cory-Slechta [4], Christina Sobin [5], Frances Champagne [6], Sue Makris [7], Andrew Kraft [7]

[1] *National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Durham, NC, USA* [2] *National Health and Environmental Effects Research Laboratory, Office of Research and Development, U.S. Environmental Protection Agency, Durham, NC, USA* [3] *School of Public Health, Institute for Risk Analysis and Risk Communication, University of Washington, Seattle, WA, USA* [4] *Department of Environmental Medicine, University of Rochester Medical School, Rochester, NY, USA* [5] *University of Texas El Paso, El Paso, TX, USA* [6] *Department of Psychology, Columbia University, New York, NY, USA* [7] *National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington D.C., USA*

Risk assessors have been charged with applying systematic review principles to epidemiological, toxicological, and mechanistic data sets. Potential uses for mechanistic data in risk assessment include providing biological plausibility, informing susceptibility, informing the human relevance of animal data, and establishing precursor events that are linked to apical outcomes. However, mechanistic data from developmental neurotoxicity (DNT) studies have been underutilized in risk assessment to date. A key challenge in systematically incorporating mechanistic data into human health assessments is that, as compared to studies of apical health endpoints, these data are both more abundant (mechanistic studies routinely outnumber other studies by several orders of magnitude) and more heterogeneous (e.g. species, test system, tissue, cell type, exposure paradigm, and specific assays performed). DNT evaluations are further complicated by the complex nature of the nervous system. A structured decision process for organizing, integrating, and weighing mechanistic DNT data for use in human health risk assessments will improve the consistency and efficiency of such evaluations. At last year's DNTS 2016 meeting, a symposium was held to address the application of organizing principles and frameworks for systematic evaluation of mechanistic data relevant to interpreting DNT. Importantly, several challenges were identified with framework development and implementation. For example, linking molecular and cellular events with behavior is fundamentally problematic, as behavior is a reflection of complex nervous system function. In addition, it can be difficult to determine a direction or magnitude of change in a mechanistic endpoint that can be interpreted as biologically meaningful. Furthermore, for DNT data in particular, the specific context of each exposure and outcome assessment is critical, as epigenetics, tissue type, gender, stress, age, nutrition, and other factors can modify DNT-related responses. By examining different sources of mechanistic DNT data (in vitro experiments, epidemiologic data, molecular evidence, and epigenetics), potential organizing principles and considerations were identified that have potential to advance the use of mechanistic DNT data in risk assessments. *The views expressed in this abstract are those of the authors and do not necessarily represent the views or policies of the U.S. Environmental Protection Agency.*

DNTS P04

The role of chemical speciation for manganese-induced developmental neurotoxicity through disrupting cross-talking pathways and its implication for manganese in neurodegeneration

Raul Hernandez [1], Montserrat Carrascal [2], Joaquin Abian [2], Bernhard Michalke [3], Marcelo Farina [4], David Park [5], Yasmilde González [5], Cristina Suñol [6]

[1] Federal University of São Paulo, Diadema, Canada [2] CSIC/UAB Proteomics Laboratory, Institut d'Investigacions Biomèdiques de Barcelona, IIBB-CSIC, IDIBAPS, Barcelona, Spain [3] Helmholtz Zentrum München GmbH, German Research Center for Environmental Health, Research Unit Analytical BioGeoChemistry, Neuherberg, Germany [4] Departamento de Bioquímica, Centro de Ciências Biológicas, Campus Universitário, Trindade, Bloco C. Universidade Federal de Santa Catarina, Florianópolis, Brazil [5] Cellular and Molecular Medicine. Faculty of Medicine. University of Ottawa, Ottawa, Canada [6] Department of Neurochemistry and Neuropharmacology. Institut d'Investigacions Biomèdiques de Barcelona, IIBB-CSIC, IDIBAPS, CIBERESP, Barcelona, Spain

Manganese (Mn) is an essential element, involved in several biological processes. Nevertheless; due to geogenic sources and anthropogenic activities such as mining, local levels of Mn can be significantly higher in aquatic systems and, this have become an important way in which humans, and specially infants are exposed to Mn, with increasing evidence of neurotoxicological and neurobehavioral alterations by unclear mechanisms. For that reason, we hypothesized that chemical species of manganese species can disrupt several metabolic pathways simultaneously and of manner preserved cross-species. Therefore, this study was to investigate the mechanisms mediating the toxic effects of the manganese in two well stablished developmental models such as *Danio rerio* (zebrafish) and *Mus musculus* (primary cultures of cerebellar granular cells - CGC). The biological models were exposed for $MnCl_2$, Mn(II)Cit, Mn(III)Cit, Maneb and Mancozeb respectively from 1 to 10 days; dependently of the bioanalytical approaches such as cell viability-MTT-assay, semi-quantitative proteomics - tandem mass tag (TMT), quantitative real-time reverse transcription- polymerase chain reaction (qRT-PCR), metallomics (metal bioaccumulation, metal homeostasis and its potential link with the proteome) and bioinformatics (protein-protein interaction and gene ontology analysis, using the string-database).The identification of peptides in databases for TMT was using the Protein Discovery of Thermo-Instruments software. Results were expressed as mean ± SEM of at least 3 experiments; LC50 and statistically significant differences were estimated by ANOVA (analysis of variance followed by Bonferroni's tests) and, alternative t-student, using the GraphPad Prism (GraphPad 4.0 Software Inc., San Diego, CA, USA). The study identified divalent manganese species induces calcium and iron dyshomeostasis. At the same time, independently of chemical speciation the manganese impaired the ribosome; mitochondria-energy pathway and multiple signaling pathways; which can prompt or silence the protein biosynthesis. Altogether, these findings contribute to improve the understanding about manganese in developmental neurotoxicity and neurodegenerative disorder.

