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Proceedings of the 2017 Annual Meeting of the Fetal Alcohol Spectrum Disorders Study Group

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Abstract

The 2017 Fetal Alcohol Spectrum Disorders Study Group (FASDSG) meeting was entitled "Prenatal alcohol exposure in the context of multiple factors affecting brain development." The theme was reflected in the interactions between members of the Teratology Society and the FASDSG this year. The first keynote speaker, Elaine Faustman, Ph.D., was a liaison between the societies and spoke about systems biology and the multiple genetic and environmental influences on development. The second keynote speaker, Rebecca Knickmeyer, Ph.D., discussed population neuroscience and multiple influences on brain development. The conference presented updates from three government agencies and short presentations by junior and senior investigators showcasing late-breaking FASD research. The conference was capped by Dr. John Hannigan, Ph.D., the recipient of the 2017 Henry Rosett award for career-long contributions to the field.

Keywords

Fetal Alcohol Spectrum Disorders; proceedings; annual study group meeting

The 2017 Fetal Alcohol Spectrum Disorders Study Group (FASDSG) annual meeting was held on June 24, in Denver, Colorado as a satellite of the Research Society on Alcoholism conference. The meeting was supported by members and by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) and the National Institute of Child Health and Human Development (NICHD). Over 200 investigators attended, including individuals from the United States (from 31 states and the District of Columbia), Canada, Israel, New Zealand, Romania, South Africa, South Korea, and Uruguay. The program included keynote presentations, 14 FASt Data talks (2-slide, 5-min presentations of original data) and two

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student-award talks. Many of the presentations were given by graduate students and post docs, and 8 were supported by travel awards.

Two trainees were selected to receive the Timothy A. Cudd Award and the Kenneth R. Warren Award. All trainees had the opportunity to interact with senior researchers and clinicians at a networking lunch. Representatives from the NIAAA, the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders, and the Centers for Disease Control and Prevention gave updates on Fetal Alcohol Spectrum Disorder (FASD)-related programs. A highlight of the meeting was the presentation of the Rosett Award to John Hannigan, Ph.D., to recognize lifetime contributions, achievement and service in FASD research.

The theme of the 2017 meeting was “Prenatal alcohol exposure in the context of multiple factors affecting brain development.” The theme was influenced by interactions between members of the Teratology Society and the FASDSG this year. Organizers of both meetings sought to highlight methods and frameworks (genetic, epigenetic, and systems biology approaches) for addressing the real-world complexity associated with multiple exposures (substances of abuse, toxins, and environmental exposures among others).

Keynote presentations

The first keynote presentation, given by Dr. Elaine Faustman, Ph.D, Professor of Environmental and Occupational Health Sciences at the University of Washington, was entitled “Using systems biology for linking genes and environment for alcohol research”. Dr. Faustman opened her talk with a paper by Collins et al. (2008) which laid out the potential for new high throughput tools in toxicology that would allow for 10,000+ *in vitro* assays per day and new computational approaches to pull together disparate data to prioritize chemicals for testing and to improve prediction of risk. Dr. Faustman discussed progress in sequencing human and non-human genomes, emphasizing gene by environment by time interactions. She discussed a systems biology overview (Scott, 2005) in which a cross-systems approach incorporates findings from studies of non-proliferating cells (such as epithelial fibroblasts) in understanding basic signaling pathways, cell kinetics, and viability. At a higher level, studies using neuro-progenitor cells add to the understanding of effects on cell differentiation and neuronal phenotype. At the next level, *in vivo* models, (*c. elegans*/ zebrafish) provide insights into processes that are relevant for humans including neuronal migration, brain structure and function, and behavior. Finally, human studies bring these phenomena together at a higher level of complexity. This multi-level, systems approach is necessary in addressing the 85,000 common chemicals in our environments (of which perhaps only 1000–5000 have been evaluated for neurodevelopmental impact).

Dr. Faustman next discussed a critical paper that outlined the Gene Ontology Consortium (Ashburner et al., 2000) and provided a common language for describing aspects of a gene product’s biology to allow for comparison across species. She provided an example of the results of this new framework: the insight that there are 17 key cell signaling pathways involved in almost every important developmental event (axis specification, morphogenesis, organogenesis, tissue renewal, cytodifferentiation, etc.) across organisms. Several pathways

are relevant to FASD research because of their involvement in critical stages of development and susceptibility to environmental influences. Dr. Faustman highlighted a paper by Leung et al. (2017) illustrating an evolutionary approach to cross-species examinations. The framework suggests that questions about chemical effects on oxidative stress pathways could be examined in simple organisms like yeast, but this model would yield limited insights into other developmental processes. Dr. Faustman showed the example of the top interacting genes with ethanol from the Comparative Toxicogenomics Database, which include TNF, CYP2E1, CASP3, and others (several of which are involved in metabolism and oxidative stress). An example of an alcohol-related paper using a systems biology approach in the literature (Contet, 2012) was highlighted for its examination of gene portfolios whose expression were altered by ethanol - specifically linking them to regions of the brain.

