Published in final edited form as:

Alcohol. 2014 November ; 48(7): 623–630. doi:10.1016/j.alcohol.2014.08.002.

Proceedings of the 2013 Annual Meeting of the Fetal Alcohol Spectrum Disorders Study Group

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Abstract

The 2013 Fetal Alcohol Spectrum Disorders Study Group (FASDSG) meeting was held in Orlando (Grand Cypress), FL with the theme “Developing Brain-Based Interventions for Individuals with Fetal Alcohol Spectrum Disorders”. Children with fetal alcohol spectrum disorders have significant impairments in cognitive functioning and behavioral regulation skills, which lead to a lifetime of challenges for themselves and their families; thus, developing interventions that remediate or compensate for these deficits is of great importance. The conference included 2 keynote presentations, FAS data talks, award presentations, and updates by government agencies. In addition, a lively panel discussion addressed the challenges faced by FASDSG researchers in the translation of intervention strategies developed in preclinical studies to clinical trials and, ultimately, to clinical practice.

The Fetal Alcohol Spectrum Disorders Study Group (FASDSG) held its annual meeting on June 22nd, in Orlando (Grand Cypress), FL as a satellite of the Research Society on Alcoholism meeting. The 2012/2013 FASDSG officers (Julie A. Kable, Ph.D., President; James N. Reynolds, Ph.D., Vice-President; C. Fernando Valenzuela, M.D., Ph.D., Treasurer; and Alexandre E. Medina, Ph.D., Secretary) organized the meeting. Approximately 200 individuals attended the study group meeting, including 146 professionals and 57 students. Attendees were largely from the United States but included researchers from Canada, Australia, Brazil, France, South Africa, and the United Kingdom. The theme of the meeting was: Developing Brain-Based Interventions for Individuals with Fetal Alcohol Spectrum Disorders (FASDs).

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Milestones in the clinical care of children with an FASD

FASDSG is composed of a tapestry of researchers who focus on various aspects of FASD research, including basic and clinical investigations. The unique combination of researchers coming from multidisciplinary backgrounds has greatly facilitated the advancement of knowledge pertaining to the impact of prenatal alcohol exposure (PAE) and the basic mechanisms of action of alcohol on neural development. This combination of research skills is also needed as we attempt to advance our science in the area of intervention research. The study of the impact of PAE on development was initiated in the applied clinical setting following the identification of clusters of children with common dysmorphia and neurodevelopment problems after a history of PAE (Jones & Smith, 1973; Lemoine, Harousseau, Borteyru, & Menuet, 1968). For over 20 years, the FASDSG's primary focus was on education, prevention, and identification of the nature of the negative impact and the basic mechanisms involved in the teratogenic effects of alcohol. The overwhelming amount of information regarding the teratogenic effects of PAE and the negative ramifications on quality of life resulted in 3 major professional organizations in the United States recently recommending alterations in their practice to appropriately accommodate individuals with FASDs (American Academy of Pediatricians, 2012; American Bar Association, 2012; American Psychiatric Association, 2013). The massive amount of scientific evidence generated over many years by FASDSG researchers directly contributed to these dramatic societal changes in policy and practice toward alcohol-affected individuals.

The science of brain-based interventions for individuals with FASDs is relatively young when compared to other areas of FASD research. In the mid-1990s, targeted diagnostic clinics began to engage in the process of assisting with the identification of children impacted by PAE and to aid in treatment and habilitative care of the affected children and the families who care for them. Around the same time, the Institute of Medicine's report (Stratton, Howe, & Battaglia, 1996) was released, providing guidelines regarding diagnosis and a plan for advancing knowledge of how to care for children with FASD. At the turn of the century, the field began to focus on targeted habilitation and intervention efforts because of a prevailing belief that the existing interventions and systems of support were not adequately meeting the needs of these individuals.

Although we have made some definite gains in our understanding of how to habilitate children with a history of PAE, considerable effort is still needed to meet the needs of those with FASD. Key areas in need of development were identified at the onset of the meeting, providing a focus for discussions throughout the day. One of the biggest challenges to advancing the care of individuals with PAE is the limited number of treatment clinics that are available. Although more a public advocacy issue than a research issue, it is vital that there be improvements in access to care for individuals affected by PAE. Improving recognition and availability of services will also aid in advancing treatment science by the creation of databases of affected individuals from which participants may be recruited for clinical trials. The development of new behavioral interventions that address differences in family characteristics is needed, to facilitate use among the various individuals and families impacted by PAE. Additional work is also needed to develop innovative pharmaceutical interventions, since traditional psychiatric medications have had limited success. It is also

necessary to expand our methods for assessing treatment effects using emerging technologies that will aid in objectively determining whether interventions are targeting specific alcohol-related brain damage. In order to expedite evaluation of treatment programs and facilitate transmission of our interventions across clinics, multi-site clinical trials need to be pursued. Finally, there is a need to develop standardized methodologies and protocols for evaluating treatments, such that valid comparisons of treatment effects across different interventions can be made.