DNTS P05

The behavioral and cognitive effects of chronic taurine exposure in C57BL/6 J mice: a dose-response study

Yislain Villalona, Jamie Weimer, Lisa Massie, Katelyn Dunn, Junessa Lanada, Cecile Marczinski, Christine Curran.

Northern Kentucky University, Highland Heights, KY, USA.

Energy drinks often contain high levels of taurine that could exceed recommended limits when combined with a standard diet. Since the major consumers of energy drinks are adolescents and young adults, we developed a mouse model to examine the effects of chronic, high-dose taurine consumption. In our previous studies, we found learning and memory deficits in mice treated with 0.12% taurine in drinking water from P28 to P60. The greatest deficits were seen in male mice. To follow up on these studies, we conducted a dose-response study using 0, 0.06, and 0.12% taurine in male and female C57BL/6J mice. Mice were treated from postnatal day 28 (adolescence) through completion of behavioral testing (early adulthood). Our behavioral battery includes three tests of behavior and three tests of learning and memory. Here we report results from locomotor activity with and without a caffeine challenge and tests of spatial and non-spatial learning and memory. We found no difference in baseline locomotor activity; however, taurine-treated mice showed an attenuated response to the caffeine stimulant challenge ($P = 0.001$). We found significant deficits in non-spatial learning and memory ($P < 0.05$) in the Novel Object Recognition test at both doses used. In the Morris Water Maze, we found a significant sex * treatment interaction in the Reverse Phase probe trial, but the trend was the opposite of our original findings. Males on high-dose taurine out-performed low-dose taurine mice and controls. The high-dose males also performed significantly better than high-dose females ($P < 0.01$). Together, these studies suggest caution when consuming high quantities of energy drinks during adolescence and early adulthood despite improved performance on some cognitive tests. Supported by ES020053 and GM103436.

DNTS P06

Developmental deltamethrin exposure causes adult learning and memory deficits

Emily Pitzer [1,2], Rebecca Bailey [1,2], Michael Williams [1,2], Charles Vorhees [1,2]

[1] University Of Cincinnati College of Medicine, Cincinnati, OH, USA [2] Division of Neurology, Cincinnati Children's Research Foundation, Cincinnati, OH, USA

Attention-deficit hyperactivity disorder (ADHD) is one of the most common behavioral disorders estimated to affect 8–12% of school age children. Exposure to environmental agents, such as pesticides, may contribute to the ADHD etiology. We exposed Sprague-Dawley rats to the Type II pyrethroid deltamethrin (DLM) by gavage at doses of 0, 0.25, 0.5, and 1.0 mg/kg from postnatal day (P)3–20 in a split-litter design, and rats were tested beginning at P60. DLM increased mortality at the highest dose and reduced growth at mid and high doses. DLM reduced open-field activity in females during the first 30 min of a 60 min test ($P < 0.02$). There was no effect of DLM on Morris water maze (MWM) acquisition. In MWM reversal, path efficiency and average heading error were affected ($P < 0.03$); DLM rats in mid and high dose groups had worse performance than controls. During MWM shift, there was a treatment × sex interaction on path efficiency ($P < 0.03$) and average heading error ($P < 0.02$), with the effect in males (path efficiency $P < 0.007$; average heading error $P < 0.003$). In Cincinnati water maze (CWM) there were effects on latency ($P < 0.009$) and errors ($P < 0.008$) in high dose males. Acoustic and tactile startle (ASR/TSR) showed effects of DLM ($P < 0.006$) in which high and mid-dose DLM groups had increased startle compared with controls. DLM males had increased response amplitudes compared with controls (treatment × sex interaction: $P < 0.02$). For conditioned fear, there was a treatment × sex interaction ($P < 0.02$). During conditioning, DLM males were less active before and after tone-shock pairings (P

< 0.02) compared with controls. The high dose DLM group showed reduced fear behavior (P < 0.04) for contextual memory. There were no effects for cued fear. There was a treatment effect (P < 0.01) on MK801-induced activity in which the high dose group had reduced activation in response to the drug compared with controls. The data indicate that neonatal DLM exposure has adverse long-term effects on learning, memory, startle, and glutamatergic responsiveness and these effects are more prominent in males but no ADHD-like behaviors were observed. (Supported by NIH training grant T32 ES007051).

DNTS P07

Does High Quality Maternal Care Ameliorate the Effects of Prenatal Stress?

Leah Grande [1], Curt Sandman [2], Laura Glynn [2,3], Elysia Davis [1]

[1] University of Denver, Denver, CO, USA [2] University of California Irvine, Irvine, CA, USA [3] Chapman University, Orange, CA, USA

This prospective, longitudinal study evaluated whether high quality maternal care can ameliorate the consequences of prenatal stress. Maternal stress is a well-known teratogen that affects a broad range of child development outcomes (Bea et al., 2004; Bergman et al., 2007). Very little is known about postnatal effects that may mitigate the impairments induced by prenatal stress. Animal studies find that postnatal care can reverse the long-term impairments induced by prenatal stress (Maccari et al., 1995; Wakshlak et al., 1990). However, only a few human studies have evaluated whether postnatal care can reduce the impact of prenatal maternal stress on infant outcomes (Bergman et al., 2008; Bergman et al., 2010; Kaplan et al., 2008). Highly sensitive maternal care has been shown to be one of the most potent influences on child development. Thus, it is plausible that high quality maternal care may buffer or even reverse the effects of prenatal stress. This study sought to evaluate whether high quality maternal care could mitigate cognitive impairments associated with prenatal stress exposure.