Dr. Faustman discussed another study employing microRNA (Balaraman et al., 2016) that illustrates the predictive possibilities of “omic” techniques in identifying individuals with exposures and neurodevelopmental changes as a result of those exposures. She pointed out how computational models can be used to integrate findings across disparate levels of data, highlighting a paper (Gohlke, Hiller-Sturmhofel, & Faustman, 2008) that modeled effects on neurogenesis and synaptogenesis using data from primate, rodent, and cell-system studies. These approaches also allow for modeling across multiple organ systems for predictive purposes and may help determine relative contributions of factors in multi-exposure scenarios. Dr. Faustman showed a promising systems biology framework for laying out Adverse Outcome Pathways (AOPs) – a framework that attempts to build a path between the toxicant, molecular interactions, cellular responses, organ-level responses, organism responses, and population-level responses. Although AOPs have been published for alcohol-related liver damage, there is no published AOP for neurodevelopmental damage from alcohol. Dr. Faustman discussed two additional papers as “case examples” of systems biology, both of which examined the role of oxidative stress in adverse outcomes from alcohol (Jilek et al., 2015; Wells, Bhatia, Drake, & Miller-Pinsler, 2016).

Moving to the integration of genetic and toxicogenomic information, Dr. Faustman described the work of David Threadgill and colleagues who have examined key biological and toxicological processes across a wide range of mouse strains, mimicking human diversity, and pointing out the high level of diversity in even basic processes such as ethanol clearance depending on genetics. Challenges ahead include moving to the level of “three-dimensions” – understanding effects at the organ level - which is clearly impacted by interactions rather than just single pathways. To close her presentation, Dr. Faustman suggested a widened scope for thinking about “systems biology” in human health and provided insights into future directions in examining multiple chemical exposures.

The second keynote presentation was given by Dr. Rebecca Knickmeyer, Ph.D, Associate Professor of Psychiatry at the University of North Carolina. Dr. Knickmeyer’s research program focuses on identifying genes and molecular pathways that influence early brain development with the goal of early identification of abnormal trajectories and, eventually, early intervention. The approach she utilizes, population neuroscience, attempts to link genome, envirome, and phenome. She discussed the importance of infancy, highlighting a paper by Tebbenkamp et al. (2014) that contrasts the developmental timelines of expression

of genes involved in different aspects of neurodevelopment (ex. genes involved in cell proliferation are highly expressed in the early post-conception period whereas genes involved in synaptogenesis are expressed at increasing rates over gestation and stay high throughout child and adolescent development). A paper by Birnbaum et al. (2014) was discussed, that illustrated whole genome trends such that genes involved in neurodevelopmental disorders (autism and intellectual disabilities) tend to be more heavily expressed prenatally whereas genes associated with adult-onset conditions like Bipolar Disorder are equally expressed in the prenatal and postnatal period. Genes associated with neurodegenerative disorders (e.g. Alzheimer's disease) are preferentially expressed in adulthood. Dr. Knickmeyer showed data (Knickmeyer et al., 2008) demonstrating the brain growth spurt during the early postnatal period (with 96% volume reached by age 4) and the dramatic shift toward myelinated tissue by the age of 2 years. Magnetic Resonance Imaging (MRI) studies also demonstrate significant cortical surface area expansion (especially primary sensory areas in the first year of life and association areas in the second year) (Li et al., 2013). Additional papers demonstrated a rapid shift in white matter microstructure as demonstrated by diffusion tensor imaging (Yuan et al., 2014) and increases in functional connectivity within the first year to two of life (Gao, Alcauter, Smith, Gilmore, & Lin, 2015).

Dr. Knickmeyer next discussed a genome-wide association study (GWAS) of structural brain development in hundreds of neonates (Xia et al., 2017) in which the gene *IGFBP7* and a nearby "master regulator" gene for neurogenesis (*REST*) were implicated in relation to gray matter volumes especially. Variants at an additional gene, *WWOX*, had trend-level associations with white matter volumes. Examining the expression patterns over development, *IGFBP7* is increasingly expressed over the prenatal and early postnatal period whereas *REST* is highly expressed post-conceptually and then decreases. Using more liberal thresholds for exploratory purposes, a clear pattern emerges showing that genetic variants associated with neonatal brain volumes are preferentially expressed prenatally. Examining data from two large-scale genomic projects (Enhancing Neuroimaging Genetics through MetaAnalysis or ENIGMA and the Philadelphia Neurodevelopmental Cohort or PNC) and using a polygenic risk score for brain volume, it appears that the neonatal score is associated with white matter volume all the way out to adolescence. Despite this, overall, there is relatively little overlap between genetic variants associated with brain volumes at different stages of development. Using data from the Psychiatric GWAS Consortium, polygenic risk scores for autism-spectrum disorders and schizophrenia were not found to be related to neonatal brain volumes. Dr. Knickmeyer pointed out that a general sense is developing that polygenic risk factors may only be predictive of structural brain outcomes in the presence of additional environmental risk factors. Lastly, she presented data examining the relationship between copy number variants and brain volumes which essentially found no association.

Dr. Knickmeyer then provided an overview of studies testing the influence of the gut microbiome-brain-axis on brain development. For instance, it is known that manipulating the gut microbiome leads to changes in behavior, brain structure, neurochemistry, and gene expression. Restoring the microbiome can "rescue" the behavior, brain structure, and chemical changes when it is carried out prior to weaning. Gut bacteria influence brain structure, cognition, and behavior though numerous mechanisms including the stimulation of

neurotransmitter production, alterations in immune function, production of neuroactive metabolites including gamma-aminobutyric acid and 5HT precursors, and direct signaling via the vagus nerve. In a paper by her research group, Carlson et al. (2017) showed that microbiome composition at age one year was associated with global cognitive functioning at age two years. After controlling for breastfeeding, vaginal vs. cesarean birth and other factors, one cluster of gut bacteria was associated with higher cognitive functioning at two years. Contrary to expectations, higher levels of diversity in gut bacteria were associated with lower cognitive functioning. Relatively few associations between microbiome and regional brain volumes were seen. However, significant associations were seen between microbiome diversity and amygdala-temporal cortex connectivity as well as associations between diversity and amygdala-insula connectivity assessed via resting state functional magnetic resonance imaging. Associations were seen between inter-network connectivity and gut bacterial composition. One particular pair of networks was found to be associated with language functioning in the child.

