Neurotoxicology and Teratology 55 (2016) 58–75

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

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

Fortieth Anniversary Annual Meeting of the Developmental Neurotoxicology Society Held in Conjunction with the 56th Annual Meeting of the Teratology Society Grand Hyatt San Antonio, San Antonio, Texas June 25–29, 2016

2016 Richard Butcher Travel Awards, Supported by San Diego Instruments
Jennifer Walters
National Center for Toxicological Research (NCTR)/FDA
Single and repeated exposures to the volatile anesthetic isoflurane do not impair operant performance in aged rats

Kelsey Dzwilewski
Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign
Associations of prenatal exposure to phthalates and bisphenol A with measures of cognitive function in 7.5-month-old infants

2016 Patricia Rodier MidCareer Award
Christina D. Chambers (Nominated by Ludmila Bakhireva)
University of California San Diego, Center for Better Beginnings, Department of Pediatrics
Research on long term outcomes following prenatal exposures: rarely studied but sorely needed

DNTS Conference Awards
Jenna Sprowles (supported by DNTS Board)
Cincinnati Children's Research Foundation, Division of Neurology
Perinatal citalopram exposure alters spatial learning and memory, acoustic startle response, anxiety, and sociability in adult Sprague-Dawley rats

Mellessa Miller (supported by DNTS Board)
University of Memphis
DOPAMINE TRANSPORTER (DAT) and Vesicular Monoamine Transporter (VMAT) expression in the Striatum AND medial PREFRONTAL CORTEX IN WEANLING and ADULT, Cocaine-exposed RATS is altered by PERINATAL PCB exposure

DNTS 2016 Program

Saturday, June 25, 2016

8:00 AM–12:00 Noon	**Teratology Society Education Course Session I** *(Separate Registration Required)* Embryology in Modern Times	**Texas Ballroom D**
12:00 Noon–5:00 PM	**DNTS Registration**	**Texas Ballroom F Foyer**
1:00 PM–2:00 PM	**DNTS Public Affairs Committee Meeting**	**Republic B**
1:30 PM–5:00 PM	**Teratology Society Education Course Session II** *(Separate Registration Required)* Development and Teratology of the Heart	**Texas Ballroom D**
2:00 PM–3:00 PM	**DNTS Publications Committee Meeting**	**Republic B**
3:00 PM–4:00 PM	**DNTS Strategic Planning Committee Meeting**	**Republic B**
4:00 PM–6:00 PM	**DNTS Council Meeting**	**Republic B**

Sunday, June 26, 2016

7:30 AM–8:00 AM	**Morning Coffee and Pastries** (Joint with the Teratology Society)	**Texas Ballroom A**
8:00 AM–5:00 PM	**DNTS Registration**	**Texas Ballroom F Foyer**

http://dx.doi.org/10.1016/j.ntt.2016.04.003

8:00 AM–8:15 AM	**DNTS President's Welcome** *President: Lynn Singer, Case Western Reserve University, Cleveland, OH*	**Texas Ballroom F**
8:15 AM–9:00 AM	**Josef Warkany Lecture** (Joint with the Teratology Society and OTIS) DNTS 01: Framing Our Birth Defects Questions with Systems Biology: Learning from Our Mentors *Chairperson: Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.* *Lecturer: Elaine M. Faustman, University of Washington*	**Texas Ballroom D**
9:00 AM–10:00 AM	**DNTS 40th Anniversary Celebrating our Past and Future**	**Texas Ballroom F**
9:00 AM–9:05 AM	Introduction *Lynn Singer, Case Western Reserve University*	
9:05 AM–9:35 AM	DNTS 02: Origins of the Developmental Neurotoxicology Society Charles Vorhees, *Cincinnati Children's Research Foundation & University of Cincinnati, Cincinnati, OH, USA*	Texas Ballroom F
9:35 AM–9:45 AM	DNTS 03: Discussant Jane Adams, *University of Boston, MA, USA*	Texas Ballroom F
9:45 AM–9:55 AM	DNTS 04: Discussant Edward Riley, *State University, SD, California, USA, San Diego* *State University, San Diego, CA, USA*	Texas Ballroom F
10:00 AM–10:15 AM	Break (Joint with the Teratology Society)	Texas Ballroom A
10:15 AM–11:00 AM	DNTS 05: Reversal of Neurobehavioral Teratogenicity with Cell Transplantation: Animal Models and the Prospect for Translation Joseph Yanai[1,2], Adi Pinkas[1], Asher Ornoy[3], Itamar Altman[1], Dana Pulver[4], Gadi Turgeman[4] *[1]The Ross Laboratory for Studies in Neural Birth Defects, Department of Medical Neurobiology, IMRIC, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, [2]Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, NC, USA, [3]Department of Medical Neurobiology, IMRIC, The Hebrew University-Hadassah Medical School, Jerusalem, Israel, [4]Department of Molecular Biology, Ariel University, Ariel, Israel*	Texas Ballroom F
11:00 AM–11:30 AM	DNTS 06: Marijuana and Development of the Brain Diana Dow-Edwards, *State University of New York, Downstate Medical Center, Brooklyn, NY, USA*	Texas Ballroom F
10:00 AM–11:00 AM	**Spouse/Guest Meet-and-Greet***	**Republic Room A**
12:00 Noon–1:30 PM	**Lunch on Your Own**	
1:30 PM–5:30 PM	**Systematic Evaluations of Mechanistic Data for Developmental Neurotoxicity Outcomes** *Chairperson: Andrew Kraft, US Environmental Protection Agency*	**Texas Ballroom F**
1:30 PM–1:35 PM	Introduction: Challenges in the Systemic Evaluation of Mechanistic Data for Developmental Neurotoxicity Risk Assessment *Andrew Kraft, US EPA*	Texas Ballroom F
1:35 PM–2:00 PM	DNTS 07: The Critical Role of Context in Defining Developmental Neurotoxicity Deborah Cory-Slechta, *University of Rochester School of Medicine, Rochester, NY, USA*	Texas Ballroom F
2:00 PM–2:35 PM	DNTS 08: Epigenetic Effects of Prenatal Exposures: Issues of Timing, Tissue, and Sex Frances Champagne, *Columbia University, New York, NY, USA*	Texas Ballroom F
2:35 PM–3:20 PM	DNTS 09: Phenotypic Screening for Developmental Neurotoxicity: Mechanistic Data at the Level of the Cell William Mundy, *Integrated Systems Toxicology Division, US Environmental Protection Agency, RTP, NC, USA*	Texas Ballroom F
3:20 PM–4:00 PM	DNTS 10: Incorporating New Knowledge and Known Complexity for Systematic Evaluation of Mechanistic Data for Developmental Neurotoxicity: Considering Behavioral Outcome as a Primary Organizing Principle Christina Sobin, *University of Texas, El Paso, TX, USA*	Texas Ballroom F
4:00 PM–4:15 PM	Break (Joint with the Teratology Society and OTIS)	Texas Ballroom A
4:15 PM–5:00 PM	DNTS 11: Developmental Neurotoxicity: Structured Frameworks for Evaluation Elaine Faustman, *University of Washington, Seattle, WA, USA*	Texas Ballroom F
5:00 PM–5:30 PM	Panel Discussion	Texas Ballroom F
5:30 PM–6:00 PM	**Patricia Rodier Mid-Career Award for Research and Mentoring** (Joint with TS) *Chairpersons: Bruce K. Beyer, Sanofi U.S. Inc. and Patricia Janulewicz, Boston University* *Lecturer: Christina D. Chambers, University of California San Diego*	**Texas Ballroom D**
6:00 PM–7:30 PM	**Welcome Reception, Student and Postdoctoral Fellow Research Showcase**, and Exhibits** (Joint with the Teratology Society)	**Texas Ballroom B**

Monday, June 27, 2016

7:30 AM–8:00 AM	**Morning Coffee and Pastries** (Joint with the Teratology Society)	**Texas Ballroom B**
8:00 AM–5:00 PM	**DNTS Registration**	**Texas Ballroom F Foyer**

(continued on next page)

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9:00 AM–12:00 Noon	**Wiley-Blackwell Symposium** (Joint with the Teratology Society) **Neurodevelopmental Deficits from Fetal Exposure to Methamphetamine, Cocaine and Alcohol: Emerging Mechanisms and Human Consequences** *Chairpersons: Charles V. Vorhees, Cincinnati Children's Hospital Medical Center and Peter G. Wells, University of Toronto*	**Texas Ballroom D**
9:00 AM–9:05 AM	Introduction *Peter G. Wells, University of Toronto*	Texas Ballroom D
9:05 AM–9:45 AM	Neurodevelopmental Deficits Initiated by Methamphetamine and Ethanol Peter Wells[1,2], Sacha Bhatia[1], D. Drake[1] *[1]Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada, [2]Dept. of Pharmacology & Toxicology, Toronto, Ontario, Canada*	Texas Ballroom D
9:45 AM–10:25 AM	DNTS 13: Effects of Methamphetamine on Brain and Behavioral Development Charles Vorhees, *Cincinnati Children's Research Foundation & University of Cincinnati, Cincinnati, OH, USA*	Texas Ballroom D
10:25 AM–10:45 AM	Break (Joint with the Teratology Society)	Texas Ballroom B
10:40 AM–11:20 AM	DNTS 14: Dopaminergic Mechanisms of Cocaine-Initiated Neurodevelopmental Deficits Gregg Stanwood, *Florida State University, Tallahassee, Florida, USA*	Texas Ballroom D
11:20 AM–12:00 Noon	DNTS 15: Human Neurodevelopmental, Behavioral and Growth Consequences of Exposure to Prenatal Methamphetamine and Alcohol Lynne Smith[1,2], Linda LaGasse[2], C. Derauf[2], E. Newman[2], Amelia Arria[2], Marilyn Huestis[2], S. Della Grotta[2], L. Dansereau[2], Charles Neal[2], Barry Lester[2] *[1]Harbor-UCLA, Torrance, California, USA, [2]IDEAL Community Research Network, Torrance, California,USA*	Texas Ballroom D
12:00 Noon–1:30 PM	**Lunch on Your Own**	
12:00 Noon–1:30 PM	**NTT Editorial Board Luncheon** *(For Board Members Only)*	**Crockett C**
1:30 PM–5:30 PM	**Integrative *In Vitro* Models for Neurovascular Development Function Symposium** (Joint with the Teratology Society) *Chairpersons: Thomas B. Knudsen, US Environmental Protection Agency and William Slikker Jr., National Center for Toxicological Research, US FDA*	**Texas Ballroom D**
1:30 PM–1:35 PM	Introduction *Thomas Knudsen, NCTR, US FDA*	Texas Ballroom D
1:35 PM–2:20 PM	DNTS 16: Assembly of Stem Cell-Derived Human Tissues for Screening Applications William L. Murphy, *University of Wisconsin, Madison, Wisconsin, USA*	Texas Ballroom D
2:20 PM–3:05 PM	DNTS 17: Blood-Brain-Barrier Development and Function Sherry A. Ferguson, John J. Panos, *National Center for Toxicological Research, Jefferson, Arkansas, USA*	Texas Ballroom D
3:00 PM–3:20 PM	Break (Joint with the Teratology Society and OTIS)	Texas Ballroom B
3:20 PM–4:05 PM	DNTS 18: High-Throughput Screening of Zebrafish to Identify Modifiers of Nervous System Development and Function Randall Peterson[1,2] *[1]Massachusetts General Hospital, Boston, Massachusetts, USA, [2]Harvard Medical School, Boston, Massachusetts, USA*	Texas Ballroom D
4:05 PM–4:50 PM	DNTS 19: Human Neurovascular Unit On-A-Chip: Microscale Systems for Tissue-Level Response John Peter Wikswo Jr, Aaron B. Bowman, J.B. Brown, Simona G. Codreanu, Dmitry A. Markov, J.A. May, Lisa J. McCawley, John A. McLean, Diana Neely, Virginia Pensabene, Stacy D. Sherrod, Mingjian Shi, Donna J. Webb *Vanderbilt University, Nashville, Tennessee, USA*	Texas Ballroom D
4:50 PM–5:30 PM	Discussion	Texas Ballroom D
5:30 PM–7:30 PM	**Poster Session 1 and Exhibits Attended** (Joint with the Teratology Society and OTIS)	**Texas Ballroom B**

DNTS P01: Behavioral Consequences following Deletion of the Dopamine D2 Receptor in Forebrain GABAergic or Glutamatergic Neurons
Devon Graham, Taylor Trammell, Lisa Anderson, Gregg Stanwood
Florida State University College of Medicine, Biomedical Sciences, Tallahassee, FL, USA

DNTS P02: Comparison of Developmental Effects across Multiple Phthalate Esters
Erin Yost[1], Xabier Arzuaga[2], Brandiese Beverly[1], Todd Blessinger[2], Susan Euling[2], Andrew Hotchkiss[1], Susan Makris[2], Teneille Walker[2], Andre Weaver[1]
[1]National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Research Triangle Park, NC, USA, [2]National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Washington, DC, USA

DNTS P03: Single and Repeated Exposures to the Volatile Anesthetic Isoflurane Do Not Impair Operant Performance in Aged Rats
Jennifer Walters, John Chelonis, Charles Fogle, Merle Paule
National Center for Toxicological Research (NCTR)/FDA, Jefferson, AR, USA