Keynote addresses

The 2 keynote speakers addressed specific areas in need of further development in our treatment science. The first speaker was **Craig Garner, Ph.D.**, of the Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, CA, who spoke on his work attempting to understand synaptic mechanisms that underlie neurodevelopmental disorders and his efforts to develop pharmacotherapies. Dr. Garner first discussed his efforts in understanding the neural basis of the cognitive deficits seen in children with Down syndrome, and in developing a pharmaceutical intervention to improve their cognitive functioning. The deficit in cognitive functioning among children with Down syndrome that was discussed was the presence of excessive inhibitory tone in the neural circuitry. His initial work was done in the context of an animal model and focused on improving cognitive outcomes by using different drugs that reduce inhibitory tone (i.e., NOR 2) (Garner & Wetmore, 2012). In an animal model, this approach resulted in improved cognitive performance on a discrimination-learning task and normalization of synaptic plasticity. Dr. Garner discussed his involvement in a Phase II placebo-controlled study to evaluate the safety and tolerability of Bilobalide (BTD 001) in adolescents and young adults with Down syndrome (13–35 years), where they also will be assessing neurodevelopmental outcomes, including memory, reaction time, language skill, daily activities, and behavioral functioning.

Dr. Garner provided insightful commentary on his experiences moving an intervention from the bench to a clinical trial phase in order to develop novel treatments for children with Down syndrome. Dr. Garner then presented his work investigating potential molecular mechanisms underlying Autism Spectrum Disorder (ASD) and the contribution of genetic and environmental insults to specific ASDs. ASDs have been associated with loss or mutations of individual synaptic proteins (i.e., ProSAP2 and Shank3) that can alter synaptic transmission, neural circuits, behavior, and cognitive functioning (Arons et al., 2012). As deletions or mutations of ProSAP2/Shank3 have been associated with ASD, and other synaptic molecules that are associated with ProSAP2/Shank3 have been found to be mutated in patients with ASD, Dr. Garner explored whether ProSAP2/Shank3 was a key regulator of synaptic function, coordinating pre- and post-synaptic maturation via the neuroligin-neurexin (NLG/Nrx) trans-synaptic signaling complex. He found that ProSAP2/Shank3 functions to couple pre/postsynaptic signaling and that this trans-synaptic signaling requires the activation of ProSAP2/Shank3 by zinc and a functional NLG/Nrx signaling complex. He also found that ASD mutations in ProSAP2/Shank3 disrupt trans-synaptic signaling by reducing zinc sensitivity. He concluded that several forms of ASD appear to result from disruption of a common synaptic signaling pathway and that the second messenger signaling molecule zinc appears to be a key component of this signaling pathway. Data suggest that

low dietary zinc may similarly adversely affect this pathway, neuronal circuit function, and behavior, suggesting that nutritional variability in the diets of children with ASD may differentially affect the expression of the protein mutations involved in the ProSAP2/Shank3 trans-synaptic signaling.

The second keynote speaker was **Brian Christie, Ph.D.**, of the Division of Medical Sciences, Island Medical Program University of Victoria, Victoria, BC, Canada, who spoke on his experiences in studying the recovery of function after a history of PAE and his recent, innovative work assessing the impact of traumatic brain injury and recovery of function (Boehme et al., 2011). Dr. Christie's research has included using an animal model to explore recovery of function after a history of PAE. Providing physical exercise activity resulted in improvements in neurogenesis, synaptic plasticity, increased levels of brain-derived neurotrophic factor, and improved behavioral performance on learning tasks. The positive results in animal models led him to initiate a clinical study with children impacted by PAE. He designed a study to use cardiovascular exercise to elevate levels of brain-derived neurotrophic factor to enhance cognitive functioning. Unfortunately, he experienced difficulties with obtaining enough subjects for these studies, which points to the need for multi-site studies to aid in recruiting sufficient participants to complete clinical trial studies in a timely manner.

Dr. Christie then turned his attention to exploring recovery of function after mild traumatic brain injury (mTBI), which has become a timely area of investigation because of the media focus on the impact of mTBI among professional athletes. Statistics on the prevalence of mTBI or concussions dramatically underestimate the number of individuals impacted, as many athletes are reluctant to report their symptoms. When asked to report anonymously about symptoms of mTBI, Dr. Christie reported that the prevalence of symptoms is dramatically higher. He then discussed innovative methodologies being used to assess the mild cognitive impairment seen after mTBI, including application software and computer programs (i.e., Sport Concussion Assessment Tool 2, Immediate Post-Concussion Assessment Cognitive Test, and CogniSens) that appear to be sensitive to both the impact of the injury and the recovery of function. These tasks have not yet been used among children with FASD but may provide a mechanism for evaluating recovery of function because of a given treatment protocol.

Roundtable discussion

A roundtable discussion was then held to identify challenges and potential solutions to moving forward in FASD intervention research. The panel consisted of *Claire Coles*: Emory University, School of Medicine; *Dan Savage*: University of New Mexico Health Sciences Center; *Alexandre Medina*: University of Maryland, School of Medicine; *Brian Christie*: University of Victoria; *Heather Carmichael-Olson*: University of Washington School of Medicine; and *Jennifer Thomas*: San Diego State University. The panel considered whether the field could become more standardized in defining the outcomes of interventions and in reporting the results. While the diversity of animal models and alcohol exposure paradigms have been crucial for our understanding of the mechanisms of alcohol exposure, and for the development of potential interventions, the panel recognized the importance of standardized

methods in clinical research. For instance, comparisons were made to the successes found in the Children's Oncology Group/Pediatric Oncology Group (O'Leary, Krailo, Anderson, Reaman, & Children's Oncology, 2008) and with the Neonatal Intensive Care Networks (Eunice Kennedy Shriver National Institute of Child Health and Human Development, 2013), where standardized protocols and assessment procedures have allowed rapid and dramatic changes in outcomes, although concerns were expressed about the loss of investigator control and creativity.