To close, Dr. Knickmeyer discussed a third set of influences on early brain development that are related to maternal depression and maternal selective serotonin reuptake inhibitor (SSRI) use. Jha et al. (2016) compared control infants to infants in two cohorts of women with depression: one taking SSRIs throughout the pregnancy and one not taking them. No volumetric differences were seen between the controls and either cohort. The SSRI-exposed infants did show alterations in white matter microstructure (including lower fractional anisotropy and higher mean diffusivity, radial diffusivity, and axial diffusivity – suggesting abnormal tissue microstructure) in numerous tracts, especially projection tracts, compared to controls. The infants born to mothers with depression who were not taking SSRIs did not show these patterns, suggesting that SSRI exposure or some associated factor is associated with altered white matter development in the offspring. To summarize her talk, Dr, Knickmeyer provided an overview of how understanding very early brain developmental trajectories and being able to place individuals on those trajectories might serve identification and intervention well.

Timothy A. Cudd Award

Lussier, A. (University of British Columbia), Bodnar, T., Mingay, M., Hirst, M., Chudley, A.E., Kobar, M.S., and Weinberg, J. *Epigenetic Signatures of Prenatal Alcohol Exposure.* Mr. Lussier was given the Timothy A. Cudd Merit Award in recognition of his dissertation work examining deoxyribonucleic acid (DNA) methylation patterns that may serve in the future as an important tool to help screen at-risk children, aiding in the early diagnosis of FASD and implementation of interventions to mitigate the deficits caused by PAE. Ethanol-related changes in DNA methylation are emerging as potential mediators and/or biomarkers for the effects of PAE due to temporal stability and malleability in response to environmental cues. In Mr. Lussier's work, the epigenetic changes have been investigated through a fetal programming framework, focusing on events in early life that can influence developmental trajectories later. Such events as exposure to stress, drugs and alcohol, maternal malnutrition and infection can lead to increased risk of cardiovascular, metabolic disorders and changes in immune function later in life. By integrating findings from both clinical and animal models, Mr. Lussier and his colleagues aimed to identify possible mechanistic roles of

changes in DNA methylation in the etiology of FASD and characterize an epigenetic signature that could serve as a biomarker of PAE.

Mr. Lussier's study assessed the DNA methylation profiles of buccal epithelial cells from two Canadian cohorts of children with FASD (NDN I - 110 FASD: 96 age- and sex-matched controls; NDN II - 24 FASD: 24 controls). 658 differentially methylated regions were identified as either up- or down-regulated, including regions coding for *SLC226A3* and dopamine receptor *DRD4* (Portales-Casamar et al., 2016). The DNA methylation signature of FASD that the group identified in the NDN I cohort was validated in the second independent cohort (NDN II), with 161 sites showing differential methylation across both cohorts, including *SLC226A3* and dopamine receptor *DRD4*. In parallel, using a rat model of PAE in which pregnant dams were fed liquid ethanol diet matched with pair-fed controls and undisturbed controls, the group analyzed genome-wide DNA methylation patterns in the hypothalamus during early development (postnatal days 1, 8, 15, 22) and in leukocytes at postnatal day 22 to compare central and peripheral markers. Similar to the results from human studies, PAE caused persistent alterations to DNA methylation patterns in the rat hypothalamus across all four developmental time points, and several differentially methylated regions were common across tissues. Of note, a single gene, the dopamine receptor *DRD4*, was hyper-methylated in both rats and humans, pointing to potential mechanistic implications in FASD. Persistent DNA methylation changes in the hypothalamus may explain some of the long-term deficits observed in both animal models and clinical studies of PAE, while correlations between peripheral and central nervous system tissues may prove vital to the development of therapeutic targets. Mr. Lussier concluded that the gene for dopamine receptor *DRD4* may represent an important target for therapeutic interventions, given its altered DNA methylation patterns following PAE in both the rat hypothalamus and peripheral tissue in humans. Furthermore, the identification of a characteristic DNA methylation profile shows promise as a potential screening tool for FASD, which may help promote early interventions to mitigate some of the deficits caused by PAE.

Kenneth R. Warren Merit Award

Wong, E.L. (University of Rochester) & Mejewska, A.K. *Live imaging of microglia, dendritic spines, and their interactions in adolescent mouse cortex after brain growth spurt alcohol exposure.* Ms. Wong was given the Kenneth R. Warren Merit Award in recognition of her dissertation studies of the effects of binge alcohol exposure during the brain growth spurt (BGS) on synaptic plasticity and the role of microglia in this process. In her talk, Ms. Wong concentrated on BGS ethanol effects on adolescent microglia, the brain's resident immune cells, which can rapidly activate in response to insults, injuries or inflammation. Microglia also have physiological roles critical for synaptic development and plasticity. For example, highly ramified microglia processes contact dendritic spines (which are the postsynaptic sites for the majority of excitatory synapses) and influence their functional remodeling. High binge ethanol exposure during the BGS is known to impair synaptic plasticity long-term. Specifically, in adolescent mice dosed with 3.6g/kg subcutaneous ethanol daily from postnatal day 4 through 9, this group demonstrated that visual cortex neurons are less able to remodel in response to changes in visual experience (Lantz, Sipe,