DNTS P04: High-Taurine Consumption by Adolescent C57BL/6J Mice Alters Biogenic Amines in a Sex-Dependent Manner
Christine Curran, Jamie Weimer, Clare Ludwig, Josephine Brown
Northern Kentucky University, Highland Heights, KY, USA

DNTS P05: Prioritization of Polychlorinated Biphenyl Congeners to Support Human Health Risk Assessment
Laura Macaulay[1], Jenny Li[2], Geniece Lehmann[1]
[1]National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Research Triangle Park, NC, USA, [2]National Center for Environmental Assessment, Office of Research and Development, Environmental Protection Agency, Washington, DC, USA

DNTS P06: Circadian Disruption, Cognitive Function and Neurotransmission in a Rodent Model
Rekha Balachandran[1], Michael Leventhal[1], Audrey Robertson[1], Stephane Beaudin[2], Megan Mahoney[1], Paul Eubig[1]
[1]University of Illinois at Urbana-Champaign, Urbana, IL, USA, [2]University of California Santa Cruz, Microbiology and Environmental Toxicology, Santa Cruz, CA, USA

DNTS P07: Identifying Attention Problems in Children and Adolescents with the Behavioral Assessment and Research System (BARS)
Clara Sears[1], Lonnie Sears[2], Carol Hanchette[3], Barbara Polivka[4], Kristina Zierold[1]
[1]University of Louisville School of Public Health and Information Sciences, Louisville, KY, USA, [2]Department of Pediatrics, Louisville, KY, USA, [3]Department of Geology and Geosciences, Louisville, KY, USA, [4]School of Nursing, Louisville, KY, USA

DNTS P08: Dopamine Transporter (DAT) and Vesicular MOnoamine Transporter (VMAT) expression in the Striatum and Medial Prefrontal Cortex in Weanling and Adult, Cocaine-Exposed Rats is Altered by Perinatal PCB Exposure
Mellessa Miller, Jenna Sprowles, Abby Meyer, Helen Sable
University of Memphis, Memphis, TN, USA

DNTS P09: Gender-Specific Effects of Prenatal Cocaine Exposure of Emotional Behavior in Adolosecent Rats: Implications for Antidepressant Efficiay
Elijah Clark, Jr.[1], Sonya K. Sobrian[2]
[1]Howard University, Washington, DC, USA, [2]Howard University College of Medicine, Washington, DC, USA

DNTS P10: The Relation between Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) and Performance on the Ages and Stages Questionnaire (ASQ)
Jolene Borchelt[1], Kerri Bertrand[1], Patricia Janulewicz Lloyd[2], Anna Rosofsky[2], Jocelyn Lutes[3], Kelly Kao[1], Christina Chambers[1], Kenneth Jones[1], Jane Adams[3]
[1]University of California San Diego, San Diego, CA, USA, [2]Boston University, Boston, MA, USA, [3]University of Massachusetts Boston, Boston, MA, USA

DNTS P11: Effects of Prenatal Cocaine Exposure on Responses to Stress in Adolescence
Meeyoung Min, Sonia Minnes, June-Yung Kim, Adelaide Lang, Lynn Singer
Case Western Reserve University, Cleveland, Ohio, USA

DNTS P12: Prenatal Tobacco and Cannabis Exposure: Effects on Infant Regulation via Fetal Growth, Maternal Stress, and Anger/Hostility
Rina Eiden[1], Pamela Schuetze[1], Marilyn Huestis[2]
[1]University at Buffalo, State University of New York, Buffalo, NY, USA, [2]National Institute on Drug Abuse, Baltimore, MD, USA

7:30 PM–10:00 PM	**Teratology Society/MARTA Student Career Event** *(Open to Teratology Society, DNTS, and OTIS Student and Postdoctoral Fellows)*	**Texas Ballroom A**

Tuesday, June 28, 2016

8:00 AM–5:00 PM	**DNTS Registration**	**Texas Ballroom F Foyer**
8:00 AM–8:30 AM	**Morning Coffee and Pastries** (Joint with the Teratology Society)	**Texas Ballroom B**
9:00 AM–12:30 PM	**Public Affairs Symposium** (Joint with the Teratology Society and OTIS)	**Texas Ballroom D**
	Depression and Its Treatment in Pregnancy *Chairpersons: Kembra L Howdeshell, National Institute of Environmental Health Sciences and Asher Ornoy, Hebrew University Hadassah Medical School*	
9:00 AM–9:05 AM	Introduction *Kembra L Howdeshell, National Institute of Environmental Health Sciences*	Texas Ballroom D
9:05 AM–9:45 AM	DNTS 20: Depression Treatment in Pregnancy: Are We Asking the Right Questions? Katherine L. Wisner, *Northwestern University, Chicago, Illinois, USA*	Texas Ballroom D
9:45 AM–10:25 AM	DNTS 21: What Can Prenatal Exposure to SSRI Antidepressants Teach Us About Child Development? Tim Oberlander, *University of British Columbia, Vancouver, British Columbia, Canada*	Texas Ballroom D
10:25 AM–10:45 AM	Break (Joint with the Teratology Society and OTIS)	Texas Ballroom A
10:40 AM–11:20 AM	DNTS 22: The Safety of Tricyclic Antidepressants and Mood Stabilizers in Pregnancy: What Should We Use for The Treatment of Bipolar Disorders? Asher Ornoy, *Hebrew University Hadassah Medical School, Jerusalem, Israel*	Texas Ballroom D
11:20 PM–12:00 Noon	DNTS 23: New Insights into the How SSRIs Shape the Developing Brain: From Mice to Public Health Implications Jay A. Gingrich[1,3], Heli Malm[5], Mark A. Ansorge[1,3], Arango Brown[1,3], Martha Cagliostro[1,2], Victoria Arango[1,2], Myrna M. Weissman[1,3], Andre Sourander[4,1] *[1]Columbia University, New York, New York, USA, [2]New York Psychiatric Institute, New York, New York, USA, [3]Sackler Institute, New York, New York, USA, [4]Turku University, Turku, Finland, [5]Helsinki University, Helsinki, Finland*	Texas Ballroom D
12:00 Noon–12:30 PM	Panel Discussion: Mild Psychiatric Diseases in Pregnancy: To Treat or Not Treat	Texas Ballroom D

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12:30 PM–2:00 PM	**Lunch on Your Own**	
2:00 PM–3:00 PM	**DNTS 24: Elsevier Distinguished Lecturer Mouse Models of Autism to Identify Genetic Causes and Discover Therapeutics** Chairperson: *Lynn Singer, Case Western Reserve University, Cleveland, OH* Lecturer: *Jacqueline Crawley, Robert E. Chason Endowed Chair in Translational Research, UC Davis, Sacramento, CA*	**Texas Ballroom F**
3:00 PM–4:30 PM	**Platform Session 1** *Chairperson: Jerold Meyer, University of Massachusetts, Amherst*	**Texas Ballroom F**
3:00 PM–3:30 PM	DNTS 25: Hair Cortisol in Newborn Macaque Monkeys: Use As a Biomarker of Prenatal Cortisol Exposure and Relationship to Infant Behavior Jerrold Meyer[1], Melinda Novak[1], Kimberly Grant[2], Tom Burbacher[2], Julie Worlein[2], Rose Kroeker[2] *[1]University of Massachusetts Amherst, Amherst, MA, USA, [2]Washington National Primate Research Center, Seattle, WA, USA*	Texas Ballroom F
3:30 PM–3:45 PM	Break (Joint with the Teratology Society and OTIS)	Texas Ballroom A
3:45 PM–4:10 PM	DNTS 26: Long-Lasting Cognitive Deficits in Rhesus Monkeys after Neonatal General Anesthesia Induced by Isoflurane/Nitrous Oxide: Protection by Acetyl-L-carnitine Merle Paule[1], Mi Li[1], Xuan Zhang[1], Shuliang Liu[1], Joseph Hanig[2], William Slikker[1], Cheng Wang[1] *[1]National Center for Toxicological Research US FDA, Jefferson, AR, USA, [2]Center for Drug Evaluation and Research US FDA, Silver Spring, MD, USA*	Texas Ballroom F
4:10 PM–4:30 PM	DNTS 27: Associations of Prenatal Exposure to Phthalates and Bisphenol A with Measures of Cognitive Function in 7.5-Month-Old Infants Kelsey Dzwilewski[1,2], Andrea Aguiar[2,3], Mahsa Yazdy[4,5], Susan Korrick[4,6], Susan Schantz[2,3] *[1]Neuroscience Program, Univrsity of Illinois at Urbana-Champaign, Urbana, IL, USA, [2]Bekman 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]Channing Division of Network Medicine, Department of Medicine,Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, [5]Department of Epidemiology,Harvard T.H. Chan School of Public Health, Boston,MA, USA, [6]Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, USA*	Texas Ballroom F
4:30 PM–5:30 PM	**DNTS Business Meeting and Awards Presentation**	**Texas Ballroom F**
6:00 PM–8:00 PM	**DNTS Social Event**	

Wednesday, June 29, 2016

7:30 AM–8:00 AM	**Morning Coffee and Pastries** (Joint with the Teratology Society)	**Texas Ballroom A**
9:00 AM–10:30 AM	**Platform Session 2** *Chairperson: Rina Eiden, State University of New York, Buffalo*	**Texas Ballroom F**
9:00 AM–9:30 AM	DNTS 28: Impact of Gestational Serotonin Availability on Brain Function & Social Behavior Valentina Garbarino, Marshall Edwards, Anjuli Goring, Tyler Pryzbyla, Lynette Daws, Georgianna Gould *UTHSCSA, San Antonio, TX, USA*	Texan Ballroom F
9:30 AM–10:00 AM	DNTS 29: Perinatal Citalopram Exposure Alters Spatial Learning and Memory, Acoustic Startle Response, Anxiety, and Sociability 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]Cincinnati Children's Research Foundation, Division of Neurology, Cincinnati, OH, USA, [2]University of Cincinnati College of Medicine, Cincinnati, OH, USA*	Texas Ballroom F
10:00 AM–10:30 AM	DNTS 30: Developmental Outcomes for Infants of Mothers with Major Depressive Disorder or Bipolar Disorder Aimee Santucci[1], Lynn Singer[2], Stephen Wisnewski[3], James Luther[3], Heather Eng[3], Dorothy Sit[3], Katherine Wisner[4] *[1]St Jude Children's Research Hospital, Memphis, TN, USA, [2]Case Western Reserve University, Cleveland, OH, USA, [3]University of Pittsburgh, Pittsburgh, PA, USA,[4]Northwestern University, Chicago, IL, USA*	Texas Ballroom F
10:30 AM–11:00 AM	Warkany Tea (Joint with the Teratology Society)	Texas Ballroom A
11:00 AM–11:30 AM	DNTS 31: Interactive Effects of Prenatal Tobacco Exposure, Prenatal Maternal Depression, and Child Sex on Attention Problems at Preschool Age Rina Eiden, Danielle Molnar, Pamela Schuetze, Shannon Shisler, U*niversity at Buffalo, State University of New York, Buffalo NY, USA*	Texas Ballroom F
11:30 AM–12:00 Noon	DNTS 32: Effects of Prenatal Cocaine Exposure on Self-Reported Mental Health at Age 17 Sonia Minnes, Lynn Singer, Meeyoung Min, Adelaide Lang *Case Western Reserve University, Cleveland, OH, USA*	Texas Ballroom F
12:00 Noon	**DNTS 2016 Formally Adjourned**	

Thank you for coming. Have an excellent and productive year ahead.
See you in Denver in 2017.

*Spouse/Guest Meet-and-Greet: This event will provide an opportunity for you to ask the hotel's concierge and San Antonio tour guides (provided by the San Antonio Convention and Visitors Bureau) their suggestions for must-see attractions or have them answer any questions you may have about the city and its history. This event is free and open to guests of all registered attendees.

**Student and Postdoctoral Fellow Research Showcase: The Student and Postdoctoral Fellow Research Showcase is new and exciting opportunity for students and postdoctoral fellows to showcase their research. The showcase will take place during the Welcome Reception on Sunday, June 26, 2016 from 6:00 pm–7:30 pm and is open to all students and postdoctoral fellows assigned to a Poster or Platform Session.

Platform Presentations

DNTS 01

Framing Our Birth Defects Questions with Systems Biology: Learning from Our Mentors

Chairperson: Tacey E.K. White, Aclairo® Pharmaceutical Development Group, Inc.