The panel also identified several challenges to the development of therapeutic interventions. Among these challenges are the lack of more mechanistic interventions, the complexity of monitoring outcomes, and the need for interventions to cease being restricted to the individual level and to be extended to families and communities as well. The panel also discussed the implications of the National Institute of Mental Health's document that specifies research domains for assessing mental health disorders and the impact of interventions. Methods and infrastructure needed to facilitate translational science from "bench" to clinical trials were also discussed, including increasing connections/communications between human and animal researchers, establishing a network of potential human participants that could be contacted for clinical trials, and increasing psychiatric involvement. The panel considered the complexity of the combined negative impact of prenatal alcohol exposure and the adverse life experiences, such as stress, presence of other drugs of abuse, and an altered diet (often seen in clinical samples), and the need for more animal models of this interaction to further inform treatment science. Finally, the panel discussed the patient-oriented care movement and the need to incorporate this perspective into our intervention research.

FASt data presentations

From abstracts submitted by FASDSG members, 15 were selected to provide brief presentations on new research findings. Research from both students and established investigators was selected for these 1-slide, 5-min presentations. Ten of these presentations were by students and postdoctoral fellows. The presentations were given over 3 sessions focusing on 1) biological mechanisms and consequences of prenatal alcohol exposure, 2) intervention studies for FASD, and 3) neurobehavioral and functional studies of FASD.

FASt data presentations 1 – Biological mechanisms and consequences of PAE

Chronic ethanol exposure during the 3rd trimester-equivalent promotes neuroinflammation in the rat dentate gyrus; Lauren Topper, C. F. Valenzuela, University of New Mexico Health Sciences Center.

During development, the neuroimmune system has been shown to play an important role in pruning and wiring of neural circuits, and binge-type ethanol exposure during the third trimester-equivalent period has been demonstrated to cause activation of microglia and increased production of inflammatory cytokines. Using an intermittent ethanol-exposure paradigm (ethanol vapor chamber), rat pups were exposed to ethanol for 4 h per day during the third trimester-equivalent period (postnatal day 2 through postnatal day 16), producing peak blood ethanol concentrations of approximately 150 mg/dL. On day 17, the dentate

gyrus region of the hippocampal formation was microdissected, and RNA was extracted for the determination of expression profiles of chemokines and cytokines that participate in the inflammatory response of the neuroimmune system. Exposure to ethanol increased the expression of mRNA for the chemokine Ccl5, which plays a role in the recruitment of leukocytes into regions of inflammation. In contrast, ethanol exposure decreased the expression of both mRNA and protein for IL-11, a multi-function cytokine that plays key roles in hematopoiesis, nitrogen, and carbon metabolism, synthesis of the cellular antioxidant glutathione, apoptosis suppression, and endothelial-dependent relaxation. Ethanol exposure also blunted the neuroimmune response to the bacterial endotoxin, lipopolysaccharide. These data suggest that ethanol exposure causes alterations of inflammatory pathways in the developing brain, which may have long-term consequences for synaptic plasticity.

Social interaction and stress affect executive function in adult male and female rats prenatally exposed to alcohol; **Parker Holman**, W. Comeau, J. Weinberg, The University of British Columbia.

The goal of this study was to assess the effects of adolescent stress in modulating the interaction between adult social distraction and executive function in prenatally ethanol-exposed and control rat offspring. Pregnant rats were assigned to 1 of 3 treatment groups: PAE via a liquid ethanol diet, a pair-fed group, or control. During adolescence, offspring from the 3 treatment groups were either exposed to a 10-day chronic mild stress paradigm to simulate psychological stress, or remained undisturbed. In adulthood, rat offspring were trained on a delayed non-match to sample task using an 8-arm radial maze to evaluate executive function, utilizing a 20-min delay between training and testing. After reaching criterion, the animals were re-tested with the introduction of an unfamiliar, age- and sex-matched rat (social distractor) placed into the holding cage during the 20-min delay. There were sexually dimorphic effects of PAE, stress, and social distraction on task performance. In female offspring, introduction of the social distractor increased errors in the radial arm maze in prenatally ethanol-exposed, but not control, offspring independent of chronic mild stress. In contrast, chronic mild stress and social distraction impaired performance across all groups.

Acute ethanol exposure alters the histone modification profile in the mouse brain; **Alexandre Lussier**, K. Hamre, D. Goldowitz, M. Kobor, The University of British Columbia; University of Tennessee.

In this study, global changes in histone acetylation and methylation were examined in the brain of mice following an acute ethanol exposure. C57Bl/6J mice were exposed to ethanol (5 g/kg in 2 divided doses) on postnatal day 7, and brain tissue (cerebellum, hippocampus, cerebral cortex) was collected 7 h after ethanol exposure. Histones were extracted from the tissues and changes in various chromatin marks were assayed by Western blot analysis. There were shifts in histone modifications that would tend to favor transcriptional activity in brain tissues obtained from ethanol-exposed mouse pups. More specifically, ethanol exposure resulted in altered levels of H3K9 and H3K14 acetylation, as well as H3K27 trimethylation. These effects were most evident in cerebral cortex tissue, with relatively less

change in hippocampus. These data provide evidence that changes in histone acetylation and methylation may be an important mechanism by which ethanol alters gene expression in the developing brain.