Wong, Majewska, & Medina, 2015). However, the mechanism behind this plasticity deficit is not well understood. Ms. Wong hypothesized that long-term changes in the dynamics of interaction between dendritic spines and microglia could possibly underlie deficits in synaptic plasticity induced by developmental ethanol exposure. Using in vivo two-photon microscopy in mice with microglia, or a subset of layer V pyramidal neurons, or both, labeled transgenically, Ms. Wong assessed the effects of BGS ethanol on microglial process dynamics, microglial interactions with dendritic spines, and the remodeling of dendritic spines during critical period for visual cortex development at postnatal day 28 (early adolescence). They found that, indeed, postnatal exposure to ethanol in their mouse model resulted in impairment of the neuronal network remodeling in the visual cortex. They analyzed ocular dominance plasticity (first reported by Dr. Alexandre Medina's group) in response to monocular deprivation in control and ethanol-exposed C57BL/6 mice. In control animals with monocular deprivation, the neurons in the binocular region of the visual cortex gradually respond more to the signals from the open eye, demonstrating structural plasticity and ocular dominance shift after 4 days of deprivation. However, Ms. Wong's study demonstrated that in ethanol-exposed animals, such a shift did not occur after four days of deprivation. Instead, seven days of monocular deprivation was needed to produce effects on neuronal plasticity. Surprisingly, this finding was not mirrored by any morphological signs of microglia activation: microglia-specific Iba-1 immunocytochemical staining followed by measurements of density and distribution of microglia, arborization area, and circularity were not different between two control and ethanol-exposed groups. Next, Ms. Wong reported that using in-vivo two-photon microscopy of visual cortex of green florescent protein (GFP) mice allowing visualization of microglia motility (extension and retraction of the processes over a 5-minute period) demonstrated no changes in microglial processes' motility in control vs. ethanol-exposed animals. There were also no detectable effects of prenatal ethanol on the microglial transcriptome (as determined by flow cytometry).

To study the effect of BGS ethanol directly on the spine plasticity, Ms. Wong and her colleagues looked at the spines in the somatosensory cortex of GFP-expressing mice. Neither dendritic spine density, nor spine morphology was significantly affected by postnatal ethanol exposure. In-vivo imaging of the spines revealed no changes in the baseline stability of dendritic spines in mouse adolescent somatosensory cortex.

In conclusion, Ms. Wong stated that in certain brain regions (such as visual cortex and somatosensory cortex), both microglia and excitatory synapses can show long-term resilience to developmental alcohol exposure. However, the overall neuronal network plasticity can still be affected by ethanol. Future studies will address whether inducing a change in experience may be necessary to uncover any lasting effects of BGS ethanol on microglial dynamics and dendritic spine remodeling, which could underlie the plasticity deficit observed.

FASt Data Presentations

Barrett, C.E. (Emory University), Kable, J.A., Coles, C.D. & the CIFASD. *The impact of prenatal alcohol exposure on cortical function assessed with functional near infrared spectroscopy.* Dr. Barrett presented on measures of oxygenated and deoxygenated

hemoglobin levels obtained with functional near infrared spectroscopy to assess neural activity in medial prefrontal cortex (PFC) during a cognitive inhibition task. Dr. Barrett described the non-invasive and significantly more economical method of functional near infrared spectroscopy (as well as its limitations) recently utilized in neonatal research. She then explained that the goal of the study was to establish if PFC activity during computerized tasks requiring inhibition distinguishes children with PAE from both typically-developing controls and a clinical contrast group of children with other neurobehavioral problems. Oxygenation levels were reduced during the components of the game requiring inhibition, which is reflective of decreased brain activity. Prenatal alcohol exposure (PAE) may impair prefrontal cortex neural activity when inhibitory control is required. In addition, increased PFC activity during non-inhibitory tasks was detected in children with PAE and may reflect compensatory enhancements for reduced neural efficacy.

Gursky, Z. (Univ. of Delaware) & Klintsova, A.Y. *Third trimester-equivalent alcohol exposure in rat produces hippocampo-thalamic-prefrontal circuit-specific damage and behavioral impairment in adulthood.* Mr. Gursky presented data from a rodent model of binge-drinking during the third trimester (postnatal day 4–9 alcohol exposure in rat). His study of the multiple midline thalamic nuclei (nucleus reuniens (RE), mediodorsal thalamus, rhomboid nucleus) revealed significant cell loss in RE (≈30%) of adult female rats exposed to alcohol on PD4–9 (only females were examined for this thalamic effect). This thalamic cell loss was specific to RE, a ventral thalamic nucleus serving as a relay between medial PFC and hippocampus, since no significant cell loss is found in two other neighboring thalamic nuclei. In addition, both male and female animals from the same alcohol exposure paradigm displayed alterations in novel object recognition and object-in-place memory in adulthood that are strongly correlated to blood alcohol content (measured on postnatal day 4). Further, alcohol-exposed animals displayed impairments in rule switching in a plus maze-based operant conditioning task (taking 2–4 times as many trials to learn a new rule). These data suggest that RE (in addition to hippocampus and PFC) is damaged in both alcohol-exposed males and females and that this damage persists into adulthood indicating that the integrity of RE may be a structural indicator of impaired executive functioning observed in some manifestations of FASD.