Lecturer: Elaine M. Faustman, University of Washington

A special aspect of the Teratology Society has been the role that mentors play in nurturing the next generation of scientists. What better time to remember this, than during our Warkany Lecture. From his summer visits to Seattle some 25 years ago that helped to shape the nascent field of teratology, to today; Dr. Warkany's inspiration in setting the stage for multidisciplinary research on birth defects has not been lost. Three themes will be highlighted in this talk that represent hallmarks of Dr. Warkany's legacy. First, must be the recognition of the environment in the etiology of birth defects. How have our early ideas of environment evolved to influence current experiences with Zika virus? Second to this theme is the role of genetics and environment in child health and development. Third, but not least, is the role of timing and the dynamics of response across the lifecourse. Using examples from Dr. Warkany's visits to the Pacific Northwest, this lecture will focus on early origins of adult disease, genes x environment x time and mechanisms of both normal and abnormal development. In developmental toxicology we embrace both reductionist as well as organism-based high content models and Dr. Warkany was instrumental in stimulating clinical and pathological frameworks for interpreting these models of developmental health outcomes. These early Seattle-based think tanks provided a wealth ofinspiration, influencing Dr. Warkany as well as Drs. Shepard, Streissguth, Juchau and Emmanual. Dr. Junchau created the pharmacological context for our discussions by providing concepts of dose response and tested our beliefs in metabolism that still are challenging our approaches today in prenatal and pediatric care. Dr. Emmanual, who hosted Dr. Warkany's visits at our Center for Child Health and Human Development, provided the epidemiological stimulus for our themes on epigenetic and multigenerational challenges. Current interpretations for complex endpoints, such as behavior, only serve to reinforce our need for multidisciplinary mentors, and systems based approaches for tracing environmental impacts on healthy child development. Dr. Warkany exemplified the melding of art and science to define these challenges and opportunities that we continue to build upon today.

DNTS 02

Origins of the Developmental Neurotoxicology Society

Charles Vorhees

Cincinnati Children's Research Foundation & University of Cincinnati, Cincinnati, OH, USA

The field traces its origins to the 1960s and the work of Jack Werboff who first coined the term 'behavioral teratology' (1963). However, not until the 1970s did enough investigators focus on the field to make a difference. These investigators met at first within the Teratology Society but then in 1977 formed a separate organization: the Behavioral Teratology Society. The Society coexisted with the Behavioral Toxicology Society (BTS) for >20 years. In 1990 the Behavioral Teratology Society changed its name to the Neurobehavioral Teratology Society (NBTS) and invited BTS to joint in cosponsoring *Neurotoxicology and Teratology*. In 2009 BTS merged with NBTS. In 2015 NBTS changed its name to the Developmental Neurotoxicology Society (DNTS) in recognition of its wider scope to include brain development throughout the lifespan. The Society grew from 1977-2005, then lost ground for 5 years before it began to grow again. Early scientific influences were fetal Minamata Disease, Fetal Alcohol Syndrome, and developmental Pb exposure. Later, prenatal cocaine, marijuana, PCBs, and Accutane became important. Early human investigations evolved into prospective epidemiological studies. Animal models were developed for each of these and reinforced the human data. There were also a number of early proof of principle studies in animals that formed the theoretical basis of the field. Among these were studies of prenatal MAM, hypervitaminosis A, aspirin, and 5-azacytidine. Later studies included nicotine and antiepileptics, pesticides and other heavy metals (tin, manganese, arsenic). In the 1990s methamphetamine and ecstasy emerged, but oddly opiates barely made an impact, a situation that many need to be revisited in light of societal trends. More recently, flame retardants, endocrine disrupters, antidepressants, and others have emerged and marijuana seems poised for further investigation. Advances in neuroscience, molecular biology, and genetics have strengthened the field, examples include transgenic models, genome editing, molecular genetics, neuroimaging, fetal programming, and confocal and 2-photon microscopy. Even newer areas likely to influence the field include the microbiome, epigenetics, microRNA, and the connectome, all of which will contribute to how the brain is altered by early events and reflected in behavior.

DNTS 03

Discussant: Jane Adams, University of Boston, Massachusetts, USA

DNTS 04

Discussant: Edward Riley, San Diego State University, California, USA

DNTS 05

Reversal of Neurobehavioral Teratogenicity with Cell Transplantation: Animal Models and the Prospect for Translation.

Joseph Yanai[1,2], Adi Pinkas[1], Asher Ornoy[3], Itamar Altman[1], Dana Pulver[4], Gadi Turgeman[4]

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The study of behavioral birth defects has evolved from a mostly descriptive science (behavioral teratology) to the ascertainment of the associated mechanisms (neurobehavioral teratology). In our studies, prenatal (mice) and prehatch (avian) exposure to various neuroteratogens, mainly heroin or chlorpyrifos evoked deficits in mice hippocampal spatial abilities and in chick imprinting performance with concomitant alterations in cholinergic pathways, related to deficiencies in cholinergic control of PKCγ and β activation/translocation. Identifying these mechanisms has enabled to design various therapies to reverse the impairment, most relevant, neural grafting of cholinergic neurons and recently, transplantation of various stem cells. Both neural grafting and cell transplantation reversed the behavioral deficits and the mechanistically associated neural alterations. Further studies showed that one major mechanism by which the transplanted cells exert their therapeutic action is by induction of neurogenesis. The present studies were designed to ascertain the expression of genes related to the neurobehavioral deficits and their reversal. Mice and chick embryos were exposed to the

neuroteratogens and later transplanted with mesenchymal stem cells (MSC). Chicks received the teratogen on incubation day (ID) 0 and 5 and were subjected to intravenous transplantation of MSC on ID 13. Brains were removed on posthatch day 1. Mice were exposed to a single injection of the teratogen on gestation days 9-18 and were transplanted i.c.v. at the age of 3 months; Brains were removed 3.5 weeks later. The expression of genes related to neurogenesis and/or various innervation (cholinergic, serotonergic and catecholaminergic) were assessed with real time PCR. Prenatal/prehatch exposure to the teratogens altered the expression of most genes; a tendency mostly for a decrease in neurogenesis genes and for an increase expression in the neurotransmission genes. Transplantation with MSC reversed those alterations. It is expected that the mechanism of both the defects and repair by MSC are attributed to regulating mechanisms of neurogenesis related gene expression. Indeed our preliminary studies suggest global epigenetic changes as indicated by changes in DNA methylation. The prospect for translation of these findings will be discussed.

Supported by the Israel Anti-Drug Authority and the Ross Endowment Fund.

DNTS 06

Marijuana and Development of the Brain

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Abstract: Marijuana is the most highly abused illegal substance during pregnancy and in adolescence and yet, many people are not aware that it can be addicting to the user and toxic to the developing nervous system. This talk will outline of the role of cannabinoids in normal brain function and illustrate how marijuana causes chaotic neuronal growth early in development. I will review the longitudinal human studies of both maternal and adolescent smoking and illustrate the role of natural cannabinoids in stress responses. The effects of adolescent marijuana use on cognition, mental health and substance abuse will be discussed. I will present human imaging studies showing how adolescent marijuana abuse alters brain development including cortical thickness, white matter integrity and functional responsivity. The goal is to better understand the role of natural endogenous cannabinoids in development and how smoking marijuana during sensitive periods can permanently alter the developmental trajectory of important neuronal circuits.

DNTS 07

The Critical Role of Context in Defining Developmental Neurotoxicity

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Given the large number of environmental chemicals on which toxicity information is lacking, the goal of high throughput screening to identify those with the potential to produce developmental neurotoxicity is logical. However, the attainment of this goal may be seriously hampered by the critical roles of context and timing in the functions of molecules and the consequent impacts of chemicals. For example, while microglial activation is generally presumed to be an adverse consequence, it is actually required for neurogenesis and gliogenesis to occur during brain development. Another example comes from brain hemispheric differences (brain laterality), which are present even under 'control' conditions. With respect to chemical effects, our prior studies have demonstrated that the impact of developmental lead (Pb) exposure can differ significantly by brain hemisphere, and, moreover, the profile of hemispheric differences in the effects of Pb also differ by sex. These effects were even further differentiated by the condition of behavioral testing vs. no behavioral testing experience. Subsequent studies show that the trajectory of the effects of Pb can differ in relation to the specific nature of the behavioral experience, with differential biochemical effects of Pb seen in rodent offspring who were exposed to early positive behavioral experience (food-rewarded behavioral responding) in comparison to their littermates that were subjected to early negative behavioral experience (forced swim experience). When combined with another environmental context, maternal stress, even further differentiation of Pb effects is seen. Brain region is also a critical modulator, as for example, in studies demonstrating stark differences in Pb effects on dopamine function in mesolimbic vs. nigrostriatal dopamine systems, while the opposite occurs with MPTP. Another context involves non-linearity of effects of environmental chemicals in vivo, coupled with the non-linearity of many receptor systems in brain, including glucocorticoids, dopamine, muscarinics, opioids, NMDA, testosterone and estrogen. As these examples make clear, the ability to generalize findings for any given chemical may require an extensive series of in vitro and ultimately in vivo approaches, and any definition of adverse outcome pathways derived from such studies likely to require significant qualification as to conditions under which it is neurotoxic.

DNTS 08

Epigenetic Effects of Prenatal Exposures: Issues of Timing, Tissue, and Sex

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Dysregulation of gene expression during development in response to toxicological exposures likely plays a critical role in resulting neurodevelopmental effects. This dysregulation may be the consequence of altered epigenetic factors, including post-translational histone modifications, non-coding RNAs, and DNA methylation. However, these effects are tissue specific, vary dependent on sex, and timing of exposure is predictive of the neural systems that are altered by exposure. We have examined how exposure to stress and exposure to bisphenol A (BPA) during pregnancy alters DNA methylation within the placenta and cord blood in humans and in the placenta, blood and brain of laboratory mice. Both exposures result in sex-specific effects on gene expression and DNA methylation. In the case of prenatal stress, exposure effects vary within different layers of the placenta and within different anatomical regions of the brain. We observe stress-associated decreases in expression of DNA methyltransferases and of expression of genes involved in stress hormone metabolism (11-beta hydroxysteroid dehydrogenase 2, 11B-HSD2) within the rodent placenta and increased DNA methylation of 11B-HSD2 in human placental tissue. BPA exposure similarly alters placental expression of 11B-HSD2 in rodents and exerts sex-specific effects on the expression of imprinted genes. Within the brain, there are region specific alterations in the expression of genes involved in neuroplasticity and altered DNA methylation may account for these effects. Collectively, these studies highlight the role of epigenetic mechanisms in mediating the effects of prenatal exposures. However, these studies also suggest that more systematic analyses across tissues in both male and female offspring will be essential to determining the impact of these exposures and in establishing the link to neurodevelopmental outcomes.

DNTS 09

Phenotypic Screening for Developmental Neurotoxicity: Mechanistic Data at the Level of the Cell

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There are large numbers of environmental chemicals with little or no available information on their toxicity, including developmental neurotoxicity. Because of the resource-intensive nature of traditional animal tests, high-throughput (HTP) methods that can rapidly evaluate chemicals for the potential to affect the developing brain are being explored. Typically, HTP screening uses biochemical and molecular assays to detect the interaction of a chemical with a known target or molecular initiating event (e.g., the *mechanism of action*). For developmental neurotoxicity, however, the mechanism(s) is often unknown. Thus, we have developed assays for detecting chemical effects on the key events of neurodevelopment at the cellular level (e.g., proliferation,

differentiation, neurite growth, synaptogenesis, network formation). Cell-based assays provide a test system at a level of biological complexity that encompasses many potential neurotoxic mechanisms. For example, phenotypic assessment of neurite outgrowth at the cellular level can detect chemicals that target kinases, ion channels, or esterases at the molecular level. The results from cell-based assays can be placed in a conceptual framework using an Adverse Outcome Pathway (AOP) which links molecular, cellular, and organ level effects with apical measures of developmental neurotoxicity. Testing a wide range of concentrations allows for the distinction between selective effects on neurodevelopmental and non-specific changes in cell viability. It is often difficult, however, to extrapolate effective *in vitro* concentrations to *in vivo* doses. The relative value of mechanistic data at the cellular level can be considered in terms of both the biological relevance (e.g., primary cells versus cell lines, brain region, animal versus human origin) and complexity (e.g., number of cell types represented, connectivity) of the cell models used. For example, chemical effects on synaptogenesis in a complex primary neural culture would be interpreted differently than effects observed in a neural cell line. Similarly, results from human neural models can be different from those derived from rodent models, and may be more relevant to human adverse effects.

This abstract does not necessarily reflect U.S. EPA policy.

DNTS 10

Incorporating New Knowledge and Known Complexity for Systematic Evaluation of Mechanistic Data for Developmental Neurotoxicity: Considering Behavioral Outcome as a Primary Organizing Principle

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Determining "mode of action" for risk assessment decision-making is based on a convergence of mechanistic data that support effects on a given pathway or biological system. For the purposes of characterizing developmental neurotoxicity outcomes, behavioral assessment reveals functional effects, specifically, how environmental exposure alters an organism's ability to act in ways that promote survival. The complexities involved in quantifying and interpreting behavioral outcomes, and linking them to a broad range of mechanistic changes, requires consideration. How we conceptualize the role of behavioral evidence in the systematic evaluation of mechanistic data may be important for ensuring the inclusion of behavior as a central outcome. On the simplest level, by suggesting which mechanistic effects are associated with quantifiable functional change, behavioral outcomes might be used as a guide in organizing large amounts of data from new "high-throughput" methods. Using examples from translational (child and animal) studies of early chronic low-level lead exposure, this talk will consider whether, when and what types of behavioral outcome data might be used to understand and organize mechanistic data, and how behavioral data might be used to guide the direction and focus of ongoing mechanistic studies. Current assumptions of and possible alternative approaches for behavioral assessment in this context will be discussed.