Ethanol increases the release of inhibitory proteoglycans from astrocytes; **Marina Guizzetti**, X. Zhang, S. Bhattacharyya, H. Kusumo, J. K. Tobacman, University of Illinois at Chicago.

During brain development, neurons extend neurites that follow precise trajectories and are guided by permissive and inhibitory cues. Brain-specific chondroitin sulfate proteoglycans such as neurocan, produced by astrocytes, constitute one such inhibitory cue that prevents the extension of neurites in improper directions. In this study, it was hypothesized that ethanol inhibits the activity of the enzyme, arylsulfatase B, which removes sulfate groups from chondroitin-4-sulfate and ultimately results in degradation of chondroitin sulfate proteoglycans. Exposure of cultured astrocytes to ethanol resulted in a concentration-dependent inhibition of arylsulfatase B. This effect was associated with an increase in total glycosaminoglycans and chondroitin sulfate glycosaminoglycans in astrocyte cultures, and an increase in the expression and release of neurocan. Specific silencing of arylsulfatase B activity using small interfering RNA produced effects on neurocan expression and release that were similar to ethanol exposure. Ethanol inhibition of arylsulfatase B activity, leading to upregulation of neurocan expression, may contribute to the inhibition of neuritogenesis observed when neurons are cultured with ethanol-treated astrocytes, and may represent a novel mechanism by which ethanol leads to altered brain connectivity and decreased synaptic plasticity.

Effects of neonatal ethanol exposure on BDNF and TrkB protein expression in wild-type and adenylyl cyclase 1/8 knockout mice; **Laura Susick**, J. L. Lowing, S. M. Hool, A. C. Conti, Wayne State University School of Medicine.

Brain Derived Neurotrophic Factor (BDNF) is a known mediator of neuronal and dendritic development and its expression is believed to be regulated by adenylyl cyclase. Although ethanol exposure has been reported to decrease BDNF expression in various brain regions, less is known about the impact of neonatal ethanol exposure on the BDNF receptor, tyrosine-related kinase B (TrkB). This study examined the impact of an acute ethanol administration (2.5 g/kg) at postnatal days 5–7 in wild-type mice and adenylyl cyclase 1/8 double knock-out mice on BDNF production and TrkB expression in the cerebral cortex and striatum. Postnatal ethanol administration had no effect on BDNF production at any time point examined (2, 4, 6, 24, 48 h, and 14 days). Similarly, deletion of adenylyl cyclase 1/8 had no impact on basal BDNF production in either brain region. However, genetic deletion of adenylyl cyclase 1/8 increased TrkB expression in the striatum at 2 h, 4 h, and 14 days compared with wild-type controls, with no further effect of ethanol on TrkB expression in wild-type or knock-out animals.

FASt data presentations 2 – Intervention Studies for FASD

Mathematics intervention for children with Fetal Alcohol Spectrum Disorder and prenatal alcohol exposure; Katrina Kully-Martens, J. Pei, J. Kable, C. Coles, G. Andrew, C. Rasmussen, University of Alberta; Emory University.

In this study, a replication and extension of the Math Interactive Learning Experience (MILE) program, which consists of individualized math tutoring with a focus on habilitation of underlying cognitive functions, was evaluated in a group of children with FASD or a history of PAE. The study was modified from its original format in the following ways: 1) implementation in a school rather than a laboratory setting, 2) elimination of the significant parental component, and 3) use of a social skills intervention comparison group rather than a “sham” intervention. Seventeen children had completed the study at the time of reporting, of which 11 (5 FASD, 6 PAE) were enrolled in the MILE program and 6 (2 FASD, 4 PAE) were enrolled in the social skills program. From pre- to post-test, children in the MILE program exhibited significant gains in mathematics achievement compared to children in the social skills group. Importantly, the increases in mathematics standard scores achieved by the children who completed the MILE program were maintained at 6 months follow-up. The results of this study support the notion that implementation of the MILE program in a school setting, requiring minimal parental involvement, can have significant and lasting positive impact on mathematics achievement scores in children with FASD/PAE.

The parenting style of parents with children affected by prenatal alcohol exposure participating in a math intervention program; Shital Gaitonde, J. Kable, Emory University School of Medicine.

The goal of this study was to examine the impact of specific parenting styles (authoritarian, authoritative, permissive) on an individual child’s learning during a psycho-educational intervention program that targets core deficits in learning ability, working memory, and visuo-spatial skills. Parents of children (3–10 years of age) with an FASD were recruited. Parents completed a demographic questionnaire and the Parenting Styles and Dimensions Questionnaire, whereas children received a neurodevelopmental evaluation and completed the Test of Early Mathematical Ability, 2nd Edition (TEMA-2), pre- and post-intervention. The results of this study indicated that measures of the effectiveness of the interventions (change in TEMA-2 scores) differed significantly across the 3 parenting styles. More specifically, children whose parents followed the Authoritative parenting style showed the greatest improvement in math scores, compared with both the Authoritarian and Permissive parenting styles. Moreover, Authoritative parenting was found to be a significant predictor of treatment effectiveness even after controlling for the effects of years of caregiver education. The results of this study suggest that parenting style and the level of caregiver education should be considered before beginning intervention studies, to ensure that the child receives maximum benefit from the intervention.