Maternal prenatal and postnatal stress was assessed via self-reports of depression, trait and state anxiety, pregnancy-specific anxiety, and perceived stress for 145 individuals at 15, 19, 25, 31 and 36 gestational weeks. Quality of maternal care was evaluated at one year using a standardized laboratory observational measure which emerged from the NICHD Early Child Care Research Network. The Bayley Scales of Infant Development (BSID-II), particularly the Mental Developmental Index (MDI), was administered to assess infant cognitive development at two years. Maternal IQ was assessed via the WAIS and prenatal, obstetric, and socioeconomic factors were collected.

Elevated maternal psychological stress during pregnancy predicted poor child cognitive performance at 2 years of age ($r(145) = -4.610$, $p = 0.005$). Notably, there was a significant interaction between prenatal stress and postnatal sensitivity ($r(145) = 1.865$, $p = 0.028$), indicating high quality care postnatally mitigated the effects of prenatal stress. This association remained after considering maternal postnatal stress, sociodemographic covariates, as well as maternal intelligence. These findings suggest that maternal sensitivity may ameliorate adverse cognitive outcomes associated with prenatal stress exposure.

DNTS P08

Exposure to Traumatic Events in Childhood Shapes Stress Physiology during Pregnancy: Implications for the Intergenerational Transmission of Risk

Danielle Swales [1], Stephanie Stout [1], Laura Glynn [2], Curt Sandman [2], Deborah Wing [3], Elysia Davis [1]

[1] Department of Psychology, University of Denver, Denver, CO, USA [2] Department of Psychology, Chapman University, Orange, CA, USA [3] Obstetrics and Gynecology, University of California, Irvine, Irvine, CA, USA

Childhood exposure to traumatic events can have a profound and dysregulating impact on stress physiology that may persist into adulthood. Relatively little however is known about how childhood trauma may influence maternal physiology during pregnancy. Pregnancy is a time in which the next generation may be particularly vulnerable to the disorganizing influence of dysregulated cortisol, a key stress hormone and end product of the hypothalamic pituitary adrenal (HPA) axis. The current study therefore seeks to evaluate whether childhood traumatic events predict prenatal cortisol concentrations, assessed in hair as an index of cumulative cortisol production. **Method:** The current study included 88 pregnant women ($M = 28.6$ gestational weeks, SD = 3.2). Maternal life events in childhood (0–10 years), adolescence (11–17 years), adulthood (18 + years), and during the current pregnancy, were assessed using a modified form of the Life Events Checklist (LEC). Maternal hair cortisol concentrations were assessed during the beginning of the third trimester, providing a measure of cumulative cortisol production over the previous three months of gestation. **Results:** Linear regression models revealed that exposure to a greater number of traumatic events in childhood predicted elevated hair cortisol concentrations during pregnancy ($\beta = 0.10$, $p < 0.01$), even after accounting for exposures in adulthood and gestational age at the time of sample collection ($\beta = 0.7$, $p = 0.03$. Further, analyses revealed an interactive effect between child and adult experiences, suggesting that childhood exposure to a traumatic event sensitize the HPA-axis to the impact of subsequent exposure in adulthood ($\beta = 0.04$, $p = 0.02$). **Discussion:** Our findings highlight the profound impact of childhood traumatic experiences on maternal stress physiology. Given that the prenatal period is a sensitive window of neurodevelopment, the fetus may be particularly susceptible to the adverse consequences of dysregulated cortisol production. Childhood exposure to traumatic events and associated changes in prenatal maternal cortisol production, may therefore have important implications for the next generations. Taken together, this finding suggests that maternal HPA-axis function may be an important biological pathway underlying intergenerational consequences of childhood trauma.

DNTS P09

Identifying Predictors of Intimate Partner Violence during Pregnancy to Deter the Intergenerational Transmission of Maternal and Fetal Risk

Victoria Atzl, BS [1], Angela Narayan, PhD [1], Luisa Rivera, MPH [2], Alexandra Ballinger, BS [3], Melanie Thomas, MS, MD [3], Alicia Lieberman, PhD [3]

[1] University of Denver, Denver, CO, USA [2] Emory University, Atlanta, GA, USA [3] University of California, San Francisco, San Francisco, CA, USA

Background: There is growing support for identifying social stressors in addition to biochemical hazards that impact fetal health and neurodevelopment during pregnancy (e.g., Wright, 2009). Intimate Partner Violence (IPV) during pregnancy is a social stressor that may profoundly impact maternal and child perinatal health by leading to maternal injury and fetal morbidity or alternatively, contributing to maternal psychological distress, infant low birth weight and pre-term birth, which can have detrimental neurodevelopmental effects (e.g., Shah & Shah, 2010). Scant evidence, however, examines *predictors of* IPV during pregnancy. Identifying predictors could inform how to deter prenatal IPV, thereby protecting mothers and infants' neurodevelopmental health. The current study examined maternal history of childhood maltreatment, a known precursor to IPV (Narayan et al., 2013), and IPV *before* pregnancy as predictors of IPV during pregnancy. We hypothesized that IPV before pregnancy would mediate childhood maltreatment and IPV during pregnancy.

Method: Participants were 101 ethnically diverse pregnant women ($M = 29.10$ years, $SD = 6.56$, range = 18–44). Childhood maltreatment was assessed using the first five items of the Adverse Childhood Experience questionnaire (emotional, physical and sexual abuse, and emotional and

physical neglect between 0 and 18 years). Bidirectional IPV before and during pregnancy were measured with the Conflict Tactics Scale, where 0 = no maternal IPV perpetration or victimization, 1 = either, 2 = both.

Results: Linear regression analyses indicated that childhood maltreatment significantly predicted more bidirectional IPV during pregnancy ($b = 0.11$, $p < 0.05$) but this relationship became non-significant ($b = 0.07$, $p < 0.05$) when IPV before pregnancy was added to the model ($b = 0.26$, $p < 0.05$). A Sobel test confirmed that IPV before pregnancy significantly mediated childhood maltreatment and IPV during pregnancy, as hypothesized ($z = 2.03$, $p < 0.05$). These results held while controlling for prenatal perceived stress, maternal age and education, weeks pregnant, first pregnancy, and Spanish/English language.