DNTS 11

Developmental Neurotoxicity: Structured Frameworks for Evaluation

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Advances in comparative biology have allowed researchers in development to identify new pathways of interest for normal as well as perturbed neurobiological responses. These same databases have also provided a framework for scientists to interpret consistency of signal responses across populations and from remote and related test organisms. A systems biology approach can be used to frame this complex information from genomic to whole organism level responses and from molecular to functional changes. For model test systems used for evaluating developmental response, the conservation of gene ontologies has allowed us to interpret adverse responses in mice as well as drosophila, c. elegans and zebra fish for human relevant processes. The question whether such framing can allow us to interpret and extrapolate mechanistic information for complex neurobehavioral responses remains unanswered but will be explored in this presentation. Recent advances in cancer assessment have provided examples of including basic mechanistic information from Hallmarks of Carcinogenesis into systematic reviews of chemical carcinogenesis. Many of these pathways are also of importance for neurodevelopmental endpoints but without cellular, temporal, domain and morphological context these generic pathways may be less informative. Three examples using these hallmarks will be explored for framing our systematic reviews for function and outcome. Qualitative and quantitative data will be discussed especially as it informs our dose response relationships across platform, levels of biological observation and endpoint. Our working hypothesis is that toxico kinetic and dynamic models are both essential in order to achieve these extrapolations and use of mechanistic data.

DNTS 12

Oxidative Stress Mechanisms of Neurodevelopmental Deficits Initiated by Methamphetamine and Ethanol

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In utero exposure of mouse progeny to alcohol (ethanol) and methamphetamine causes substantial postnatal neurodevelopmental deficits. One emerging pathogenic mechanism underlying these deficits involves fetal brain production of reactive oxygen species (ROS) that oxidatively damage DNA leading to altered gene expression, likely via epigenetic mechanisms. Mechanisms of fetal ROS production include induction of ROS-producing NADPH oxidases and drug bioactivation to free radical intermediates by prostaglandin H synthases. Antioxidative enzymes like catalase in the fetal brain, while low, provide critical protection. In addition to altering signal transduction, ROS can oxidatively damage cellular macromolecules including lipids, proteins and DNA, the latter of which may be repaired by various enzymes. Fetal deficiencies in several DNA repair proteins, including oxoguanine glycosylase 1 (OGG1) and breast cancer protein 1 (BRCA1), enhance the risk of both drug-initiated postnatal deficits and deficits in untreated progeny, the latter of which may be relevant to conditions like autism spectrum disorders. Risk is further regulated by fetal nuclear factor erythroid 2-related factor 2 (Nrf2), a ROS-sensing protein that upregulates an array of proteins including antioxidative enzymes and at least some DNA repair proteins. (Support: Canadian Institutes of Health Research).

DNTS 13

Effects of Methamphetamine on Brain and Behavioral Development

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Rats treated with (+)-methamphetamine (MA) during neonatal development (equivalent to third trimester brain development in humans) results in allocentric learning and memory (L&M) deficits in the Morris water maze, egocentric learning deficits in the Cincinnati water maze, and working and reference memory deficits in the radial water maze. Neonatal MA causes sharp increases in plasma ACTH and corticosterone. To test whether these changes contribute to the L&M deficits, we severed and autotransplanted the adrenals at P10 and then treated pups with MA or saline from P11-20. This reduced MA-induced corticosterone increases by approximately 50% but did not attenuate the adult L&M deficits. In adult offspring treated with MA from P11-20, we found reduced neostriatal dopamine levels, D_2 receptor density, and PKA activity. To test the functional consequences of these

changes, we treated rats neonatally with MA as before and tested them as adults for locomotor activity. MA-exposed rats exhibited exaggerated hyperactivity in response to the D_1 agonist SKF-82958, reduced hyperactivity to the NMDA antagonist MK-801, and mild under-response to D_2 autoreceptor agonist, quinpirole, but no changes in response to serotonergic agonists. MA increases reactive oxygen species (ROS) prenatally in mice and in adult rats. We tested the involvement of ROS in neonatal MA's effects two ways: by measuring F_2 isoprostanes (F_2-IsoPs; markers of ROS) and by pretreatment with the spin trapping agent alpha-phenyl-N-tert-butyl nitrone (PBN) prior to each dose of MA. There was no change in F_2-IsoPs in striatum or hippocampus after the first day, nor after the completion of neonatal MA treatment. PBN did not attenuate MA-induced L&M deficits. In order to investigate striatal D_1 effects after P6-15 MA exposure, we used microPET/CT imaging using the D_1 ligand TISCH during adulthood. We found no effects of MA treatment; we also examined brain oxygen activity using 2-fluoro-2-deoxyglucose and found no changes in activity in response to SKF-82958. In sum, third trimester-equivalent MA (P11-20 or P6-15) in rats leads to long lasting L&M impairments on multiple tests and changes in dopaminergic and glutamatergic receptor function assessed pharmacologically. However, the exact mechanism of MA-induced brain changes remains to be elucidated.

DNTS 14

Dopaminergic Mechanisms of Cocaine-Initiated Neurodevelopmental Deficits

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In a low-dose intravenous animal model, in utero cocaine exposure produces a permanent reduction in dopamine D1 receptor signaling, elongations of dendritic morphology of cortical pyramidal cells, and changes in structure and protein expression in subtypes of cortical interneurons. Specific cognitive and motor behaviors are altered in adolescent and adult offspring as a result, and these deficits have strong parallels in the clinical literature. The abnormalities are elicited during a specific period of embryonic development and occur only in brain regions receiving dense dopaminergic input. Very similar changes are present in the medial frontal cortex of dopamine D1 receptor null mice, and D1 receptors potently modulate both dendritic outgrowth and interneuron migration. These results suggest that loss of D1 receptor-mediated signaling during development in both the genetic knockout and following prenatal cocaine produces analogous alterations in cellular organization. Studies in specific biogenic amine transporter mutants suggest complex roles for dopamine and norepinephrine transporters in mediating the effects of gestational cocaine on the developing cerebral cortex. Conditional approaches are allowing us to now examine cell-type heterogeneity in dopamine D1 and D2 receptor modulation of brain development. Moreover, emerging data from several labs now point to transgenerational effects mediated at least in part through epigenetic mechanisms. Taken together, these studies demonstrate the mechanisms by which alterations in dopaminergic activity during critical epochs of development alters circuits mediating cognitive and emotional behaviors, and may lead to subsequent psychiatric disease later in life.

DNTS 15

Human Neurodevelopmental, Behavioral, and Growth Consequences of Exposure to Prenatal Methamphetamine and Alcohol

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Numerous adverse effects on childhood neurodevelopment and behavior have been attributed to prenatal methamphetamine exposure. However, these data have been limited by a small sample size, lack of a control group and reliance on maternal self-report instead of objective measures of drug exposure. We report findings from the Infant Development and Lifestyle (IDEAL) Study, to our knowledge the first longitudinal, prospective study of prenatal methamphetamine exposure in children up to age 7.5 years. We enrolled 412 mother-infant pairs (204 methamphetamine-exposed and 208 unexposed matched comparisons) with exposure determined by maternal self-report and/or positive meconium toxicology. Serial assessments of growth, development and behavioral assessments were conducted from birth through age 7.5 years. In the newborn period, no withdrawal syndrome was observed though there was a heightened risk for being born growth restricted. Newborns demonstrated more signs of stress, which normalized to the level of comparison neonates by one month of age. From ages 12 months to 7.5 years, subtle fine motor, attention and behavioral deficits were observed with some findings associated with heavier drug exposure. The data suggest children exposed to methamphetamine have increased risks for targeted, subtle neurodevelopmental and behavioral issues in a dose dependent manner. Possible mechanisms will be explored including a discussion of existing neuroimaging data in methamphetamine-exposed children. Findings will also be discussed in the context of the prenatal drug co-exposures of nicotine, marijuana and alcohol, with a particular emphasis on fetal alcohol effects.

DNTS 16

Assembly of Stem Cell-Derived Human Tissues for Screening Applications

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The need for human, organotypic culture models coupled with the requirements of contemporary drug discovery and toxin screening (i.e. reproducibility, high throughput, transferability of data, clear mechanisms of action) frame an opportunity for a paradigm shift. The next generation of high throughput cell-based assay formats will require a broadly applicable set of tools for human tissue assembly and analysis. Toward that end, we have recently focused on: i) generating iPS-derived cells that properly represent the diverse phenotypic characteristics of developing or mature human somatic cells; ii) assembling organotypic cell culture systems that are robust and reproducible; iii) translating organotypic cell culture models to microscale systems for high throughput screening; and iv) combining genomic analyses with bioinformatics to gain insights into organotypic model assembly and the pathways influenced by drugs and toxins. This talk will emphasize recent studies in which we have explored biologically driven assembly of organotypic vascular and neural tissues. These tissues mimic critical aspects of human tissues, and can be used for predictive neurodevelopmental toxicity, and for identification of vascular disrupting compounds. We have also begun to use assembled human tissues to develop models of developmental disorders, degenerative diseases, and infectious disease effects.

DNTS 17

Blood-Brain-Barrier Development and Function

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The study of BBB development and function is critical. Certain diseases/toxicants can alter permeability (e.g., prenatal dioxin exposure alters BBB permeability in vitro (Miyazaki et al., 2015)). However, there is little research describing appropriate in vivo rodent models, suggesting that the rat is not an adequate model. Characterizing BBB development, maintenance, and disease states in vivo is time consuming and daunting, potentially leading to a preference for in vitro models (Lippmann et al., 2013). Further, BBB permeability differs across species (Sinha, 2003), brain development rates are not consistent across species, birth is not a consistent marker across species for BBB development (Engelhardt, 2006), and human and rodent brain glucose usage

is dissimilar at birth (Nehlig, 1997). Results of studies using PET radioligands have indicated profound differences in glycoprotein transport in rats and guinea pigs compared with minipigs, nonhuman primates, and humans (Syvanen et al., 2009). Such differences have contributed to the development of human stem cell-based BBB models (Aday et al., 2016). However, recent advances in mouse models have aided in the study of BBB development, maintenance, and aging (Sohett & Daneman, 2013). Such models have produced convincing information indicating a functioning BBB during rodent embryogenesis (Daneman et al., 2010). Several of those models affect the BBB by acting on endothelial cell (EC) function to enact changes in angiogenesis and BBB maintenance. ECs of the BBB are unique compared to those of other tissues in that they incorporate intracellular tight junctions (TJs), absence of fenestrations, and reduced transcytosis (Obermeier et al., 2013). Novel models to aid in the cost effective and high throughout study of BBB permeability, including zebrafish and grasshopper, are being developed (Geldenhuys et al., 2012). Stem cell modeling of angiogenesis and BBB maintenance using rat cortical neural progenitor cells can provide high throughput screening of BBB function in vitro (Lippman et al., 2013). The combination of in vivo and in vitro models will likely be powerful tools for assessing CNS access to drugs and toxicants whether this is a desired or unwanted effect.

DNTS 18

High-Throughput Screening of Zebrafish to Identify Modifiers of Nervous System Development and Function

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Assessing the effects of chemical compounds on the nervous system is a complex and laborious task, making it difficult to apply the tools of modern, high-throughput science. As a result, drug discovery and toxicology for the nervous system lag behind other organ systems. In an effort to address this problem, we have developed a panel of automated, high-throughput behavioral and developmental assays that can be performed with live zebrafish in 96-well plate format. These assays, which incorporate robotics, optics, and high-throughput video analysis, can be used to screen >1000 small molecules per day and detect behavioral or developmental changes caused by compounds with diverse mechanisms of action. We have validated the assays with a training set of 700 existing neuroactive compounds affecting several distinct neurotransmitter systems. Compounds from each functional class produce distinctive behavioral profiles that resemble each other but are distinct from those of other functional classes, suggesting a strong correlation between zebrafish behavioral profiles and compound mechanisms of action. We have also screened 25,000 diverse small molecules and discovered more than 800 compounds that alter zebrafish behavior or development in diverse ways. Some of these novel compounds function via well-characterized pathways, while others appear to function via novel pathways. We anticipate that this in vivo approach to compound assessment will enlarge significantly the toolset of neuroactive compounds for neuroscience research, will facilitate screening of compounds for cerebrovascular or nervous system toxicity, and will also provide novel therapeutic avenues for treating various CNS disorders.

DNTS 19

Human Neurovascular Unit On-A-Chip: Microscale Systems for Tissue-Level Response

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To truly understand the contribution of genetics, environment, drugs, and maternal health to fetal development and resulting birth defects, we need new tools to model and investigate these complex interactions. Animal studies have been invaluable, but in many cases they fail to recreate human physiology, and traditional cell culture models lack the complexity to capture the full disorder. To help bridge this gap and give investigators a new tool in their experimentation arsenal, we are developing organs-on-chips that provide highly accessible – but still complex – cell culture models of a target organ. With these engineered tissues and their accompanying perfusion systems, it is possible to model blood-brain barriers (BBBs), fetal membranes, mammary glands, or other organs. These microfluidic platforms and associated pumps and valves let us create tissue-specific microenvironments and test the effects of drug exposure over time, including immune response (which is often an evolving response), tissue recovery, and repair. In our human Neurovascular Unit (NVU), for example, we have seen BBB disruption soon after toxin exposure but partial recovery after 24 hours, and we have identified compounds capable of preventing blood-brain barrier disruption. Through ion mobility-mass spectrometry analysis we have also demonstrated that disruptions to the BBB lead to metabolic changes within the NVU. An important challenge will be to address the urgent need to screen the effects of common environmental hazards on fetal development and overall health by adapting our NVU to adequately recapitulate specific stages in the development of the fetal BBB, either as a static system or as one whose temporal development tracks that of the fetus. This should be a feasible goal, given our success with the adult NVU. Research reported herein was supported by Assistance Agreement No. 83573601 awarded by the U. S. Environmental Protection Agency to Vanderbilt University, and by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award Number UH3TR000491. The views expressed in this document are solely those of the authors and do not necessarily reflect those of either agency. EPA does not endorse any products or commercial services mentioned in this publication.