Tang, S. (University of Maryland), Gullapalli, R.P., & Medina, A.E. *Early alcohol exposure disrupts the functional connectivity of the ferret rostral posterior parietal cortex.* Ms. Tang presented a study on a ferret model of FASD on the functional connectivity in the multisensory areas using ferret rostral posterior parietal cortex (PPr) as an example. The PPr receives convergent inputs from a visual (PPC or posterior parietal cortex) and a somatosensory (S3) source and is a major multisensory processing area in the cortex. To test the hypothesis that developmental alcohol exposure would lead to poor connectivity refinement, the group applied resting-state functional MRI (rsfMRI) to assess connectivity between PPr, PPC and S3. Ferrets were given 3.5g/Kg i.p. ethanol or saline between postnatal day 10–30 to model alcohol exposure during the last months of human gestation and scanned thrice in a 7 tesla horizontal bore MRI scanner between PD40–50. Connectivity between PPr to PPC, but not between PPr to S3, was increased in the alcohol-exposed animals. Ms. Tang concluded that her findings support the hypothesis that developmental alcohol exposure disrupts the functional organization between PPC (visual) and PPr (visual-

tactile) and that one possible mechanism of such disruption could be decreased pruning and the consequent presence of aberrant connections.

Boschen, K.E. (University of North Carolina), Fish, E.W., Gong, H., van Venrooy, A.I., & Parnell, S.E. *Primary cilia defects as a novel mechanism of prenatal ethanol-induced craniofacial and CNS abnormalities.* In her talk, Dr. Boschen summarized a set of experiments using a mouse model of FASD with exposure during the first trimester-equivalent. The study sought to establish if some of the craniofacial and ocular defects associated with FASD are due to disruptions in primary cilia, as prenatal ethanol exposure could induce a “transient” ciliopathy in the embryo. The investigators examined cilia gene-ethanol interactions and used a time course to observe morphological and functional changes in primary cilia 6, 12, or 24 hours following ethanol exposure during mid-neurulation (gestational day 9). Several cilia-specific genes in the rostroventral neural tube were found to have either significantly increased (*Hap1* and *Rilpl2*, associated with ciliogenesis) or decreased (*Cep41*and *Mns1*, associated with cilia stability) expression. Next, the number of cilia in the rostroventral neural tube was estimated directly with a cilia-specific protein. Cilia density was increased significantly 12 hours after ethanol exposure. Finally, upregulation of the expression of cilia-regulated cell-cycling genes was detected 12 hours after ethanol exposure. Dr. Boschen concluded that these data identified cilia dysregulation as a novel mechanism of prenatal ethanol pathogenesis.

Wagner, J.L. (University of New Mexico), Moezzi, A.H., Lujan, K.S., Hamilton, D.A., & Savage, D.D. *Prenatal alcohol exposed-induced deficits in spatial memory are ameliorated by the histamine H_3 receptor agonist SAR152954*. Dr. Wagner reported on the effects of a histamine H3 receptor inverse agonist (SAR152954) (which has completed Phase 1 clinical trials in healthy adult human males) on spatial navigation in saccharin control and moderate PAE rat offspring. Male offspring were weaned at PD24 and group-housed until six months of age. On the first day of training only, offspring were given either 0.1 mg/kg SAR152954 or vehicle 30 minutes prior to the first training trial on a Morris water maze. Offspring were then given 12 place-training trials in series that required about four hours to complete. There were no main or interactive effects of prenatal group or drug treatment on acquisition during the initial place training. After a 7-day interval during which no additional training occurred, rats were given 6 trials in series to test for retention of the fixed platform location. Dr. Wagner reported that saline-treated PAE rats performed significantly worse than either control group during the test trials. However, performance by SAR152954-treated PAE rats was significantly better than the saline-treated PAE rats and not different than control groups. These results indicate that SAR152954 reversed PAE-induced deficits in spatial memory and support consideration of H3 receptor inverse agonists for advancement to clinical trial.

El Metwally, D. (University of Maryland), Al-Mudares, F., Stefanak, M., Jones, J.W., Kane, M.A., and Bearer, C.F. *Ethanol metabolites of infants exposed to postnatal ethanol-containing medications in the neonatal intensive care unit.* Dr. Bearer presented a study on the exposure of infants in the neonatal intensive care unit (NICU) to a concerning level of ethanol contained in the medications given to infants in this clinical setting. The objective of the study was to determine if ethanol metabolites in urine of infants exposed to ethanol-

containing medications (ECM) is greater than those infants not exposed (NECM). Overall 59 NECM and 17 ECM infants were enrolled in the study. Two ethanol biomarkers - urinary ethyl sulfate (EtS) and ethyl glucuronide (EtG) - were quantified using liquid chromatography/tandem mass spectrometry. There was no difference between corrected gestational age and weight in ECM and NECM. One or both ethanol biomarkers EtS or EtG were detected in 82.3% of ECM compared to 27.1% of NECM infants. In the NECM group, 3 of 59 babies had ethyl sulfate greater than cutoff compared to 7 out of 17 in the ECM group. Dr. Bearer concluded that ECM infants were more likely to have ethanol biomarkers in their urine and had a higher incidence of EtS values over the adult cutoff. Some infants in both the NECM and the ECM had ethanol biomarkers at alarming levels indicative of adult alcohol consumption.