Discussion: Childhood maltreatment activates a legacy of violence through IPV in adulthood to increase the risk for bidirectional IPV during pregnancy. Prevention and policy efforts to deter child maltreatment and deescalate IPV before pregnancy would have enduring positive effects on fetal and infant development.

DNTS P10

Predictors of Substance Use Disorders among Emerging Adults with Prenatal Cocaine Exposure

Sonia Minnes [1,2], Meeyoung Min [1,2], June-Yung Kim [1,2], Sun Kyung Kim [1,2], Paul Weishampel [1,2], Lynn Singer [1,3]

[1] Case Western Reserve University, Cleveland, OH, USA [2] Mandel School of Applied Social Science, Cleveland, OH, USA [3] School of Medicine, Cleveland, OH, USA

Introduction: Prenatal cocaine exposure may increase the risk of substance use disorders (SUD) during emerging adulthood through direct neurotoxic effects on monoamine rich areas of the brain associated with self-regulatory behaviors during fetal development or indirectly through suboptimal environmental conditions. **Methods:** Preliminary results of 189 primarily low socioeconomic status, African American subjects (94 non-cocaine exposed (NCE) and 95 prenatally cocaine exposed (PCE)), recruited at birth for a study of the developmental effects of prenatal cocaine exposure were assessed for substance use disorders at age 21 using the Substance Abuse Module (SAM-5). Logistic regression was completed for positive diagnosis with at least 10% of the group reporting positive cases of mild, moderate or severe SUD. Confounding maternal/caregiver and environmental variables, including other prenatal drug exposures, caregiver psychological distress, quality of the home environment, exposure to violence sexual maltreatment were examined. **Results:** Substance use disorders were reported at 30% for tobacco, 23% for alcohol and 31% marijuana, with no group differences by prenatal cocaine exposure status. After adjusting for confounders, there were no PCE or other prenatal drug exposure (alcohol, tobacco, marijuana) effects. However, higher HOME score (quality of home environment) was related to a lower odds of a tobacco use disorder (OR = 0.93, 95%CI (0.88–0.99), p < 0.02) and marijuana use disorder (OR = 0.91, 95%CI (0.86–0.96), p < 0.002). Experiencing sexual maltreatment increased the odds of tobacco use disorder by 3.3 times (OR = 3.28, CI (1.48–7.27), p < 0.004) and marijuana use disorder by 4 (OR = 4.13, 95%CI (1.72–9.94), p < 0.002). Childhood experience of maltreatment increased the odds of alcohol use disorder by 3 (OR = 2.89, 95%CI (1.01–8.24), p < 0.05). There were no interactions between PCE and gender or PCE and childhood victimization or maltreatment. Externalizing behavior at age 15 was also associated with tobacco use disorder (OR = 1.07, 95%CI (1.03–1.12), p < 0.001) and marijuana use disorder (OR = 1.06, 95%CI (1.02–1.11), p < 0.007). **Discussion:** Lower quality of home environment, childhood victimization and early externalizing symptoms, frequently co-occur with prenatal cocaine exposure, and were predictors of substance use disorders in emerging adulthood. Results indicate that early interventions to improve childhood environmental experiences and specifically tailored drug use prevention programs are needed.

DNTS P11

Prenatal and postnatal tobacco and cannabis exposure: Effects on focused attention in infancy

Rina Eiden [1], Shannon Shisler [1], Pamela Schuetze [2]

[1] State University of New York, Buffalo, NY, USA [2] Buffalo State College, Buffalo, NY, USA

Although cannabis is one of the most common substances used with tobacco during pregnancy, few studies have examined the effects of prenatal exposure to both substances together (PTCE). This is especially critical for aspects of child cognitive functioning that have long-term implications for learning and development such as focused attention. We examined the association between prenatal tobacco exposure (PTE) and PTCE on infant focused attention at 9 months of age. The sample consisted of 251 pregnant women (75 PTE, 103 PTCE, 73 control) recruited in the first trimester of pregnancy and assessed once in each trimester. Prenatal exposure was assessed using multiple methods: maternal self-report, maternal saliva, and infant meconium. Mothers and infants were assessed at 2 and 9 months. Infant salivary cotinine and maternal self-reports of postnatal tobacco and cannabis use were obtained at both time points. Maternal prenatal anger/hostility was included in the model given associations with continued maternal substance use and child outcomes. Infants were placed in a high chair and presented with a series of four novel toys in a specific order for the measure of focused attention. This was videotaped and coded by two raters blind to group status using a 5-point global rating scale that included several dimensions of focused attention such as duration of attention, latency to look, number of focused looks, and vigor of movement following guidelines by Lawson and Ruff (2001). There were no associations between focused attention and infant birth outcomes. Results from MANOVA with group status as the independent variable indicated a significant group difference on focused attention, $F(8, 422) = 2.19$, $p = 0.03$. Univariate analyses indicated significant group differences on focused attention for toys 1 and 2. Infants in the PTCE group had the lowest focused attention, especially compared to infants who were exposed to PTE only. Higher infant salivary cotinine at 9 months was associated with lower focused attention to toys 1 and 4. Results highlight the importance of examining joint effects of both tobacco and cannabis on infant focused attention.