DNTS 20

Depression Treatment in Pregnancy: Are We Asking the Right Questions?

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Major Depressive Disorder (MDD) is a common complication of pregnancy, with 7.5% of women having a new episode during pregnancy and 6.5% with an incident episode postpartum. Suicide accounts for 20% of deaths in postpartum women and it is the second leading cause of mortality. Screening for perinatal depression was recommended by the USPSTF; however, for many pregnant women, accessible and acceptable mental health intervention is limited. MDD is associated with poor nutrition, obesity, smoking, alcohol and drug use, interpersonal violence and poverty. Severe maternal antenatal stress is associated with offspring mental disorders and multiple birth defects. Children exposed to maternal MDD in utero have higher cortisol levels than infants of non-depressed mothers, a biochemical change that continues through adolescence which places the offspring at higher risk for mental illness. Notably, maternal treatment of MDD during pregnancy normalizes infant cortisol levels. Investigations of SSRI antidepressant use in pregnancy have largely yielded studies on adverse outcomes, including preterm birth, cardiac defects, poor neonatal adaptation, persistent pulmonary hypertension of the newborn, and psychomotor developmental effects. The challenge is to separate the impact of these two exposures (SSRI and MDD) on the reproductive outcome. A major methodological challenge in interpreting observational studies is the problem of confounding. Few studies have evaluated the benefit of antidepressant treatment that justifies the risk. The prescriber is left with the responsibility of deciphering whether the "benefits outweigh the risks" with limited information on benefits and a large literature on risks. However, evaluating the efficacy of any drug requires establishment of the dosing regimen. Data to inform SSRI dose requirements across pregnancy are meager. Pregnancy induces alterations in cytochrome (CYP) 450 isoenzymes. CYP3A4, 2D6 and 2C9 are increased, and doses of drugs metabolized by these CYPs must be increased. CYP2C19 activity decreases and dose reductions are needed. We must provide the optimal drug doses across the changing milieu of pregnancy to maximally reduce disease burden while minimizing adverse effects. A strategy for optimal pharmacologic treatment for

pregnant women will facilitate exploring potential benefits to balance the extensive literature on risks to the maternal-fetal pair.

DNTS 21

What can Prenatal Exposure to SSRI Antidepressants Teach Us About Child Development?

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Selective serotonin reuptake inhibitor (SSRI) antidepressants are commonly used during pregnancy and the postpartum period. SSRIs inhibit the reuptake of a key neurodevelopmental signal, serotonin (5HT), thereby increasing central 5HT levels during developmentally sensitive periods. Given serotonin's key role in early brain growth, SSRI use in pregnancy raises critical and unanswered questions about the long term developmental effects associated with early changes in brain 5HT levels. Recent attention has focused on increased risks for disordered or delayed development associated with prenatal exposure to SSRIs, particularly related to risks for attentional and mood disorders, as well as autism spectrum disorder (ASD). However, recent preclinical data are now showing that under particular developmental circumstances, SSRIs may protect against the effects of early exposure to maternal stress. Similar human findings remain very limited. This presentation will explore the question of whether there is similar clinical evidence in early childhood illustrating that prenatal SSRI exposure could - either directly or indirectly - confer a potential developmental benefit against the effects of perinatal maternal mood disturbances. With this in mind, this keynote will focus on a review of recent clinical findings that illustrate a variety of developmental outcomes in children with in utero SSRI exposure. This presentation will seek to offer a broader perspective that illustrates risks and possible benefits that may be associated with the use of SSRIs during pregnancy, thus also potentially offering key lessons about child development in general.

DNTS 22

The Safety of Tricyclic Antidepressants and Mood Stabilizers in Pregnancy: What Should We Use for The Treatment of Bipolar Disorders?

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Although the most widely used antidepressant drugs are the SSRIs and SNRIs, a significant proportion of patients with depression or bipolar disorder are still treated with "elder" antidepressants or with mood stabilizers. The mood stabilizers (lithium, valproic acid (VPA), carbamazepine, oxcarbazepine and lamotrigine) are generally more effective in the manic phase, while the tricyclic and tetracyclic drugs are generally used during depression. Imipramine, desipramine and other tricyclic drugs are not teratogenic in humans or pregnant animals, but the exposed infants may have withdrawal symptoms. The tetracyclic drugs like mirtazapine and maprotiline are also not considered to be teratogenic, but the human data in pregnancy is limited. Among the mood stabilizers, lithium was more commonly used for the treatment of pregnant patients. However, lithium exposure during pregnancy was shown to increase the rate of rather severe cardiac anomalies including Ebstein's anomaly, hence pregnant women are advised to perform fetal echocardiography but not to stop treatment. No neurodevelopmental damage has been demonstrated in infants exposed in utero to tricyclics or lithium. Carbamazepine and oxcarbazepine are similar structurally and have similar pharmacologic effects. Carbamazepine is a known human teratogen that increases the rate of neural tube defects (NTD) to 0.5-1% as well as the rate of other congenital anomalies, especially cardiovascular. Although there is relatively little data on the safety of oxcarbazepine in pregnancy, judging from animal studies, it seems to have a similar teratogenic effect. Carbamazepine may also cause neurodevelopmental delay. VPA seems to be the most teratogenic antiepileptic drug causing 1-2% of NTD and a significant increase in the rate of major congenital anomalies: ie, cardiac and limb anomalies, facial clefts, hypospadias. Treatment with VPA may be associated with a specific "valproate syndrome" with facial dysmorphic features and neurodevelopmental delay, especially in language. It may also significantly increase the rate of Autism Spectrum Disorder. Lamotrigine seems to be without significant teratogenic or neurotoxic effects. Indeed, the use of lamotrigine in pregnant women with bipolar disorder is steadily increasing. It is the physician's role to choose the most appropriate drug for treatment of depression in pregnancy rather than withholding treatment.

DNTS 23

New Insights into the How SSRIs Shape the Developing Brain: From Mice to Public Health Implications

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Serotonin exerts profound effects on neurodevelopment before assuming its mature role as a neurotransmitter. SSRI augmentation of serotonin signaling during sensitive periods of development produces changes in rodent anxiety- and depressive-like phenotypes that are long lasting, and delayed in their onset. The rodent SSRI-sensitive period overlaps with human 2nd and 3rd trimester but the long-term effects of human gestational SSRI exposure remain unknown. One of the curious features of the serotonin transporter is that it is transiently expressed in non-serotonergic neurons of the limbic forebrain. SSRI blockade of these transiently expressed, “ectopic” transporters might underlie the enduring effects of early SSRI exposure on limbic circuitry. In this presentation, we review the biologic basis for how SSRIs interact with the developing brain to produce late onset changes in anxiety and depression-like behaviors in rodents. He reviews his recent finding that like rodents, the fetal rhesus macaque also expresses transient, “ectopic” serotonin transporters in the forebrain. He also discusses recent findings showing that human fetal exposure to SSRIs during pregnancy is associated with higher rates of depression in adolescents than expected based on familial loading alone. This association with mood disorders is specific as there are no effects of gestational SSRI exposure on subsequent rates of autism or ADHD. These human findings have potential public health relevance as antidepressant treatment is currently recommended for the management of mood and anxiety symptoms during pregnancy. Consequently, the use of SSRIs in pregnant women has increased steadily over the past 20-years. Alarmingly, our findings indicate that the use of SSRIs during pregnancy to mitigate maternal symptoms may paradoxically alter brain development of the growing fetus in ways that lead to an iatrogenic increase in mood disorders. More research is needed to effectively guide the clinical management of peri-partum mental illness to optimize outcomes for both the mother and her fetus.

DNTS 24

Elsevier Distinguished Lecturer

Mouse Models of Autism to Identify Genetic Causes and Discover Therapeutics

Chairperson: *Lynn Singer, Case Western Reserve University, Cleveland, OH*

Jacqueline Crawley

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Autism is a neurodevelopmental disorder diagnosed by two classes of behavioral criteria: (a) social interaction and communication deficits, and (b) repetitive behaviors with restricted interests. Over 100 risk genes for autism spectrum disorder have been identified over the past decade. Mice with targeted mutations in many of these risk genes are increasingly available to test hypotheses about genetic causes of autism. Our laboratory designed mouse behavioral paradigms with conceptual analogies to the diagnostic and associated symptoms of autism. Reciprocal social interactions are assayed

longitudinally across developmental stages with simple automated measures of sociability, and with in-depth scoring of reciprocal social interactions. Communication in mice is inferred from the emission, detection, and responses to olfactory and auditory social cues. Repetitive behaviors are assayed for spontaneous motor stereotypies, repetitive self-grooming, marble burying and perseveration during the reversal phase of water maze spatial navigation. Mouse behavioral assays relevant to associated symptoms of autism, including anxiety, hyperactivity, cognitive impairments, and reactions to sensory stimuli, provide further insights into genetic substrates of additional phenotypes. Forward and reverse genetic models will be presented, including BTBR T+ Itpr3tf/J, an inbred strain that displays abnormalities on multiple autism-relevant behavioral tasks, *Engrailed2*, a knockout mouse with a haplotype variant associated with autism, *Shank3*, a knockout mouse with a mutation in a central risk gene for autism and Phelan-McDermid syndrome, and 16p11.2 deletion, a human syndrome associated with autism and intellectual disabilities. Mouse models further offer preclinical translational tools to discover pharmacological targets and to evaluate treatment efficacy. We employ lines of mice with the most robust autism-relevant traits for the discovery of effective therapeutic targets. Proof-of-principle results will be presented on hypothesis-driven pharmacological interventions that reversed components of autism-relevant behavioral phenotypes in mouse models.

DNTS 25

Hair Cortisol in Newborn Macaque Monkeys: Use As a Biomarker of Prenatal Cortisol Exposure and Relationship to Infant Behavior

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Elevated glucocorticoid concentrations associated with prenatal stress can produce adverse effects on pregnancy outcome, fetal growth, and postnatal offspring development. Moreover, maternal stress is often a significant confounding variable when studying the influence of prenatal drug exposure on infant/child behavior and cognitive function. Until recently, assessing the effects of prenatal stress on the hypothalamic-pituitary-adrenocortical (HPA) system was limited to measurement of maternal and/or infant plasma or salivary cortisol (CORT), or, in rare cases, measurement of CORT in cord blood or in amniotic fluid samples obtained by amniocentesis. We have developed a new approach involving measurement of CORT concentrations in the hair of the newborn macaque monkeys. We propose newborn hair CORT to be a biomarker of cumulative gestational CORT exposure during roughly the second half of gestation (based on the time of onset of fetal hair growth in macaques). The present study applied this approach to a convenience sample of mother-infant pigtail macaques (Macaca nemestrina) obtained from the breeding colony at the Washington National Primate Research Center. We found that newborn infant hair CORT levels were extremely high compared to the levels observed in mother monkeys sampled at the same time as their offspring. Moreover, newborn hair CORT levels were positively correlated with the rise in maternal hair CORT from the time of pregnancy verification by ultrasound to parturition. Behavioral testing of the offspring showed that high levels of infant hair CORT were associated with delayed cognitive development (A-not-B task) and lower scores on a Behavioral State composite category on the macaque Neonatal Behavioral Assessment Scale (which includes attention and alertness during testing along with assessments of irritability and consolability). Additional data on infant temperament are currently being analyzed. We conclude that even in the absence of an experimentally imposed stressful manipulation, greater exposure to CORT prenatally is associated with poorer developmental outcomes. This approach can be applied to human studies using either hair samples or nail clippings (another keratinous tissue that accumulates CORT) obtained from young infants.

DNTS 26

Long-Lasting Cognitive Deficits in Rhesus Monkeys after Neonatal General Anesthesia Induced by Isoflurane/Nitrous Oxide: Protection by Acetyl-L-carnitine

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We showed previously that general anesthesia induced by 8 hours of nitrous oxide/isoflurane (70%/1%; NO/Iso) during the first week of life causes significant increases in neuronal cell death and permanent cognitive deficits in rhesus monkeys. In the present study monkeys received the same NO/Iso treatment (n = 8) or NO/Iso plus 100 mg/kg of the antioxidant and mitochondrial stabilizer acetyl-L-carnitine (ALC) 1 hr before and 4 hr after the start of anesthesia (n = 6). Controls were exposed to room air for 8 hours with (n = 7) or without (n = 8) ALC. At 7 months of age all animals began training to perform a series of cognitive function tasks as part of the National Center for Toxicological Research (NCTR) Operant Test Battery (OTB). Tasks included those for assessing aspects of learning, motivation, color discrimination, and short-term memory. Subjects responded for banana-flavored food pellets by pressing response levers and press-plates during daily (M-F) test sessions (50 min) and were assigned training scores based upon their individual task performance. ALC prevented the adverse effects of NO/Iso on motivation [decreased response rate (RR) and %task completed (PTC)] throughout most of the two year study and on learning task performance [accuracy (ACC), RR, PTC] manifest during the last year of observation. ALC alone delayed acquisition of learning (PTC, ACC and RR) and color discrimination (PTC) task performance over the first year of testing and slowed acquisition of recall delays in a short-term memory task. Thus, ALC prevents the cognitive dysfunction associated with NO/Iso-induced general anesthesia but, by itself has adverse effects of its own at the dose tested. It remains to be determined whether lower doses of ALC can also be protective and yet not exhibit any adverse effects of its own.