Lindinger, N.M. (University of Cape Town), Jacobson, J.L., Dodge, N.C., Molteno, C.D., Meintjes, E.M., & Jacobson, S.W. *Cognitive markers identified in early infancy predict risk of impaired cognitive development.* Dr. Lindinger presented a study on early infancy cognitive markers that could be important for identifying which children are at greatest risk for adverse effects and warrant referral for early intervention. The Fagan Test of Infant Intelligence was administered to 148 infants with PAE and non-exposed controls at 6.5 months and 12 months postpartum; in addition 145 infants were tested on symbolic play at 12 months. Mothers were recruited during pregnancy and interviewed three times about their alcohol use prior to giving birth. Diagnoses were made as part of clinical care. Higher levels of PAE exposure correlated with more severe FASD diagnosis and was associated with worse recognition memory at 6.5 months and when averaged across the two ages, and with slower processing speed at 12 months when averaged across the two ages. PAE was also associated with less mature symbolic play (r=−0.17; p=0.046). These measures were related specifically to PAE but not to prenatal exposure to smoking, marijuana, or methamphetamine.

Dr. Lindinger concluded that these data confirm findings from two previous studies that PAE is associated with poorer performance on recognition memory, processing speed, and elicited play.

Noor, S. (University of New Mexico), Sanchez, J.J., Davies, S., Savage, D.D., and Milligan, E.D. *Characterizing immune cell phenotype and function in middle-aged prenatal alcohol exposed rats.* Dr. Noor reported on a study of an animal model of PAE revealing enhanced pathological sensitivity to light mechanical touch (allodynia) following adult-onset sciatic nerve injury in young adult PAE rats, which is mediated by increased spinal cord glial and cytokine actions that hyper-excite pain neurons and possibly create the susceptibility for neuropathic pain after even a minor injury. Dr. Noor examined whether PAE-induced peripheral immune cell activation persists in the immune organs of the spleen, thymus, and medial iliac lymphnode later in adulthood in 10-month old male rats. First, she reported that PAE rats had an increased sensitivity to pain after a minor injury (second challenge) that did not affect sensitivity in control, saccharine-treated rats. Further analysis of the immune system response demonstrated no significant change in the overall T and B cell numbers compared to non-PAE controls, however the data suggest basal increases in natural killer cells numbers are present in the lymph nodes. Moreover, the proportions of $CD11b^{+}$

leukocytes were increased both in the spleen and lymph node, indicating basal activation in the absence of immune challenge. Interestingly, peripheral leukocytes (splenocytes and peritoneal exudate cells) from PAE rats reveal exaggerated expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNFα) and interleukin (IL)-1β following *in vitro* immune stimulation. Dr. Noor concluded that these data indicate that peripheral immune cells are primed in PAE rats to produce aberrant immune responses and may underlie a susceptibility to developing autoimmune disease and inflammatory conditions following immune challenge in adulthood.

Carter, R.C. (Columbia University), Senekal, M., Molteno, C.D., Duggan, C.D., Dodge, N.C., Meintjes, E.M., Jacobson, J.L., and Jacobson, S.W. *Poor maternal caloric intake and weight gain during pregnancy exacerbate fetal alcohol growth restriction in humans.* Dr. Carter presented a study on the effects of poor maternal nutrition and anthropometry during pregnancy on FASD outcomes. 113 heavy drinking Cape Coloured pregnant women and 73 abstaining/light-drinking controls were recruited in Cape Town, South Africa. His study concentrated on evaluation of maternal energy intake (average daily caloric intake) and the amount of weight gain over the course of pregnancy. Infant World Health Organization Z-scores were calculated for weight, length, and head circumference, measured at ages 2 weeks to assess fetal growth and 6.5 and 12 months to assess postnatal growth. The data suggested that under-nutrition in drinkers was common: 41.7% of women reported daily calorie intake below their estimated energy requirement; 56.2% had gestational weight gain below the recommended 0.45 kg/wk. Dr. Carter reported that the effects of PAE on both fetal and postnatal growth were exacerbated by lower maternal daily caloric intake; alcohol-related growth restriction was seen primarily in the lowest tertile (alcohol × calories interaction term p's<.10). Poorer maternal gestational weight gain exacerbated the effects on postnatal weight, length, and head circumference, with growth restriction mainly seen in the lower two tertiles (alcohol × weight gain interaction term p's<.05). Dr. Carter concluded that postnatal growth restriction is a biomarker for long-term severity of cognitive deficits in FASD and concluded that these data warrant further studies investigating the moderating role of these maternal nutritional measures and the potential for dietary interventions in FASD.

Mahnke, A.H. (Texas A&M University Health Science Center) & Miranda, R.C. *Dose-dependent effects of chronic ethanol exposure and withdrawal on intracellular calcium dynamics in neural stem cells.* Dr. Mahnke reported on a study of aberrant cortical development (neuronal maturation and migration and cortical thinning) due to exposure to alcohol that can lead to FASD phenotypes. The study examined stem cells populations that would produce excitatory cortical neurons, deriving them from murine gestational day 12.5 neural stem cells, growing them into neurospheres and exposing them to five days of chronic ethanol at sub-binge (60mg/dL), binge-like (120mg/dL), or high (320mg/dL) doses. Neurospheres loaded with fluo-4 acetoxymethyl ester were imaged using confocal microscopy directly after the five days of chronic treatment or after an additional two days of ethanol withdrawal. This study found that chronic treatment with ethanol affected the resting calcium levels and the sub-binge dose had the largest effect. Basal calcium levels from binge-like and high dose of ethanol groups did not recover to control levels after 2 days of withdrawal. There were additional dose-dependent effects on the frequency and amplitude

of basal calcium events. Dr. Mahnke stressed that, when examining calcium dynamics across the neurosphere, chronic ethanol exposure increased the calcium response to the commonly co-abused drug nicotine, indicating that ethanol exposure can sensitize neurogenic niche to other drugs of abuse. Dr. Mahnke concluded that these data provide novel insight into cellular behavior within the neural stem cell niche and could help to elucidate novel interventional approaches to restore normal neural stem cell function after prenatal alcohol exposure.