DNTS P12

Placental CRH predicts risk of preterm imminent delivery: Implications for the timing of betamethasone administration

Leah Grande* [1], Danielle Swales* [1], Michelle Edelmann [1,4], Curt Sandman [2], Laura Glynn [2,3], Deborah Wing [2], Elysia Davis [1] (Note: *First and second authors contributed equally)

[1] University of Denver, Denver, CO, USA [2] University of California Irvine, Irvine, CA, USA [3] Chapman University, Orange, CA, USA [4] University of Colorado Anschutz Medical Campus, Aurora, CO, USA

Background: The administration of synthetic glucocorticoids (sGCs) to women at risk of preterm delivery is a lifesaving intervention that promotes fetal lung maturation and decreases morbidity and mortality among preterm infants born between 24 and 34 gestational weeks.

Glucocorticoid treatment is maximally efficacious for lung maturation when administered within a week of delivery for infants born before 34 weeks. In addition to these positive benefits, sGCs have been associated with a number of adverse outcomes in infancy and childhood, including impaired brain development and cognitive functioning, and emotional dysregulation. Accurately identifying the timing of preterm delivery therefore is critical for two reasons: first, to ensure that sGCs are administered to preterm infants within a week of delivery; and second, to avoid unnecessary sGC administration among infants who will be born full term. A plausible biomarker for predicting time of delivery is placental corticotropin-releasing hormone (pCRH). **Method:** The current study included 121 pregnant women at risk for spontaneous preterm labor who were prescribed betamethasone (M = 28.4 gestational weeks, SD = 3.2). pCRH concentrations were evaluated prior to betamethasone administration and the timing of delivery was recorded. **Results:** Cox proportional hazard models revealed that for every increase of 10 pmol/L of pCRH, the risk of imminent delivery increased by 5.8% (β = 0.0057, p

< 0.0001). Receiver operating characteristic (ROC) curves were conducted to evaluate the sensitivity and specificity of pCRH in predicted delivery with a week of sGC administration. At the optimal cutoff of 15.5 pmol/L, the model correctly identified 96% of women who delivered with a week (sensitivity), whereas 69% of women were falsely identified and delivered outside that window (1 - specificity). **Discussion:** The current study provides evidence that maternal pCRH levels may be a clinically relevant diagnostic tool to identify women who may benefit from sGC treatment. Increasing the sensitivity and specificity in the prediction of delivery within a week may optimize sGC treatment, providing necessary benefits to fetal lung growth while avoiding the consequences of unnecessary administration.

DNTS P13

Associations of maternal prenatal stress with measures of cognition in 4.5-month-old infants.

Francheska M. Merced-Nieves [1,2], Salma Musaad [4], Andrea Aguiar [2,3], Kelsey L.C. Dzwilewski [1,2], Susan A. Korrick [5,6], Susan L. Schantz [1,2,3]

[1] Neuroscience Program, University of Illinois at Urbana-Champaign, Urbana, IL, USA [2] Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, Urbana, IL, USA [3] Department of Comparative Biosciences, University of Illinois at Urbana-Champaign, Urbana, IL, USA [4] Deparment of Human Development and Family Studies, University of Illinois at Urbana-Champaign, Urbana, IL, USA [5] Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA [6] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA

Recent studies suggest that prenatal stress can alter sex-specific characteristics, including anogenital distance and play behavior. This analysis of 87 infants from a prospective birth cohort assessed whether prenatal stress disrupts the sexually dimorphic pattern typically observed on a physical reasoning task. Maternal stress was assessed at 10–14 and 34–36 gestational weeks using the Perceived Stress Scale. The median was used to classify women: those scoring below the median at both times (low stress), above the median at one of the two times (medium stress), and above the median both times (high stress). At 4.5 months infants saw videos of two events: one impossible and the other possible. In the impossible event a gloved hand placed a box against a wall without support underneath. In the possible event the hand placed the box against the wall, supported by the floor. Looking time was recorded via infrared eye-tracking. At 4.5 months, typically, girls realize the unsupported box should fall and look at this event longer, while boys don't and look at both events about equally. A Wilcoxon test showed that the difference in looking time between the two events was higher among females than males (4.0 vs − 1.1 s; p = 0.005). A generalized linear model was used to examine the association of child sex, maternal stress and their interaction, after adjusting for household income, maternal education, child age, order of event presentation and the sex by order interaction. The model revealed a significant sex by stress interaction (p = 0.006). A larger difference was observed between low stress males and females relative to the difference between high stress males and females ($\beta_{standardized}$ = 0.52, p = 0.004). The difference between sexes in the medium stress category was not different relative to high stress ($\beta_{standardized}$ = 0.01, p = 0.961). Pairwise comparisons revealed that high-stress females had a smaller (more male-like) difference in looking time than low-stress females (2.4 vs 11.1 s; p = 0.017); there were no significant differences by stress in males. This suggests prenatal stress may impact sex-specific aspects of infant cognition, shifting females to a more male-like pattern, but needs corroboration in a larger sample. ES022848; RD83543401.

DNTS P14

Associations of adolescent exposure to Polychlorinated Biphenyls or Polybrominated Diphenyl Ethers with cognitive flexibility in children of sports anglers

Supida Monaikul [5], Joseph Gardiner [3], Natawut Monaikul [2], Andrea Aguiar [1], Paul Kostyniak [4], Susan Schantz [1]

[1] University of Illinois, Urbana-Champaign, Urbana, IL, USA [2] University of Illinois at Chicago, Chicago, IL, USA [3] Michigan State University, East Lansing, MI, USA [4] University of Buffalo, Buffalo, NY, USA [5] Experimur, Chicago, IL, USA

Polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) are ubiquitous environmental contaminants that persist in our environment due to their resistance to degradation. Converging human and animal data suggest that perinatal exposure to these compounds is associated with cognitive deficits, including deficits in executive functions such as cognitive flexibility. Little is known about PCB or PBDE exposure during another critical period of brain development: adolescence. During adolescence, the prefrontal cortex as well as executive functions modulated by this brain region are maturing. To explore the potential impact of PCB and PBDE exposure during adolescence on cognitive flexibility, data were collected from 115 12–18 year-old children of sport anglers in Green Bay, Wisconsin, who were exposed to these compounds through consumption of fish from contaminated waters. PCB and PBDE congeners were measured in serum by capillary column gas chromatography with electron capture detection. Median total PCB concentration in serum was 33.00 ng/g-lipid (range: 2.56 to 389.10); median total PBDE concentration in serum was 29.14 ng/g-lipid (range: 1.23 to 244.16). Cognitive flexibility was assessed using the CANTAB Intradimensional/Extradimensional (ID/ED) set-shifting task. For each chemical, total trials to complete all phases of the ID/ED task was analyzed as a count variable using a negative binomial regression adjusted for subject age, sex and IQ. The models included a sex by exposure interaction term to explore whether PCB or PBDE exposure impacted males and females differently. Lipid-adjusted values for total PCBs and PBDEs were log-transformed prior to analysis. Neither subject sex nor its interaction with exposure was significant in either model. Thus, the interaction term was dropped from the final models. A roughly 10-fold increase in PBDEs (2 SD on the log-scale) was associated with an 18% increase in trials (estimate = 1.18; 95% CI: 1.23, 2.40, p

< 0.002). PCB exposure produced a 28% increase in trials to complete the task, but was not significantly associated with total trials (for a 2 SD increase, estimate = 1.28, 95% CI: 0.90, 1.83, p = 0.17). These results suggest that exposure to PBDEs or PCBs during adolescence may negatively impact executive functions, such as cognitive flexibility, that are developing during that time.

DNTS P15

Altered Cocaine-induced Sensitization in Middle-aged Rats Following Gestational Exposure to Cocaine and/or Nicotine

Sonya K. Sobrian, Carlana Ramlochansingh, Jewel Wright, Daniella Kuhn

Howard University College of Medicine, Washington, DC, USA

We have previously shown that prenatal exposure to nicotine, either alone or in combination with cocaine, produced persistent differential effects on the induction of behavioral sensitization to nicotine in aged offspring. In a similar study, the induction and maintenance cocaine sensitization, induced by an 8-day injection paradigm, and assessed by cocaine challenge 2 weeks later, was examined in 322-day old male and female rats exposed on gestation days 8–20 to one of the following treatments: 1) low cocaine: 20 mg/kg/day [LC]; 2) high cocaine: 40 mg/kg/day [HC]; 3) low nicotine: 2.5 mg/kg/day [LN]; 4) high nicotine: 5 mg/kg/day [HN]; 5) low cocaine + high nicotine [LC/HN]; 6) high cocaine + low nicotine [HN + LC]; 7) pair-fed: food intake yoked to HC dams [PF]; and 8) saline controls: daily injection of 0.9% NaCL [SAL]. Behavioral sensitization developed only in LC, HN, LC/HN and PF offspring; horizontal activity increased between day 1 and day 8. However, daily increases were evident only in the LC groups, indicative of an enhanced rate of development. In the remaining 2 low nicotine and control groups, the initial cocaine-induced increase in activity remained stable across the induction paradigm. Drug challenge with 1, 3 and 10 mg/kg of cocaine 2 weeks later resulted in decreased horizontal activity at the two lower doses in all prenatal treatment groups, suggestive of desensitization. This decrease was exacerbated in prenatal cocaine groups. In contrast, at the 10 mg/kg challenge dose sensitization was again evident. During induction of sensitization and maintenance testing, female activity in all groups was higher than that of males. These data indicate that prenatal exposure to low dose nicotine, either alone or in combination with cocaine inhibits the induction of cocaine-induced behavioral sensitization. In contrast, prenatal exposure to low dose cocaine, either alone or combined with nicotine, enhances the induction of this phenomenon, suggestive of a greater risk of stimulant abuse later in life. Research supported by NIH grant S06GM08016–36 to SKS.

DNTS P16

An Assessment of Spatial Learning and Memory using the Morris Water Maze Following Adolescent Nicotine Exposure in Adult Long-Evans Rats

Evan Youker, Korinna Sherman, Greg Butcher, Laura Pickens

Thiel College, Greenville, PA, USA

Adolescence is a period of heightened vulnerability to nicotine exposure. Exposure to nicotine during this period may cause behavioral and neural deficits later in adulthood. In the current study, the effects of adolescent nicotine exposure on learning and memory were analyzed behaviorally and histologically in adult Long-Evans rats. For the behavioral portion of the study, we hypothesized that nicotine exposure in adolescence would not affect spatial learning, but would have a negative effect on memory retention. For the histological portion of the study, we hypothesized that rats exposed to nicotine will have a decrease in size of the CA1, CA3, and dentate gyrus regions. Adolescent rats were given once-daily intraperitoneal (IP) injections of 1.0 mg/kg nicotine or saline vehicle from post-natal day (PND) 25 through PND 59. An assessment of spatial learning in adulthood using the Morris Water Maze (MWM) began on PND 65 in which each rat completed four trials per day for a total of five days. On PND76, one week following the last day of spatial acquisition, a memory retention test was performed. The following day on PND 77, rats were sacrificed by means of transcardial perfusion, postfixed and sectioned using a cryostat. Hippocampal tissue was stained using Cresyl violet (Nissl stain) for morphological analysis. The behavioral assessment included an analysis of rats' latency to platform, total distance travelled, and velocity during MWM spatial acquisition and the 1-week retention test. It was found that adolescent nicotine exposure did not significantly impair any of these measures of spatial learning and memory. Results will also include a morphological analysis of the CA1, CA3, and dentate gyrus of the hippocampus between control and experimental rats.