Grandmaternal alcohol consumption-induced fear memory deficit is alleviated by simultaneous thyroxin treatment; Elif Tunc-Ozcan, K. M. Harper, L. Li, T. M. Ullmann, P. K. Shukla, B. M. Andrus, E. E. Redei, Northwestern University, Feinberg School of Medicine.

The effects of grandmaternal alcohol consumption on hippocampus-dependent fear memory in 2nd generation offspring were examined, along with potential mechanisms and protective effects of thyroxine (T4) administration concomitant with alcohol. Pregnant female Sprague-Dawley rats were administered 1 of the following 4 treatments from gestational day 8 to 20: a liquid diet containing ethanol, the ethanol liquid diet supplemented with T4, a pair-fed nutritional control, or normal laboratory chow. Female offspring of the 4 prenatal groups were mated with Brown Norway males to study the maternal 2nd generation inheritance of this cross. Adult offspring from this 2nd generation cross exhibited memory deficits in a hippocampus-dependent contextual fear-conditioning paradigm, and this effect was mitigated by grandmaternal T4 administration. Hippocampal insulin-like growth factor 2 (Igf2) and insulin receptor (Insr) mRNA expression were decreased in 2nd generation male offspring, and this effect was also mitigated by grandmaternal T4 administration. A T4-reversible disruption of the insulin and Igf2 signaling pathways in the hippocampus may therefore contribute to the cognitive deficit in the offspring of alcohol-consuming maternal grandmothers.

Choline reverses the redistribution of L1 into lipid rafts by ethanol in vivo; **Cynthia Bearer**, M. He, N. Tang, University of Maryland School of Medicine.

The L1 cell adhesion molecule is a protein that is critical for brain development, and is considered to be an important target of ethanol toxicity. This study tested the hypothesis that choline prevents the redistribution of L1 into lipid rafts *in vivo*. Rat pups were given choline or vehicle on postnatal days 1–6, and then were administered ethanol (6 g/kg in 2 divided doses) on postnatal day 6. Two hours later, the cerebellum was isolated and the incorporation of L1 into lipid rafts was determined. Ethanol significantly increased the proportion of L1 in lipid rafts, and choline administration reduced, but did not completely block, this effect. These data support a growing body of literature that choline, a nutrient, can block or reverse some of the neurotoxic effects of ethanol.

Nutritional deficiencies in FASD: Dietary data and preliminary safety/efficacy data from a human trial of choline supplementation; **Jeff Wozniak**, J. Eckerle, A. Fuglestad, B. Fink, C. Boys, M. Kroupina, N. Miller, A. Brearly, H. Hoecker, S. Zeisel, M. Georgieff, University of Minnesota; University of North Carolina.

This study determined the safety and tolerability of administration of choline to children with FASD. Twenty children with FASD (2–5 years of age) were randomized to receive choline (500 mg/day) or placebo for 9 months. Nutritional variables including plasma concentrations of polyunsaturated fatty acids, vitamins D, E, and K, calcium, iron and choline, as well as the incidence of adverse events were assessed. Plasma choline concentrations were increased by 105% after 1 month, and remained at this level for the 9 months of the study. Tolerability was high and adverse events were minimal; 25% of participants in the choline group reported the occurrence of a fishy odor. Neither gastrointestinal events nor changes in blood pressure were reported in the treatment group. Preliminary efficacy studies suggest improvements in working memory, global cognitive functioning, and fine motor skills, but these will need to be verified in a larger efficacy study.

FASt data presentations 3 – Neurobehavioral and functional studies of FASD

Reading dysfunction in children with prenatal alcohol exposure: Comparisons of three definitions; **Leila Glass**, E. P. Riley, S. N. Mattson, San Diego State University.

The purpose of this study was to examine the presence and prevalence of reading dysfunction in children with a history of prenatal alcohol exposure, and to evaluate the appropriateness of multiple reading dysfunction definitions. A total of 237 children (8–16 years of age) were enrolled in the study, consisting of children with PAE ($n = 122$) and non-exposed control children ($n = 115$). The groups were tested with Wechsler Intelligence Scale for Children-IV, the Wide Range Achievement Test-3, and the Child Behavior Checklist. Alcohol-exposed children performed significantly worse than controls on reading, even when the groups were matched for IQ. All definitions of reading dysfunction were found to have higher prevalence rates in children with prenatal alcohol exposure, and reading dysfunction significantly predicted School Problems. The results of this study suggest that low-achievement definitions of reading dysfunction may be best for identification of these problems in children with FASD.

Frontal lobe electroencephalography (EEG) recorded during the performance of saccadic eye movement tasks in children with FASD; **Kasey Hemington**, J. N. Reynolds, Queen's University.