This research was supported by CDER/FDA and NCTR/FDA Exp#7285.

DNTS 27

Associations of Prenatal Exposure to Phthalates and Bisphenol A with Measures of Cognitive Function in 7.5-Month-Old Infants

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Phthalates are used as plasticizers and in personal care products. Bisphenol A (BPA) is used in the manufacture of polycarbonate plastics, and food and drink container liners. Prenatal exposure to either could affect cognitive development due to their endocrine disrupting properties. However, few studies have assessed their impact on infant cognitive development. Infant looking behaviors, including average fixation duration and gaze shift rate measure information processing speed and visual attention, respectively, and predict cognitive outcomes later in childhood. In these preliminary analyses, we assessed infant looking behaviors and exposure in a subsample (n = 40) of infants born to women recruited from 2010-2012 as part of a large prospective study. BPA and phthalate metabolites were measured in a pool of five urines collected across pregnancy. We focused on the sum of di-(2-ethylhexyl) phthalate metabolites ($\sum$DEHP) as DEHP has developmental effects in animal models and $\sum$DEHP accounts for a significant proportion of phthalate metabolites in urine. 7.5-month-old infants were given a visual recognition memory test including an assessment of infant looking behavior. Each infant saw side-by-side photographs of two identical faces for 20 seconds of total looking; this was repeated with 5 different pairs of faces. Average fixation time

(average duration of looking at a single face), and shift rate (number of times the infant's look shifted from one face to the other per second of looking) were averaged across the five trials, and analyzed using a general linear model adjusted for infant age and sex, household income, maternal IQ and education, breastfeeding, and urine specific gravity. Each μmol/L increase in ∑DEHP and each μg/L increase in BPA in urine were associated with longer fixation duration (β = 2.31, 95% CI = 0.29, 4.33) and (β = 0.17, 95% CI = 0.07, 0.28), respectively. Urine BPA was also associated with lower gaze shift rates (β = -0.05, 95% CI = -0.09, 0.001). The association between ∑DEHP and longer fixation duration was attenuated substantially by removing 4 influential observations (β = 0.97, 95% CI = -1.00, 2.94). These preliminary findings support the potential for prenatal exposure to BPA and DEHP to impact infant processing speed and visual attention but need corroboration in a larger sample. ES007326, ES018163, ES022848, RD83459301, RD83543401.

DNTS 28

Impact of Gestational Serotonin Availability on Brain Function & Social Behavior

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Depression is a serious mood disorder that can diminish quality of life and increase the risk of such things as nutritional problems, reckless behavior, and suicide. For women with severe depression the need for treatment is essential, especially during and after pregnancy. However, there is debate and concern about the safety of anti-depressant medications used during pregnancy regarding the impact that these treatments may have on the neuronal development of the child in utero and postpartum. Approximately 23% of pregnant women experience at least one depressive episode, and 7% use selective 5-HT reuptake inhibitor (SSRIs) antidepressants to target and block the 5-HT transporter (SERT) to ameliorate depression. 5-HT is vital for shaping fetal neural circuitry, and reports link aberrant fetal 5-HT levels with psychiatric disorders later in life. Hence, elucidation of the relationships among mechanisms controlling maternal and fetal 5-HT availability, and how they respond to respective demands for 5-HT is critical to aid in identification of prenatal risk factors, and preventative measures. 5-HT availability in fetal brain is highly dependent upon maternal availability of tryptophan (TRP), an essential dietary amino acid. We hypothesize that genetically or pharmacologically compromised 5-HT transporter activity will increase 5-HT turnover and maternal TRP demand, such that if it is combined with dietary TRP deficiency, offspring of either gender are likely to develop behavioral symptoms consistent with autism. Offspring from SERT knock-out (-/-) mice, which are socially impaired, as well as mice born to wild-type (+/+), and heterozygote (+/-) dams treated with SSRI or vehicle throughout gestation are the focus of this study. Additionally, these groups are subjected to either standard mouse diet, TRP depleted (-0.05% or -0.1%), or TRP enhancement (+ 1%) during gestation and lactation. We predict that offspring born to SERT -/-, +/+, and +/- dams on SSRIs may develop deficits in social behavior that worsen with TRP depletion. Conversely, we predict sociability deficits will be ameliorated by maternal dietary TRP supplementation. Preliminary findings support this hypothesis, and indicate that maternal TRP dietary supplementation may offset detrimental effects of SSRI use on the developing 5-HT system to prevent sociability impairments in adolescents.

DNTS 29

Perinatal Citalopram Exposure Alters Spatial Learning and Memory, Acoustic Startle Response, Anxiety, and Sociability in Adult Sprague-Dawley Rats

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Antidepressants (ADs) primarily inhibit neurotransmitter reuptake; however, the effects of such activity on early brain development are not well understood. During fetal life, the brain rapidly develops and serotonin plays a key role, making the brain potentially vulnerable to insult from serotonergic drugs. One study suggested an increase in autism spectrum disorder (ASD) in children whose mothers took selective serotonin reuptake inhibitors (SSRIs) while pregnant (Croen et al., 2011). Another study in rats reported deficits in learning and memory after exposure to the SSRI citalopram from P11-20 (Schaefer et al., 2013). The present study investigated whether gestational and lactational exposure to citalopram affects long-term behavioral outcomes. Sprague-Dawley dams were randomly assigned to one of two treatment groups: Citalopram (10 mg/kg; Cit-10) or Saline (Sal). Dams were treated by subcutaneous injection twice daily (6 h apart) from E6-21, and pups were dosed directly from P1-20. Behavioral testing began on P60. One male/female pair from each litter was tested in the Cincinnati water maze for egocentric learning. Another pair received the Morris water maze to assess allocentric learning and memory. A third pair received elevated zero maze, open-field, marble burying, acoustic startle response with prepulse inhibition (PPI), social preference, and forced swim. Rats were tested in a straight water channel prior to water maze testing to assess motor function, motivation to escape, and to show them the escape platform. Analyses showed significant treatment effects in Morris water maze acquisition (Cit-10 rats had longer path lengths than Sal rats, $p \leq 0.05$), open-field (Cit-10 females explored less than Sal females, $p \leq 0.05$), marble burying (Cit-10 rats buried more marbles than Sal rats, $p \leq 0.001$), PPI (Cit-10 increased V_{max} across all prepulse levels, $p \leq 0.01$), and social preference (Cit-10 rats spent less time with a stranger conspecific than Sal rats, $p \leq 0.05$), but no changes in egocentric learning were seen. The results suggest that SSRI exposure during early brain development results in enduring behavioral changes in the adult offspring. If confirmed, the results could have implications for the safety of SSRIs when used during pregnancy. (Supported by NIH training grant T32 007051 and research grant DOD W81XWH-13-0306.)

DNTS 30

Developmental Outcomes for Infants of Mothers with Major Depressive Disorder or Bipolar Disorder

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Pharmacotherapy is the mainstay of treatment for both bipolar disorders (BD) and major depressive disorder (MDD). However, risks and benefits of this treatment in pregnant women must be carefully considered. Most pharmacological treatment for BD and MDD, including selective serotonin and noradrenergic reuptake inhibitors (SRIs) and mood stabilizers, cross the placenta resulting in fetal in utero exposure. Yet there are few longitudinal data on the developmental outcomes of infants prenatally exposed to MDD, BD, or pharmacological treatment for these disorders. We conducted two studies of infant outcomes related to these exposures. In both studies maternal diagnosis and pharmacotherapy exposure were assessed at or as near to 20, 30, and 36 prenatal weeks and 12, 26, 52, and 78 weeks postpartum as feasible. All infants were evaluated with the Bayley Scales of Infant Development, Second Edition, including the psychomotor (PDI), cognitive (MDI), and behavioral (BRS) components. Study 1 included 166 mother-infant dyads: 68 with prenatal SRI (n = 41) or MDD exposure (n = 27) and 98 non-exposed controls. Neither prenatal exposure significantly impacted overall MDI or BRS scores. SRI exposure was associated with lower PDI scores at 26 (M = 97.0) and 52 weeks (M = 92.9) compared with non-exposed infants (M = 101.4 and 100.5). This difference was no longer significant at the 78 week assessment. Study 2 included 197 mother-infant dyads: 81 with prenatal BD without psychotropic treatment (BD-, n = 27) or BD with psychotropic exposure (BD +, n = 54) and 116 infants exposed to neither BD nor psychotropics. Neither prenatal exposure to BD- or BD + significantly impacted overall PDI, MDI, or BRS scores. However, we observed a significant effect of BD + exposure by time interaction for the BRS Motor Quality index, with BD + exposed infants less likely to be above the 75th percentile at the 52

week assessment (M = 11.5%) compared with BD- (M = 48.4%) and non-exposed infants (M = 40.0%). Across both studies we found an effect of prenatal psychotropic exposure on infant motor functioning; however, the majority of infants were within normal limits on all developmental assessments. Future studies which longitudinally follow mother-infant pairs well into childhood are needed to define developmental trajectories.

DNTS 31

Interactive Effects of Prenatal Tobacco Exposure, Prenatal Maternal Depression, and Child Sex on Attention Problems at Preschool Age

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Maternal smoking during pregnancy is a significant public health problem with major impacts on child health and development. While a larger number of well-designed prospective studies report significant effects of prenatal tobacco exposure (PTE) on behavior problems in later childhood, the results in early childhood are mixed, perhaps due to moderating factors. The goal of this study was to examine the role of maternal prenatal and postnatal depression and child sex as potential moderators of the association between PTE and child attention and aggression. Participants were part of an ongoing longitudinal study examining developmental outcomes in children with PTE. Mothers were recruited in the first trimester. After delivery, 258 mother-infant dyads were classified into one of two groups: PTE (n = 181) and non-PTE (n = 77) based on maternal report and maternal salivary cotinine in each trimester, and infant meconium at delivery. Maternal depressive symptoms were measured in the second and third trimester, and at 2, 9, and 24 months post-delivery. Maternal reports of child attention and aggression were obtained at 36 months of child age and child salivary cotinine was measured as a marker of postnatal exposure. There were no main effects of PTE on attention or aggression and no association by trimester, infant meconium, or number of cigarettes. Path analyses with prenatal maternal depression and child sex as moderators of the association between PTE and child outcomes indicated a significant three-way interaction effect on child attention (β = -.35, p = .04). Specifically, PTE boys with mothers who experienced higher levels of prenatal depression exhibited the greatest attention problems at 36 months. In addition, postnatal maternal depression was associated with both, attention and aggression problems (β = .22 and .32 respectively, $p < .05$), and higher duration of breastfeeding was associated with lower attention problems (β = -.18, p = .004). Results add to the growing literature on sex differences in the effects of exposure to PTE and prenatal depression and suggest greater vulnerability to prenatal factors for boys.

DNTS 32

Effects of Prenatal Cocaine Exposure on Self-Reported Mental Health at Age 17

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Prenatal cocaine exposure may increase risk of mental health and substance use problems. Cocaine's direct effect on fetal monoamine neurotransmitter systems is hypothesized to disrupt self-regulatory behavior and contribute to increased rates of alcohol and substance use disorders (SUDs) and other mental health diagnoses. Three hundred twenty seven adolescents (162 with prenatal cocaine exposure (PCE); 165 without prenatal cocaine exposure (NCE)), recruited at birth for a study of developmental effects of prenatal cocaine exposure were assessed for substance use and mental health disorders at age 17 using the computerized, self-report version of the Diagnostic Interview Schedule for Children (DISC-IV). Logistic regression was completed for diagnostic scales with at least 10% of group reporting positive cases. Confounding maternal/caregiver and environmental variables, including other prenatal drug exposures, caregiver psychological distress, quality of the home environment, exposure to violence and elevated blood lead were examined. After adjusting for confounders, there was a significant cocaine by gender interaction for oppositional defiant disorder (ODD) with PCE girls having a higher percentage of positive diagnosis than NCE girls (45.5% vs 13.6%; $p < .007$). PCE adolescents also had more of any one SUD than NCE adolescents (OR = 2.58, 95%CI (1.08-6.20), $p < .03$). Exposure to violence (OR = 1.7, 95%CI (1.65-2.34), $p < .007$) was also an independent predictor of any SUD. Effects of prenatal cocaine exposure on SUD were mediated by 12 year externalizing behavior ($p < .0001$). Diagnoses of major depression were predicted by current caregiver psychological distress (OR = 1.6, 95%CI (1.01-2.63), $p < .05$) and higher prenatal exposure to alcohol (OR = 1.9, 95%CI (1.70-2.99), $p < .009$). Attention-deficit/hyperactivity disorder (OR = 1.6, 95%CI (1.08-2.32), $p < .03$) and any one mental health diagnosis (OR = 1.5 (1.01-2.22), $p < .05$) were associated with higher prenatal marijuana exposure. PCE was not associated with increased dual mental health and SUD diagnoses. Elevated lead level was not associated with increased mental health and SUD diagnoses after controlling for prenatal drug exposures and environmental factors. Results indicate that PCE is associated with increased incidence of ODD in girls and SUD regardless of gender. PCE youth with exposure to violence and early externalizing behavior may be at increased risk for SUD. Targeted drug use prevention programs may help in diverting at risk youth.