DNTS P17

Developmental Exposure to Mild Variable Stress: Adult Offspring Performance in Trace Fear Conditioning after Prenatal and Postnatal Stress.

Jason Franklin, Virginia Moser, Wendy Oshiro, Tracey Beasley, Kathy McDaniel, David Herr

U.S. Environmental Protection Agency, Office of Research and Development, Research Triangle Park, NC, USA

In utero exposure to mild variable stress has been reported to influence learning and memory formation in offspring. Our research aims to examine whether nonchemical environmental stressors will exacerbate effects from chemical exposure. This study utilized a varying stress paradigm to simulate human psychosocial stress incurred during and after pregnancy to identify phenotypic learning changes in adult offspring. In addition, we compared these behavioral outcomes to rat performance induced by perinatal exposure to manganese (Mn), a neurotoxic environmental element, at 2 or 5 g/l in drinking water throughout gestation and lactation. Pregnant Long Evans rats were exposed to an unpredictable series of mild stressful events which had previously been shown to increase maternal corticosterone levels. These nonchemical stressors were presented from GD 13 through GD 21 and included varying noise, light, housing, and confinement during both sleep and wake cycles. A subgroup of offspring was also exposed to periods of maternal separation. Starting at PND 97 offspring were trained with a trace fear conditioning protocol whereby rats were exposed to a compound cue (light and tone) followed by 30 s (trace period) and a mild foot shock (1 mA, 0.5 s). Five paired training sessions occurred on the first day. The following day, context and cue learning were assessed by measuring motor activity. Preliminary data suggests adult offspring learned the task and exhibited reduced movement in response to both context and cue regardless of stress or Mn exposure. Continued research will examine treatment related changes in the offspring of dams concurrently exposed to Mn and prenatal stress, including if there are transcriptional changes to RNA in the hippocampus or amygdala of adult offspring after learning the trace fear conditioning task. *This is an abstract of a proposed presentation and does not necessarily reflect EPA policy.*

DNTS P18

Learning and memory deficits from neonatal methamphetamine in Sprague-Dawley rats are not ameliorated by blockade of reactive oxygen species

Michael Williams, Sarah Jablonski, Charles Vorhees

Division of Neurology, Cincinnati Children's Research Foundation, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

In utero methamphetamine (MA) exposure leads to a range of adverse effects, such as decreased attention, reduced working-memory capability, behavioral dysregulation, and spatial memory impairments in exposed children. Rats exposed to MA postnatally, as a model of late-term human exposure have deficits in learning and memory as well as other behavioral disorders. In adult rats, the effects of MA can be ameliorated by the administration of the spin trapping agent, N-tert-butyl-α-phenylnitrone (PBN). In the current experiment, Sprague-Dawley rats were administered PBN 30 min prior to MA from postnatal day (P)6–15. The 4 males and 4 females in each litter were randomly divided into 1 of 4 groups given 0 (SAL) or 40 mg/kg PBN prior to each MA dose (0 or 10 mg/kg, 4 × per day), i.e. SAL-SAL, SAL-MA, PBN-SAL, and PBN-MA. Littermates underwent Cincinnati water maze, Morris water maze, and radial water maze assessment beginning on P30 (males) or P60 (females). Males were also tested for contextual and cued fear, while females were trained in one-trial passive avoidance. At both ages, neonatal MA induced deficits in all tests, except for

one-trial passive avoidance. PBN did not ameliorate these effects. Taken together, MA induced learning deficits emerge early and persist into adulthood, but may not be mediated by the generation of reactive oxygen species. (Support: T32 ES007051 and Division of Neurology).

DNTS P19

Thyroid Hormone Insufficiency Induced by Perchlorate in the Pregnant Rat Results in a Cortical Heterotopia in the Brains of Offspring

Mary Gilbert [1], Spring Stephanie [1,2], Jermaine Ford [1], Richard Ford [1,2], Susan Thomas [1,2], Katherine O'Shaughnessy [1,2], Carmen Wood [1]

[1] *US EPA, Research Triangle Park, NC, USA* [2] *ORISE, Oak Ridge, TN, USA*

We have previously reported the presence of a structural defect, a heterotopia, in the brains of rat pups exposed in utero to the thyroid hormone (TH) synthesis inhibitor propylthioruracil (PTU). TH insufficiency during late gestation/early postnatal period is required to induce this defect, and its magnitude and incidence are dose-dependent. The present study extends these observations to the environmental contaminant ammonium perchlorate. Pregnant LE rat dams were placed on an iodine-controlled diet on gestational day (GD)2. On GD6, perchlorate (0 1 30,300 1000 ppm) was administered through the drinking water. Blood was sampled from the tail on GD15. At sacrifice on GD20, blood and thyroid glands were collected from dams; blood, brain, thyroid glands from fetuses. A subset of 3 dams from each of the 0, 30, 300 and 1000 ppm dose groups were maintained on perchlorate until postnatal day (PN)15. Pups were sacrificed on PN0, 2, 15 and blood and brains collected. Increases in thyroid weight and qPCR of transcripts (*Nis, Tpo, Tg, TshR*) in the thyroid gland of the dam and the fetus on GD20 revealed activation of the thyroid axis at the two highest dose levels. Serum T4 but not T3 was reduced in dams at 300 and 1000 ppm on GD15, GD20, PN15. Serum T4 was also reduced in offspring on GD20 and PN0, but unlike dams, had returned to control levels by PN2. Expression of TH-responsive genes in the fetal cortex (*Bdnf, Bmp7, Dio2, Camk$_{iv}$, Sema7a, Klf9, Slc7A3, ThrB*) were not changed by perchlorate. A male and female pup from each litter sacrificed on PN15 revealed heterotopia (