The goals of this study were to quantify changes in frontal lobe EEG activity that result from manipulating cognitive load during the performance of a saccadic eye movement task, and to determine whether differences in frontal lobe EEG activity correlate to deficits in the performance of an eye movement task in children with FASD compared to typically developing control children. Children (8–18 years old) with or without FASD performed a delayed, memory-guided saccade task in which the spatial location and sequence of presentation of 1, 2, or 3 visual targets had to be retained in working memory, and frontal lobe EEG was recorded at the fronto-parietal 1 (FP1) position using the Neurosky Mindwave® instrument. In the 2- and 3-target conditions of the task, children with FASD made more errors in remembering the sequence of target presentation compared to controls. During the memory retention phase of the task, children with FASD, but not control children, exhibited decreases in absolute power in the alpha (8–12 Hz) and theta (4–8 Hz) frequency bands during correct trials (correct sequence and timing). Similarly, children with FASD exhibited a positive correlation with the theta/beta power ratio that was not evident in control children. These data indicate that children with FASD can perform relatively well on simple versions of a spatial working memory task, but exhibit significant deterioration in performance when the task becomes more complex. Moreover, these results are consistent with the notion that children with FASD must exert more effort and/or recruit more neural resources in order to successfully perform tasks of increasing cognitive load.

Prenatal alcohol exposure and pituitary volume: sex differences and relationship to caregiver rated behavior; **Eileen Moore**, M. A. Infante, R. Migliorini, K. L. Jones, S. N. Mattson, E. P. Riley, San Diego State University; University of California at San Diego.

As pituitary volume has been suggested to be a reliable index of hypothalamic-pituitary-adrenal (HPA) axis activity, and a predictor of internalizing behaviors in adolescents, this study tested the hypothesis that prenatal alcohol exposure produces measurable changes in pituitary volume, and that these changes are associated with problem behavior. Adolescents (12–18 years old) with or without a history of PAE completed 3T T1-weighted structural magnetic resonance imaging, and caregivers completed the Child Behavior Checklist (CBCL). Non-exposed control adolescents displayed sex differences in pituitary volume (females > males) that were not evident in adolescents with a history of PAE. In males with FASD, scores on the CBCL aggressive behavior scale were negatively correlated with pituitary volume. These data suggest that PAE may interfere with adolescent sexual dimorphism of the pituitary. In alcohol-exposed males, pituitary volume was related to aggressive behavior, such that greater pituitary volume was associated with fewer reports by caregivers of aggressive behavior.

An fMRI study of response inhibition in adolescents with and without histories of heavy prenatal alcohol exposure; Ashley Ware, M. A. Infante, J. W. O'Brien, S. F. Tapert, M. P. Paulus, K. L. Jones, E. P. Riley, S. N. Mattson, San Diego State University; University of California at San Francisco; University of California at San Diego; VA San Diego Healthcare System.

This study examined blood oxygen level-dependent (BOLD) responses in adolescents with or without PAE during an auditory response inhibition task. Two groups (13–16 years old) of adolescents underwent functional magnetic resonance imaging (fMRI) while performing a stop signal paradigm. Participant performance was measured using the total number of correct responses during Easy, Medium, and Hard inhibition trials. Group differences in BOLD signal were calculated by contrasting correct versus incorrect trials, as well as Easy, Medium, and Hard conditions. There were no differences in participant demographics between the alcohol-exposed ($n = 20$) and control groups ($n = 20$) except for full scale IQ, which was lower in the alcohol-exposed group. During correct trials, the alcohol-exposed group exhibited greater BOLD activation in sensorimotor areas, left putamen, and left middle temporal gyrus relative to controls. As task difficulty increased, the alcohol-exposed group demonstrated greater activation in regions associated with inhibition and cognitive control, including the middle and superior frontal gyri, insula, supplementary motor area, and cingulate gyrus. Consistent with previous studies, adolescents with a history of PAE demonstrated greater activation than controls in regions associated with response inhibition, despite similar task performance. As task difficulty increased, alcohol-exposed youth utilized greater neural resources, which may suggest immature cognitive processing and motor coordination, fronto-striatal inefficiency, and/or frontal compensation during executive control tasks.

New data on the prevalence of FASD from two cities in the USA and implications for methodology and future studies; Philip May, W. O. Kalberg, J. Blankenship, D. Buckley, H. E. Hoyme, University of North Carolina at Chapel Hill; University of New Mexico; University of South Dakota.

To establish the prevalence of diagnoses within the FASD continuum in 2 major U.S. cities, a population-based study was completed in 4 first-grade samples of schoolchildren in the Midwest and Mountain West regions. The study was conducted using all domains of the revised guidelines of the Institute of Medicine: dysmorphology examinations, a battery of cognitive and behavioral tests/checklists, and administration of a multivariate maternal risk factors questionnaire. Oversampling was used to maximize the inclusion of children with the most dysmorphic cases of FASD. Additionally, a random sample of all consented children was included for each sample to provide a representative comparison group of unaffected children and to provide an estimate of the prevalence of less dysmorphic cases of FASD. The rates of FASD in these 2 U.S. cities were found to exceed previous published estimates of FASD affecting 1% of the population. Estimated cases of Fetal Alcohol Syndrome were found to be 2–7 per 1,000 individuals, whereas total cases of FASD ranged from 18–28 per 1,000. Diagnosing cases for a true prevalence of Alcohol-Related Neurodevelopmental Disorder remains a challenge because of the difficulty in obtaining accurate information on maternal alcohol consumption and lack of consensus on diagnostic criteria.