Poster Presentations

DNTS P01

Behavioral Consequences following Deletion of the Dopamine D2 Receptor in Forebrain GABAergic or Glutamatergic Neurons

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Circuit formation and forebrain differentiation are key events in early brain development, and these processes are highly sensitive to alterations in the neuronal milieu. The neurotransmitter dopamine (DA), for example, is essential to appropriate neurodevelopment, and disruptions to DA homeostasis during this period have been shown to contribute to neuropsychiatric disorders such as depression, schizophrenia, and attention deficit disorders, to name a few. We and others have shown that alterations to the DA D2 receptor affects GABAergic neuron migration to the frontal cortex and alters long-term expression of a subset of these interneurons (parvalbumin +). Furthermore, D2 receptor constitutive knockout mice are less immobile during the tail suspension test, suggesting a role for the D2 receptor in depression. However, the D2 receptor is expressed in number of cell types throughout the forebrain, and the functional role of each subset of receptors is unknown. We hypothesized that these subsets of D2 receptors within the forebrain have differential roles, and that loss the receptor in either GABAergic or glutamatergic neurons would result in significantly different behavioral outcomes. To accomplish this, we utilized Cre-lox technology by breeding Drd2 floxed mice (courtesy of Dr. Marcelo Rubinstein) with either Nkx2.1-Cre or Emx1¬-Cre mice to knockout the D2 receptor in either GABAergic or glutamatergic neurons of the forebrain, respectively. Adult male and female conditional knockout mice, as well as floxed and Cre controls, were run in a behavioral battery of tests examining outcomes including locomotor activity, depression-like behavior, anxiety, learning and memory, and motor coordination. These findings will be important in pinpointing the specific, specialized roles of the D2 receptor within each of these cell types of the telencephalon.

DNTS P02

Comparison of Developmental Effects Across Multiple Phthalate Esters

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Phthalates are a group of chemicals that are widely used in the manufacture of plastics and personal care products, including cosmetics, pharmaceuticals, food packaging, and medical devices. As a result, human exposure to phthalates is ubiquitous, and biomonitoring data suggest that populations may be exposed to mixtures of multiple phthalate esters. In general, phthalates affect the endocrine system and have been associated with adverse male reproductive effects resulting from the reduction of testosterone synthesis. However, these chemicals also have been associated with a range of other adverse health outcomes, including developmental effects. A preliminary search of experimental studies suggests that common phthalate-induced alterations observed in mammalian models include reduced growth and increased incidence of internal and external malformations. In addition, neurodevelopmental outcomes are suggested to differ across compounds. In light of the potential for exposure to mixtures of multiple phthalates, it is important to understand the extent to which such developmental outcomes are consistent across different phthalate esters, and the extent to which differences exist. Here, we perform a comparison of the developmental outcomes that have been reported in the literature for five phthalates that are commonly used in commercial products: dibutyl phthalate (DBP), diethylphthalate (DEP), butyl benzyl phthalate (BBP), di-isobutyl phthalate (DIBP), and diisononyl phthalate (DINP). We have performed a systematic review of relevant scientific literature for these chemicals and compiled evidence from experimental and epidemiologic studies. Investigating the extent to which these phthalate esters are associated with common developmental outcomes will aid in future evaluations of the potential for additive developmental effects resulting from cumulative exposure to this group of chemicals. It may also allow for increased insight into mechanism of action. 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 P03

Single and Repeated Exposures to the Volatile Anesthetic Isoflurane Do Not Impair Operant Performance in Aged Rats

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Postoperative Cognitive Dysfunction (POCD) is a complication that can occur in the elderly after anesthesia and surgery and is characterized by impairments in information processing, memory, and executive function. Currently, it is unclear whether POCD is due to the effects of surgery, anesthesia, or perhaps some interaction between these two variables or other perioperative variables. Studies in rodents suggest that the development of POCD may be related directly to anesthesia-induced neurotoxicity. Volatile anesthetics have been shown to increase cellular inflammation and apoptosis within the hippocampus of aged rodents, while producing corresponding impairments in hippocampal dependent brain functions. However, it is unclear whether volatile anesthetics can affect additional aspects of cognition that do not primarily depend upon the hippocampus. The purpose of this study was to use established operant tests to examine the effects of isoflurane on aspects of behavioral inhibition, learning, and motivation in aged rats. Twenty-one adult Sprague-Dawley rats (11 male, 10 female) were trained to perform fixed consecutive number (FCN), incremental repeated acquisition (IRA), and progressive ratio (PR) tasks for a minimum of 15 months prior to receiving anesthesia. At 23 months of age, rats were exposed to 1.3% isoflurane or medical grade air for 2 h. Initial results revealed that a 2 h exposure to isoflurane had no effect on IRA, FCN, or PR performance. Thus, rats received 3 additional exposures to 1.3 % isoflurane or medical grade air: a 2 h, 4 h, and 6 h exposure with 2 weeks elapsing before exposure two, 3 weeks elapsing before exposure three, and 2 weeks elapsing before exposure four. These additional exposures had no observable effects on IRA, FCN, and PR performance. These results suggest that single and repeated exposures to isoflurane do not impair the performance of aged rats in tasks designed to measure behavioral inhibition, learning, and motivation. This lack of significant effect suggests that the impairments associated with isoflurane exposure may not generalize to all aspects of cognition, but may be selective to tasks that primarily measure spatial memory processes. If so, this would have specific implications for the development of animal models of POCD.

DNTS P04

High-Taurine Consumption by Adolescent C57BL/6J Mice Alters Biogenic Amines in a Sex-Dependent Manner

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Energy drinks are a multi-billion dollar industry, and roughly half of all college students report drinking energy drinks regularly. The amino acid taurine is a key ingredient in the top-selling energy drinks and the most abundant free amino acid in the central nervous system of mammals. Although taurine can be neuroprotective and act as an antioxidant, recent studies indicate there is a risk of neurotoxicity at high doses. We previously reported that C57BL/6J mice showed learning and memory deficits and a differential response to caffeine after being treated with 0.12% taurine (400 mg/kg) from postnatal day 30 to 60. The most severe effects were seen in male mice whereas taurine-treated females showed improved performance in Morris water maze. We followed up those findings by examining neurotransmitter levels and taurine levels in plasma. We found a significant difference in serotonin levels ($P < 0.05$) in the hypothalamus when comparing taurine-treated and control mice and a trend for a treatment x sex interaction ($P = 0.094$) for levels of the serotonin metabolite 5-HIAA. In the cortex, there was a trend for a treatment x sex interaction ($P = 0.072$) for dopamine levels with taurine-treated males showing decreased dopamine whereas taurine-treated females had higher levels than controls. In the cerebellum, there was a significant main effect of sex ($P < 0.01$) and a significant treatment x sex interaction ($P < 0.01$) for levels of the dopamine metabolite HVA. Taurine-treated females had lower levels than controls whereas males had higher levels than controls. Together, these data suggest that high taurine consumption during adolescence alters biogenic amines in multiple brain regions in a sex-dependent manner which could explain some of the behavioral deficits previously observed. Supported by ES020053 and GM103436.

DNTS P05

Prioritization of polychlorinated biphenyl congeners to support human health risk assessment

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Polychlorinated biphenyls (PCBs) are persistent organic pollutants associated with developmental neurotoxicity. Populations are generally exposed to mixtures of PCB congeners. Risk assessment of PCBs is fraught with many challenges, including differences in congener profiles between commercial PCB mixtures and environmental mixtures. These differences are important because each of the 209 PCB congeners has a unique structure and chemistry, leading to differential modes of action in exposed organisms. Some PCBs (i.e., "dioxin-like" PCBs) can bind and activate the aryl hydrocarbon receptor, eliciting the same toxicological responses observed with dioxin exposure. Dioxin-like PCB congeners have been tested in many in vivo and in vitro model systems, and their toxicological potential is relatively well-understood. However, the large majority of PCB congeners are non-dioxin-like; over half of these have not been tested in any assay. To perform a human health risk assessment accounting for the toxicological activity of all PCB congeners comprised in environmental media, tools are needed to estimate the potency of relatively untested PCBs. A pilot set of 14 references examining PCB structure-activity relationships was studied, leading to the identification of roughly 30 congeners that

have been tested across three or more studies. The knowledge of structure-activity relationships based on these 30 congeners may be further studied to develop tools to estimate the potency of relatively untested congeners. Preliminary work from our group has identified a priority list of congeners for which there is a particular need for additional toxicological data to confirm and to expand upon the findings of existing studies. Congeners have been selected for this list based on several criteria, including abundance in environmental samples (e.g., air, fish, and sediment), frequency of detection and abundance in human serum, existing in vivo congener-specific data, and known in vitro potency. Future testing of congeners from this priority list would help to fill data gaps in support of PCB risk assessment. 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 P06

Circadian Disruption, Cognitive Function and Neurotransmission in a Rodent Model

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Endogenous circadian rhythms regulate physiological and behavioral functions are synchronized to various cues such as light. Desynchrony of circadian rhythms results in physiological disorders, including cognitive impairments in attention. Shift work is the most common cause of circadian disruption in the working population in the U.S. At the molecular level, cholinergic projections from the nucleus basalis magnocellularis (NBM) modulate circadian rhythmicity in the suprachiasmatic nucleus (the brain's master clock) and also project to the medial prefrontal cortex (mPFC), where they modulate dopamine release and performance on the 5-Choice Serial Reaction Time Task (5-CSRTT), a test of attention and impulsivity. We modeled circadian disruption in adult Long-Evans rats by testing them on the 5-CSRTT during the light-phase (day rats) or the dark-phase (night rats) of their circadian cycles. Importantly, night rats were exposed to light for 1 hour daily during transport and while in the testing room. Attention was not affected by phase of testing, but premature responding (impulsivity) differed between phases. Night rats remained nocturnal and were more impulsive than day rats, which entrained to the time of testing by becoming more diurnal. Yet, in the day rats, nocturnality (% activity in the dark) was negatively correlated with premature responding. Subsequently, we determined that choline acetyltransferase (ChAT) expression in cholinergic cell bodies in the NBM was increased in day rats. Expression of ChAT and tyrosine hydroxylase (TH) in the mPFC did not differ between groups, but, in day rats, mPFC TH expression was negatively correlated with nocturnality. Our results suggest that the 1-hour exposure to light experienced by night rats in the testing room was more detrimental to circadian rhythmicity than day testing, and that premature responding in our experiment may be mediated by dopaminergic signaling. Future studies will further explore these new hypotheses.

DNTS P07

Identifying Attention Problems in Children and Adolescents with the Behavioral Assessment and Research System (BARS)

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The Behavioral Assessment and Research System (BARS) is a set of standardized tests able to be administered to children and adolescents using a child-friendly response unit and computer software for presenting stimuli, teaching the task, and recording responses. BARS tests are intended to detect decreases in cognitive function in populations exposed to neurotoxic chemicals. We studied the utility of the BARS for identifying attention impairment by comparing computer test results to daily behavioral issues identified by parents using the Child Behavior Checklist (CBC), which is a commonly-used rating scale for detecting behavioral disorders. Results indicated that the Simple Reaction Time response latency significantly predicted both ADHD problems ($p = .001$) and sluggish cognitive tempo ($p = .003$) on the CBC in a group of 20 children aged 6 to 14 years. These problem scales have been found to be highly predictive of a clinical ADHD diagnosis. Results of this study are consistent with the view that attention problems are associated with a slow processing speed and demonstrate the utility of the BARS as a neurobehavioral measure able to detect attention problems in children exposed to neurotoxic substances.

This research was partially supported by a NIEHS grant (R01ES024757) to K.M.Z.