$> 0.025 mm^3$) in 0%, 30%, 70% and 100% of animals at 0, 30, 300 and 1000 ppm dose, respectively. Although considerably smaller in size than that seen with PTU, heterotopia were larger at the highest doses of perchlorate. Although preliminary and based on a small sample size, these findings are consistent with prenatal TH insufficiency as essential for heterotopia formation. Further, they suggest that this structural anomaly may provide a brain-based biomarker of neurodevelopmental insult associated with moderate developmental TH disruption. *Does not reflect EPA policy.*

DNTS P20

Neurobehavioral and Neuroanatomical Consequences of Cell-type Specific Inactivation of Dopamine D2 Receptors in the Mouse Brain

Gloria Lee [1], Devon L. Graham [1], Lisa R. Anderson [1], Taylor S. Trammell [1], Marcelo Rubinstein [2], Gregg Stanwood [1]

[1] *Biomedical Sciences and Center for Brain Repair, Florida State University College of Medicine, Tallahassee, FL, USA* [2] *Instituto de Investigaciones en Ingeniería Genética y Biología Molecular, Consejo Nacional de Investigaciones Científicas y Técnicas, Buneos Aires, Argentina*

Neuropsychiatric disorders including depression, schizophrenia, and attention deficit disorders have a developmental basis linked with disruptions in dopamine (DA) homeostasis within the forebrain. We and others have previously demonstrated that loss of DA D2 receptors (D2R) can alter neuronal migration, cerebral cortical interneuron expression, and behavioral outputs. For example, global deletion of D2Rs.

results in a developmentally-derived and persistent upregulation of GAD67 + and parvalbumin + interneurons within the anterior cingulate cortex (Graham et al., ACS Chem Neurosci., 2015, 6:297–305). The current study is aimed at identifying which neuronal subpopulations are responsible for D2R-mediated effects on cerebral cortical development. We deleted D2R (Drd2flox/flox mice) from either telencephalic glutamatergic neurons (Emx1tm1(cre)Krj), or select GABAergic interneurons (Nkx2-1cre2Sand). Conditional knockouts from both lines (Drd2flox/flox;Emx1Cre + or Drd2flox/flox;Nkx2.1Cre +) exhibited no differences in tests of anxiety-like behaviors, depression-like behavior or working and spatial memory, relative to controls. Furthermore, GABAergic or glutamatergic D2R-cKO lines exhibited unaltered basal locomotor behavior, although there were line-specific alterations in MK-801-induced locomotion. However, D2R-cKO lines exhibited distinct differences in performance during a rotarod task such that D2R deletion in GABAergic interneurons had increased latencies while D2R deletion in glutamatergic neurons resulted in decreased latencies. These data suggest opposing roles for D2Rs within specific neuronal subtypes in the regulation of motor coordination and perhaps motor learning. At the cellular level, there were no significant changes in GAD67 + or parvalbumin + interneurons in the anterior cingulate cortex in either D2R-cKO line, suggesting that loss of D2Rs in both excitatory and inhibitory neurons may be necessary to produce frank changes in interneuron number. Ongoing studies are examining forebrain circuitry, gene expression patterns, in addition to more nuanced social and cognitive behaviors in the cKO mice. These models will allow us to identify developmental, cellular and behavioral roles of D2R within various cell types of the telencephalon and how dysfunction of D2R contributes to the development and pathophysiology of neuropsychiatric disorders. *Supported by a NARSAD Independent Investigator Award, FSU College of Medicine, and the FSU Center for Brain Repair.*

DNTS P21

Delineating the role of GLP-1R in various aspects of cocaine reward

Devon Graham [1], Michael Campos [2], Heather Durai [2], Anders Fink-Jensen [3], Aurelio Galli [2], Gregg Stanwood [1]

[1] *Florida State University College of Medicine, Tallahassee, FL, USA* [2] *Vanderbilt University, Nashville, TN, USA* [3] *University of Copenhagen, Copenhagen, Denmark*

The glucagon-like peptide-1 receptor (GLP-1R) has been implicated in a number of physiological functions, such as energy homeostasis, food and drug reward, learning and memory, and neuroprotection. We have shown that GLP-1R activation attenuates the rewarding properties of cocaine as measured by conditioned place preference (CPP). However, the development of CPP relies on delivery of the drug by the experimenter; thus, it is not contingent upon drug administration by the subject. Therefore, we sought to understand the role of GLP-1R in other reward-related aspects and hypothesized that GLP-1R would alter cocaine-induced behaviors relative to these outputs. GLP-1R-induced decrease in cocaine reward was not associated with a decrease in cocaine-induced locomotor activity. Using cocaine behavioral sensitization, a paradigm that is predictive of drug abuse liability, we found that cocaine sensitization was not altered by GLP-1R activation. In cocaine self-administration, administration of a GLP-1R agonist dose-dependently decreased the number of self-administered cocaine infusions. These data indicate that GLP-1R activation specifically decreases the rewarding properties of cocaine yet has no effect on the locomotor-stimulating properties of this drug. Furthermore, we developed a BAC transgenic reporter mouse to determine GLP-1R expression patterns in the brain. GLP-1R is highly expressed in some areas of reward circuitry of the brain, such as the lateral septum, but is sparse in other such areas such as the nucleus accumbens, ventral tegmental area, or substantia nigra. These data indicate that GLP-1R has a divergent role in functional responses to cocaine and that these behaviors indicate a role for GLP-1R outside of the prototypical regions often linked to drug reward. Furthermore, peripheral GLP-1R expression fluctuates during development, and these alterations improve the survival and health of the developing animal. We are currently studying developmental regulation of GLP-1R within the CNS to determine if receptor perturbations alter susceptibility to drugs of abuse later in life. *Supported by the McManus Charitable Trust, R21DA035588 (GDS, AG), FSU College of Medicine, and the FSU Center for Brain Repair.*