Agency updates

Representatives from 5 governmental agencies provided highlights of news related to progress on FASD programs. Holly MacKay of the Public Health Agency of Canada discussed their initiative on FASD, which is designed to prevent FASD and improve the outcomes of those with FASD. Their key objectives toward this initiative were to increase capacity for prevention and support, improve professional knowledge and public awareness, enhance knowledge and information exchange, create procedures for national screening and diagnosis, and develop data reporting tools. The collaborative relationships between the provinces/territories of Canada, various Canadian departments, and health portfolios were discussed. Funding streams associated with screening and diagnosis, child welfare and corrections, identifying prevalence estimates, and learning were outlined.

Dale Hereld, M.D., Ph.D., of the National Institute on Alcohol Abuse & Alcoholism (NIAAA), provided an overview of the NIAAA FASD portfolio. A total of 87 grants were funded in 2012, which is down from the 2 previous years (2011: 100; 2010: 101). The agency is currently funding 4 studies on developing therapeutic interventions for individuals with FASD. In order to facilitate research in a specific area, a program announcement was released to increase research on the epigenetic changes associated with PAE and adult-health outcomes. Dr. Hereld also provided discussion regarding the agencies' 3 collaborative research consortia. The first is the Collaborative Initiative on FASD (CIFASD), which is designed to improve capabilities in FASD clinical case recognition, interventions, and prevention. The second is the Prenatal Alcohol in sudden infant death syndrome (SIDS) and Stillbirth Network, which focuses on the role of PAE in the risk for SIDS and adverse pregnancy outcomes. The goal of this project is to understand the genetic, molecular, physiological, and neurodevelopmental mechanisms associated with adverse pregnancy outcomes related to PAE. The third project is the Collaboration on FASD Prevalence (CoFASP), whose goal is to determine the prevalence rate for FASDs among children within the U.S. NIAAA is also providing technical assistance and support to the World Health Organization prevalence study on FASD. Finally, to facilitate dissemination of their funded

science, the agency is making news releases of key findings to improve the media exposure regarding FASD research.

Sally M. Anderson, Ph.D., presented information on the Interagency Coordinating Committee on FASD, which is a committee to improve communication, cooperation, and collaboration among federal agencies regarding programs related to FASD. Within the ICCFASD, 4 working groups have been developed: 1) Women, Drinking and Pregnancy Work Group, 2) Justices Issues Work Group, 3) Diagnostic Issues Work Group, and 4) Education Issues Work Group. Key highlights of these groups include developing a webinar to educate caseworkers and directors of child protective agency about FASD, implementing a demonstration project in 6 states to promote healthy pregnancies, screen pregnant women and women of childbearing age, and provide training for these activities. The Indian Health Service recently added FASD training via their Telebehavioral Health Center for Excellence. The Office of Juvenile Justice and Delinquency Prevention was involved in advocating for the ABA resolution on FASD awareness and has been active in educating judges and developing guidelines for judges and other judicial staff to appropriately address individuals with FASD in the court systems. Finally, the diagnostic issues working group was successful in getting Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE) included in the Disorders in Need of Further Study Section of the DSM-5.

Elizabeth Dang, Ph.D., of the Centers for Disease Control and Prevention, updated the group on her agency's activities. The agency has focused its work on the domains of 1) prevention and intervention. and 2) health promotion and education. Within the first category, the agency has been involved in identifying the prevalence of binge drinking, and implementing and disseminating information on the CHOICES project that attempts to prevent alcohol-exposed pregnancies. In addition, they have been working in conjunction with the National Organization on Fetal Alcohol Syndrome (NOFAS) to develop resources to publicize the interventions developed from their funded intervention projects, and are continuing to support programs to develop interventions with youth and young adults with FASDs. The agency has also been collaborating with the Administration of Children and Families to assist with developing national datasets that can determine the burden of FASDs in the foster/adoptive care settings, to disseminate information through the informational channels on FASDs, and to develop an electronic developmental screen that includes questions on PAE. The agency has also established FASD Regional Training Centers to educate medical and allied health students and practitioners in the prevention, identification, and treatment of FASDs. They have also worked with the American Academy of Pediatrics to implement professional education and information dissemination using a variety of media and have been working on developing multimedia tools to provide messages and materials for women regarding alcohol use in pregnancy.

Callie Gass, of the Substance Abuse & Mental Health Services Administration's FASD Center for Excellence, discussed her agency's activities, which include capacity building, networking, technical assistance, increasing training and awareness, and information dissemination. They support state systems by holding regional meetings and facilitating communication via a listserv and newsletter. They also support regional conferences among

native leaders to address FASD within their populations. Technical assistance is provided to the professionals and the public via a toll-free number, a website, and publications. They continue to support the Birth Mother's Network and have initiated the Knowledge-Base Expansion and Services Project to disseminate information about prevention and treatment approaches for individuals with FASDs.

Award Presentations

This year 9 young investigators were presented with travel awards (Parker Holman, Alexandre Lussier, Katrina Kully-Martens, Shital Gaitonde, Elif Tunc-Ozcan, Leila Glass, Kasey Hemington, Eileen Moore, Ashley Ware) to attend the meeting. In honor of the passing of Timothy Cudd, a former FASDSG researcher, a new award (the Tim Cudd Student Award) was added to the program. The award was given to the most outstanding student FAS data submission. Rajesh Miranda, a former colleague of Dr. Cudd at Texas A&M, provided an introduction to the award and discussed Dr. Cudd's commitment to training professionals along with a summary of his career and personal interests. Onkar Sawant, a former student of Dr. Cudd at Texas A&M University, was given this award for his submission titled "Effects of maternal glutamine supplementation on fetus to mitigate the negative developmental effects of late gestational PAE".