DNTS P08

Dopamine Transporter (DAT) and Vesicular MOnoamine Transporter (VMAT) expression in the Striatum and medial Prefrontal Cortex in Weanling and Adult, Cocaine-Exposed Rats is Altered by Perinatal PCB exposure

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Previous findings demonstrate that adult exposure to PCBs alters DAT and VMAT expression. Previous findings demonstrate that adult exposure to PCBs alters DAT and VMAT expression. However, less is known about the effects of *perinatal* PCB exposure on expression of these transporters. Likewise, it is not known how *perinatal* PCB exposure may alter typical cocaine-induced changes in DAT and VMAT expression. The purpose of this project was two-fold: 1) to determine the effects of gestational and lactational exposure to an environmentally relevant mixture of PCBs on DAT and VMAT expression in the medial prefrontal cortex (mPFC) and striatum in weanling rats and 2) to evaluate whether DAT and VMAT expression in mPFC and striatum were different in perinatally PCB exposed rats in comparison to controls following repeated daily administration of cocaine during adulthood. Long-Evans dams were orally exposed to 0, 3 or 6 mg/kg/day of an environmentally relevant mixture of PCBs beginning at 4 weeks prior to breeding and continuing until litters were weaned on postnatal day (PND) 21. At weaning, the mPFC and striatum were extracted from one male and one female per litter for Western blot analysis of DAT and VMAT. The mPFC and striatum from one adult male and female offspring (PND 117) were also collected after these rats had completed a cocaine behavioral sensitization paradigm that examined locomotor activity following repeated daily intraperitoneal (IP) injections of 10 mg/kg of cocaine. Western blot analysis was again used to determined DAT and VMAT expression. It was hypothesized that DAT and VMAT expression in animals exposed to PCBs during the perinatal period would be reduced relative to non-PCB-exposed control rats. Results demonstrated alterations in both DAT and VMAT expression in the PCB-exposed weanlings relative to the non-PCB-exposed controls, particularly in the males. Likewise, DAT and VMAT expression in the adult rats following repeated cocaine exposure was also affected by perinatal PCB exposure. These findings suggest a possible mechanism for the differential behavioral response to psychostimulant drugs observed in rats perinatally exposed to PCBs.

(Supported by NIEHS R00ES015428.)

DNTS P09

Gender-specific Effects of Prenatal Cocaine Exposure of Emotional Behavior in Adolosecent Rats: Implications for Antidepressant Efficiay

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We have previously shown that prenatal cocaine exposure [PCE] alters emotional behavior in aging offspring. The present study examined the impact of PCE on the development of anxiety or depressive behavior during adolescence, and the ability of prenatal exposure to alter the efficacy

of antidepressant medication. Changes in emotional behavior were assessed using behavioral paradigms developed as animal analogs of psychiatric disorders in male and female adolescent offspring of Sprague-Dawley dams injected (s.c.) with either 20 (C 20) or 40 (C40) mg/kg of cocaine on gestation days 8-20. Pair fed (PF) and saline-injected dams (SAL) served as controls. Using a within subjects design, sucrose (2%) preference and the elevated plus maze [EPM] were used to test depression and anxiety, respectively, starting at PND 35, and again following a 21-day treatment with 10 mg/kg (.ip.) of the antidepressant venlafaxine, a serotonin and norepinephrine specific re-uptake inhibitor (SNRI). Reduced sucrose preference was not seen in any groups during adaptation. Exposure to a water-deprivation stress decreased sucrose preference in C20 males, without significantly altering intake. Results from the EPM indicated that both C20 and C40 males were more anxious, spending less time on, and exhibiting fewer entries into the open arms of the maze. Venlafaxine treatment increased sucrose preference in C20 males, thereby reversing the anhedonia. It partially reversed anxious behavior in the EMP by increasing the time spent on but not entries into the open arms, and only in C40 males. These data suggest that during adolescence, prenatal exposure to cocaine, which can prompt numerous changes in serotonergic signaling during development, can induce depressive-and anxiety-like symptoms in a dose and sex-dependent manner, and preferentially diminish the efficacy of an antidepressant drug with a similar mechanism of action.

DNTS P10

The Relation between Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) and Performance on the Ages and Stages Questionnaire (ASQ)

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Background: Nausea and vomiting of pregnancy (NVP) is present in approximately 80% of all pregnancies[1]. Typically, symptoms peak around 8-12 weeks of gestation and diminish by 20 weeks[2]. Studies have suggested that children exposed to NVP in utero exhibit behavioral differences, with one study showing enhancements in nonverbal intelligence[3] and others showing deficits in behaviors related to emotions[4], attention[4,5], learning abilities[4,5], and visual-motor skills[2]. Severity of NVP may play a role in the neurodevelopmental outcomes in the children. Objective: In this study, the relation between first trimester NVP severity, defined by the 12-hour Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) index, and children's neurodevelopment, as assessed by the Ages and Stages Questionnaire (ASQ), was examined. Methods: Study participants were enrolled in a prospective cohort study through MotherToBaby California. All participants were enrolled while pregnant and gave birth to a live-born infant between 2011 and 2013. Multiple births were excluded. A total of 103 women completed both the PUQE index and the ASQ. PUQE scores were obtained during a semi-structured phone interview during the 1st trimester of pregnancy. Participants later completed the ASQ when the child was either 12-16 months ($n = 50$) or 24-28 months ($n = 53$). Descriptive statistics and multiple linear regression models were computed using SAS 9.2. Results: A higher PUQE score, indicating greater severity of NVP, was not significantly associated with a lower total ASQ score after adjusting for birth weight, gestational age, and sex (Unadjusted β: =-2.486, $p = 0.1314$, Adjusted β: =-2.368, $p = .1631$). No statistically significant associations were observed between the total PUQE score during the first trimester and ASQ scores in the communication, gross motor, fine motor, problem solving, or personal social domains after adjusting for birth weight, gestational age, and sex. Conclusions: No statistically significant associations were observed between the PUQE score during the first trimester and ASQ scores in the various domains after adjusting for birth weight, gestational age, and sex. More research is needed to obtain a larger sample size and range of PUQE scores. Further research will include a categorical analysis and assessment of medications used to treat NVP.

DNTS P11

Effects of Prenatal Cocaine Exposure on Responses to Stress in Adolescence

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Objective: To assess differences in self-reported responses to stress and coping in prenatally cocaine exposed (PCE) and non-cocaine exposed (NCE) adolescents and to explore whether childhood maltreatment (CM) moderates the effects of PCE. Methods: Adolescents ($N = 363$; 184 PCE, 179 NCE; 194 girls, 172 boys), primarily African-American and of low socioeconomic status, were prospectively enrolled in a longitudinal study at birth (90% retention). The Responses to Stress Questionnaire (RSQ) was used to assess volitional coping (primary control, secondary control, disengagement) and involuntary responses (involuntary engagement, involuntary disengagement) to stress at the 15 and 17 year follow-up visits. CM was assessed (1 = yes; 0 = no) retrospectively at age 17 using the Juvenile Victimization Questionnaire (JVQ). A mixed model repeated measures analysis was used, controlling for covariates including other prenatal drug exposures, lead exposure, maternal psychological distress at birth, sex, race, violence exposure, home environment, and external assets (ecological resources and supports) assessed at age 15 using the Developmental Assets Profile (DAP). Results: 51 (31%) adolescents with PCE and 31 (18%) NCE adolescents reported a history of CM ($p = .005$). PCE and CM interacted to be related to primary control and disengagement, such that PCE predicted primary control and disengagement only among adolescent with a history of CM. Adolescents with PCE who experienced CM reported less use of primary control (e.g., problem solving, emotional regulation; $p < .001$) and greater use of disengagement coping strategies ($p < .001$) than adolescents with PCE who did not experience CM. Adolescents with prenatal exposure to marijuana reported more use of involuntary disengagement (e.g., emotional numbing, cognitive interference, inaction). A history of CM was related to decreased secondary control (e.g., positive thinking, cognitive restructuring) and increased involuntary engagement (e.g., intrusive thoughts, physiological and emotional arousal) and disengagement. External assets were related to all voluntary coping strategies and involuntary responses to stress (increased primary and secondary control and decreased disengagement, involuntary engagement and disengagement). Conclusions: PCE may increase sensitivity to CM. PCE was associated with poorer coping strategies only among adolescents with a history of CM, suggesting that PCE may increase vulnerability to environmental risk.

DNTS P12

Prenatal Tobacco and Cannabis Exposure: Effects on Infant Regulation via Fetal Growth, Maternal Stress, and Anger/Hostility.

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Many women who use tobacco in pregnancy also use other substances, particularly cannabis. Yet, few studies have examined unique and additive effects of tobacco only vs. the combination of tobacco and cannabis (PTCE) on infant outcomes. Moreover, although prenatal tobacco exposure (PTE) has been consistently associated with higher rates of conduct disorder and aggression, developmental mechanisms for this association are poorly understood. Thus, we examined a conceptual model for the development of behavioral reactivity and regulation among PTE only, PTE and cannabis, and demographically similar non-exposed infants. We hypothesized that PTE, maternal prenatal stress, and anger/hostility would be associated with higher behavioral reactivity and poor regulation at 9 months of age. We also hypothesized that these associations may be indirect via poor fetal

growth or continued maternal postnatal aggression or stress. Finally, we examined the role of child gender as a potential moderator of these associations. Participants were 247 dyads (173 cigarette-exposed infants, 74 non-exposed) recruited in the first trimester of pregnancy. The final measure of PTE and PTCE used in model testing was infant meconium positive for metabolites of nicotine or cannabis. Infant behavioral reactivity and regulation was assessed at 9 months using behavioral coding during an anger/frustration paradigm and via maternal self-report. Results from model testing indicated that there were no direct effects of PTE on infant reactivity/regulation, but higher prenatal stress and anger were associated with higher infant reactivity. As hypothesized, there were indirect effects from PTME to higher infant negative affect and lower behavioral regulation through reduced fetal growth, and from PTE to increased infant behavioral reactivity through higher maternal aggression/hostility. Goodness-of-fit indexes indicated that this hypothesized model fit the data well, $\chi 2\ (77) = 99.96$, $p = .04$, comparative fit index = .98, root mean squared error of approximation = .03. Gender did not moderate the association between PTE/PTCE and infant reactivity/regulation. This study fills an important gap in the literature on maternal cigarette and cannabis use and infant reactivity/regulation, highlighting the role of fetal growth, and maternal aggression/hostility and stress as important intervening variables.

Copy of DNTS 2016 Author Index

Adams, Jane
Aguiar, Andrea
Altman, Itamar
Anderson, Lisa
Ansorge, Mark A.
Arango, Victoria
Arria, Amelia
Arzuaga, Xabier
Bailey, Rebecca
Balachandran, Rekha
Beaudin, Stephane
Bertrand, Kerri
Beverly, Brandiese
Bhatia, Sacha
Blessinger, Todd
Borchelt, Jolene
Bowman, Aaron B.
Brown, Arango
Brown, J.B.
Brown, Josephine
Burbacher, Tom
Cagliostro, Martha
Chambers, Christina
Champagne, Frances
Chelonis, John
Clark, Jr., Elijah
Codreanu, Simona G.
Cory-Slechta, Deborah
Crawley, Jacqueline
Curran, Christine
Dansereau, L.
Daws, Lynette
Della Grotta, S.
Derauf, C.
Dow-Edwards, Diana
Drake, D.
Dzwilewski, Kelsey
Edwards, Marshall
Eiden, Rina
Eng, Heather
Eubig, Paul
Euling, Susan
Faustman, Elaine
Walters, Jennifer
Wang, Cheng
Weaver, Andre
Webb, Donna J.
Weimer, Jamie
Weissman, Myrna M.
Ferguson, Sherry A.
Fogle, Charles
Garbarino, Valentina
Gingrich, Jay A.
Goring, Anjuli
Gould, Georgianna
Graham, Devon
Grant, Kimberly
Gutierrez, Arnold
Hanchette, Carol
Hanig, Joseph
Hotchkiss, Andrew
Huestis, Marilyn
Hufgard, Jillian
Jablonski, Sarah
Janulewicz Lloyd, Patricia
Jones, Kenneth
Kao, Kelly
Kim, June-Yung
Korrick, Susan
Kroeker, Rose
LaGasse, Linda
Lang, Adelaide
Lehmann, Geniece
Lester, Barry
Leventhal, Michael
Li, Jenny
Li, Mi
Liu, Shuliang
Ludwig, Clare
Lutes, Jocelyn
Luther, James
Macaulay, Laura
Mahoney, Megan
Makris, Susan
Malm, Heli
Markov, Dmitry A.
May, J.A.
McCawley, Lisa J.
McLean, John A.
Meyer, Abby
Meyer, Jerrold
Miller, Mellessa
Wells, Peter
Wikswo Jr., John Peter
Williams, Michael
Wisner, Katherine L.
Wisnewski, Stephen
Worlein, Julie
Min, Meeyoung
Minnes, Sonia
Molnar, Danielle
Mundy, William
Murphy, William L.
Neal, Charles
Neely, Diana
Newman, E.
Novak, Melinda
Oberlander, Tim
Ornoy, Asher
Panos, John J.
Paule, Merle
Pensabene, Virginia
Peterson, Randall
Pinkas, Adi
Polivka, Barbara
Pryzbyla, Tyler
Pulver, Dana
Robertson, Audrey
Rosofsky, Anna
Sable, Helen
Santucci, Aimee
Schantz, Susan
Schuetze, Pamela
Sears, Clara
Sears, Lonnie
Sherrod, Stacy D.
Shi, Mingjian
Shisler, Shannon
Singer, Lynn
Sit, Dorothy
Slikker, William
Smith, Lynne
Sobin, Christina
Sobrian, Sonya K.
Sourander, Andre
Sprowles, Jenna
Stanwood, Gregg
Trammell, Taylor
Turgeman, Gadi
Vorhees, Charles
Walker, Teneille
Yanai, Joseph
Yazdy, Mahsa
Yost, Erin
Zhang, Xuan
Zierold, Kristina