Shrestha, S. (University of New Mexico), Sharkis, J., Miranda-Sohrabji, T., Davies, L., Garrison, L., Williams, S., Miranda, R., & Bakhireva, L.N. *Regional differences and correlates of prevalence of prenatal alcohol exposure in Texas assessed by PEth in newborn dry blood spots*. Mr. Shrestha presented a study on estimation of the prevalence of PAE in Texas by measuring a direct ethanol metabolite, phosphatidylethanol (PEth), in 1000 infant residual dry blood spots. In the entire sample, 8.4% of the spots were positive for PEth (>20 ng/ml) indicative of PAE within 2–3 weeks before delivery. Large regional differences were observed with the highest prevalence of positive PEth samples in urban, high median-income regions (17.7% in the Dallas metropolitan area, 8.4% in the Houston metropolitan area). Mr. Shrestha reported the outcomes of the multivariable analyses, where participants in mostly urban regions were 3-times more likely to have positive PEth results. Results of ecologic analyses on aggregate data per public health region demonstrated a weak non-significant positive association between median income and positive PEth ($r=0.28$, $p=0.41$). Results of this first systematic statewide PAE prevalence study demonstrate that PAE might be more prevalent than previously thought (as high as 8%). Mr. Shrestha argued that active case ascertainment efforts for FASD coupled with systematic objective assessment of PAE should be expanded to the national level.

Donald, K.A. (University of Cape Town), Roos, A., Fouche, J.P., Koen, N., Woods, R., Zar, H., Narr, K.L., and Stein, D.J. *Infants exposed to prenatal alcohol exposure and co-occurring maternal depression: White matter microstructural effects in the neonatal brain.* Dr. Donald reported a study of 240 infants co-morbidly exposed to prenatal alcohol and antenatal maternal depression (24% of studied cases) and unexposed control infants in a South African birth cohort. Using multimodal MRI techniques in neonates, they described alterations in white matter microstructural organization. Dr. Donald pointed out that alterations demonstrable at 2–3 weeks of age indicated that prenatal alcohol and maternal mental health affects multiple biological processes that impact the physical growth of the brain, quality and maturation of the connecting circuitry. The main affected white matter area appeared to be left longitudinal fasciculus where the damage due to prenatal alcohol alone was significant, however it was less severe than in the brains of infants co-exposed to maternal depression. Dr. Donald suggested that the identification of alcohol effects on key midline structures in the infant brain may be an early marker for later functional cognitive and behavioral deficits in prenatal alcohol exposure. However, the role of comorbid maternal mental health conditions on the developing brain should be always taken into consideration.

Rouzer, S. (Binghamton University), Cole, J., and Diaz, M. *Gestational Day 12 Moderate Prenatal Alcohol Exposure: Increased expression of generalized anxiety and impact on amygdala GABAA a1 in adolescent males.* Ms. Rouzer presented a study of the relationship

between moderate PAE (mPAE) (a common pattern in humans) and anxiety. The study used a rodent model of G12 mPAE in which pregnant Sprague-Dawley rats were exposed to either room air or vaporized ethanol for six hours (average peak blood ethanol concentrations of 87.87 ± 11.8 mg/dL at 4 hours into the exposure). Adolescent offspring were then handled for seven days prior to testing on postnatal days 41–47 in the following four anxiety conditions: elevated plus maze (EPM), light-dark box (LDB), open-field (OF), and novelty-induced hypophagia (NIH) test. Her findings revealed significant increases in measures of anxiety-like behavior (significant latency to approach familiar object) in male PAE offspring in the NIH with no differences observed in females. The same increased anxiety-like behavior in males in LDB and OF tests was found. To examine a potential neurobiological mechanism underlying increased anxiety-like behaviors, Ms. Rouzer performed immunohistochemical analysis of GABA-A α1 subunit expression within the medial subdivision of the central amygdala (CeM), which significantly contributes to the expression of anxiety. There was a significant deficit in GABA-A α1 staining levels in the CeM of male mPAE offspring compared to controls, with no differences in female offspring. GABA-A α1 levels in the basolateral amygdala are unaffected by mPAE in either sex. Ms. Rouzer concluded that these data suggest that mPAE disrupts amygdala anxiety circuit via a reduction in GABA-A α1 expression in a brain region- and sex-specific manner, which may contribute to increased anxiety-like behaviors demonstrated by adolescent males.