He delivered his presentation in the FAS data format, which evaluated the hypotheses that late gestational prenatal alcohol exposure decreases the bioavailability of amino acids, hampers fetal body growth, increases cerebellar oxidative stress, and alters fetal blood flow, and that maternal L-glutamine supplementation may mitigate these negative developmental effects. Pregnant sheep were randomly assigned to 4 groups: saline control, glutamine control, alcohol, or alcohol + glutamine. Alcohol (2.5 g/kg over 1 h) or saline infusions were given intravenously from gestation day (GD) 109 to 132 or from GD 99 to 121, 3 consecutive days per week to mimic a weekend binge drinking pattern. PAE reduced fetal body weight compared to the control group, and glutamine supplementation prevented this effect. There was a decrease in the concentrations of fetal arginine, aspartate, glutamine, taurine, and tyrosine in the alcohol group compared to both the saline control and alcohol + glutamine groups. The concentration of oxidized glutathione in maternal blood and fetal cerebellum was decreased for the alcohol + glutamine group compared to the alcohol group. Fetal cerebellar blood flow was increased in the alcohol group, and this effect was mitigated in the alcohol + glutamine group. In summary, maternal glutamine supplementation improved the bioavailability of multiple amino acids, fetal growth, and endogenous antioxidant levels in alcohol-exposed fetuses. The results of this study provide a strong foundation for further investigation into a potential role for glutamine and other nutrients as therapeutic interventions to mitigate developmental brain injury from PAE.

The 2013 Merit Award was for Outstanding FASD Research by a graduate student or postdoctoral fellow, and was presented to Kaitlyn McLachlan of the University of Alberta and The University of British Columbia. Her mentors were Carmen Rasmussen (University of Alberta) and Tim Oberlander (University of British Columbia). Her talk was titled "Early life adversity, adverse outcomes, and cortisol regulation in FASD" and it was co-authored by Tim Oberlander (The University of British Columbia), Christine Looock (The University

of British Columbia), James Reynolds (Queen's University), Jacqueline Pei (University of Alberta), Gail Andrew (University of Alberta), Joanne Weinberg (The University of British Columbia), and Carmen Rasmussen (University of Alberta). As both human studies and animal models of PAE have found elevations in basal cortisol/corticosterone (an index of hypothalamic-pituitary-adrenal [HPA] axis activity and heightened response to stress), Dr. McLachlan anticipated that cortisol regulation throughout the day would be altered in individuals with FASD and that early life adversity and adverse outcomes would impact this regulation. Cortisol regulation was found to be impacted by socioeconomic status (SES), an index score of adverse outcomes, and proportion of life spent living in a stable and caring home, such that children in higher SES environments who had experienced less adversity seemed to be less affected by the impact of PAE on cortisol regulation. Her findings suggested that PAE alters fetal and early life programming of the stress response system, and that early environmental adversity may further exacerbate the disruption in cortisol regulation. She further noted that a particular concern is that those children with a history of PAE, cortisol dysregulation, and self-regulation deficits may be at further risk for adverse outcomes because of the challenging behaviors that they present to their caregivers.

The highlight of the 2013 FASDSG program was the presentation to Sandra and Joseph Jacobson of the Henry Rosett Award, the highly prestigious award for recognition of major career contribution to the field of fetal alcohol research. Dr. Claire Coles provided an introduction to the group regarding the Jacobsons' outstanding career contributions to the area of FASDSG research and other teratogens. Dr. Joseph Jacobson did his undergraduate work at Harvard College and then completed his doctoral work in psychology at Harvard University. Dr. Sandra Jacobson received her undergraduate degree from Brandeis University and completed her doctoral work at Harvard University. Both are currently at Wayne State University, where Dr. Joseph Jacobson is a professor in the Department of Psychiatry at Wayne State School of Medicine and Dr. Sandra Jacobson is a research professor in the Department of Psychology at Wayne State University and professor in the Department of Psychiatry and Behavioral Neuroscience at the Wayne State School of Medicine. They have jointly carried out numerous prospective cohort studies examining the impact of various teratogens, including alcohol, on child development. Their various studies were carried out in inner-city Detroit, in Cape Town, South Africa, and in the Arctic with a population of Inuit people, and have resulted in over 200 original scientific publications (e.g., Jacobson, Dodge, Burden, Klorman, & Jacobson, 2011; Joseph et al., 2014; Muckle et al., 2011). Their long and distinguished careers have provided vital contributions to our understanding of the impact of teratogens on development (Jacobson, Jacobson, Stanton, Meintjes, & Molteno, 2011; Joseph et al., 2014). The Jacobsons are well known for their rigorous methodology, and their research has resulted in some of the most important findings in our field as well as in the study of other behavioral teratogens. They jointly gave a talk in which they described the key to their success as stemming from their willingness to collaborate with various leaders in the field of clinical and child development to bring novel methodologies to assist with understanding the impact of PAE on child development. Using a tag team approach, they seamlessly outlined their efforts to establish these relationships with their collaborators as they reviewed their major career contributions to FASD research.

Acknowledgments

Funding for this conference was made possible in part by funds from NIAAA and NICHD (R13 AA015661). The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services, nor do they imply endorsement by the U.S. government.

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