Rosett Award

This year, the Rosett Award was given to Dr. John Hannigan, PhD, Professor of Psychology and Obstetrics & Gynecology and former deputy director of the Merrill Palmer Skillman Institute at Wayne State University. Dr. Hannigan was honored for his career-long contributions to the field. His talk focused on three themes that emerge from his scientific work, but also from the relationships he experienced throughout his career: early experience matters, environment matters, and people matter. Dr. Hannigan identified his early mentors at Binghamton University as Dr. Bob Isaacson, Dr. Linda Spear, and Dr. Norman “Skip” Spear. Dr. Isaacson’s work at the time focused on localization of function in the brain, recovery of function, stress, and peptides. Dr. Hannigan cited an influential paper that set out a new paradigm for studies involving brain lesions and suggested that reactive changes at locations in the brain remote to the lesion site can be the source of dysfunction and provide “opportunities” for recovery (Schoenfeld & Hamilton, 1977). A number of Dr. Hannigan’s early papers focused on inducing and reversing hippocampal damage (ex. (Hannigan, Springer, & Isaacson, 1984)).

Dr. Hannigan’s post-doctoral work took place at the University of California at Los Angeles, where he studied developmental neuropsychopharmacology with Dr. Nathaniel “Nat” Buchwald, Dr. Michael Levine, and Dr. Robin Fisher among others. He then took a job at the State University of New York-Albany, where he interacted with Dr. Edward Riley, Dr. Susan Barron, Dr. Sarah Mattson, and others and participated in early work demonstrating similarities between the effects of prenatal ethanol and hippocampal lesions in rats (Riley, Barron, & Hannigan, 1986). Dr. Hannigan published a number of papers showing spatial navigation deficits in rodents following prenatal alcohol exposure (ex. (Blanchard, Riley, & Hannigan, 1987). His interests quickly broadened to include pharmacologic intervention

studies, both to learn more about the effects of prenatal alcohol on brain development and to move the field toward developing interventions. An early study showed that ethanol-exposed rats were hypersensitive to amphetamines (Blanchard, Hannigan, & Riley, 1987) and dopamine antagonists made these animals less sensitive.

Dr. Hannigan's work continued at Wayne State University, where he moved to join the Fetal Alcohol Research Center directed by Bob Sokol. Dr. Hannigan and Dr. Earnest Abel built a model of maternal risk factors for Fetal Alcohol Syndrome (FAS), with oxidative stress as the final common pathway, that maintains its relevance today (Abel & Hannigan, 1995). Recognizing the widespread effects of alcohol on brain development and the multifaceted comorbid risk factors that moderate these effects, Dr. Hannigan began searching for a global intervention to study and landed on environmental enrichment. This line of his research demonstrated the positive impact of enriched environments on ethanol-exposed animals in terms of learning and memory (Hannigan, Berman, & Zajac, 1993) and hippocampal development (Berman, Hannigan, Sperry, & Zajac, 1996). The work also showed that neuronal plasticity did not "recover" in PAE animals with environmental enrichment.

Dr. Hannigan had always been interested in clinical application of his work and, so, his research turned to the Fetal Alcohol Research Center's ability to recruit prospective cohorts in Detroit. Two studies demonstrated the role of nutritional factors (specifically docosahexaenoic acid and arachidonic acid) in prenatal alcohol exposure (Beblo et al., 2005; Stark et al., 2005). From his involvement with a study investigating effects of prenatal cocaine on behavioral development, Dr. Hannigan began learning about the challenges of screening and he began to investigate screening in the context of risk for FASD. One of the early efforts resulted in composite metric of "at-risk alcohol exposure" – which proved to be better than any single alcohol drinking measure at predicting birthweight, maturational delays, and cognitive/behavioral outcomes (Chiodo, Janisse, Delaney-Black, Sokol, & Hannigan, 2009). A more simplified approach to screening, designed to have higher specificity, based on Bob Sokol's T-ACE screen (Sokol, Martier, & Ager, 1989) (including questions about Tolerance, others being Annoyed by drinking, efforts to Cut down, and morning drinking or needing an "Eye-opener") was the TACER-3, which set the criteria higher than previously used (Chiodo et al., 2014) and more specifically identified "at-risk" drinkers. This screen could help focus clinician attention on a more manageable group of pregnant patients in greatest need of intervention. The TACER-3 predicts neurobehavioral outcomes at 4 years (Chiodo et al., 2010) and alcohol use at 19 years (Hannigan, Chiodo, Sokol, Janisse, & Delaney-Black, 2015). In another effort, Hannigan and colleagues published data demonstrating the validity and utility of retrospective maternal report data about drinking (Hannigan et al., 2010).

To close his talk, Dr. Hannigan discussed the service component that has been an important part of his career. The Fetal Alcohol Syndrome treatment and referral service, established in 1997, was an outreach program that educated professionals in the community and facilitated referrals for FASD diagnosis. Dr. Hannigan's outreach and educational impact continued as part of his position at the Merrill Palmer Skillman Institute for Child and Family Development. He brought his research interests and skills to this setting, developing an

innovative study testing environmental enrichment (motor, social, cognitive) in high-risk children in the community itself.

Dr. Hannigan closed his talk by emphasizing the importance of knowing the history of FASD research, appreciating the impact that our research has on affected individuals and families, giving back to the community, and being thankful for the opportunities we have as scientists engaged in this important work.

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Highlights

- The 2017 Fetal Alcohol Spectrum Disorders Study Group met in Denver, Colorado
- The meeting was attended by more than 200 participants
- Timothy A. Cudd Awardee: Alexandre Lussier, University of British Columbia
- Kenneth R. Warren Merit Awardee: Elissa L. Wong, University of Rochester
- 2017 Rosett Awardee: Dr. John Hannigan, Wayne State University