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Proceedings of the 2015 Annual Meeting of the Fetal Alcohol Spectrum Disorders Study Group

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ABSTRACT

The 2015 Fetal Alcohol Spectrum Disorders Study Group (FASDSG) meeting was titled "Basic Mechanisms and Translational Implications." Despite decades of basic science and clinical research, our understanding of the mechanisms by which ethanol affects fetal development is still in its infancy. The first keynote presentation focused on the role of heat shock protein pathways in the actions of ethanol in the developing brain. The second keynote presentation addressed the use of magnetoencephalography to characterize brain function in children with FASD. The conference also included talks by representatives from several government agencies, short presentations by junior and senior investigators that showcased the latest in FASD research, and award presentations. An important part of the meeting was the presentation of the 2015 Henry Rosett award to Dr. Michael Charness in honor of his achievements in research on FASD.

The 2015 Fetal Alcohol Spectrum Disorders Study Group (FASDSG) annual meeting took place on June 20, in San Antonio, TX as a satellite of the Research Society on Alcoholism meeting. Approximately 180 senior and junior investigators attended the meeting (34 of which were students or postdoctoral fellows), including individuals from the United States, Canada, and South Africa. The program included 14 brief, one-slide 5-min presentations of recent data. Thirteen of these presentations were given by graduate students and postdoctoral fellows (5 of these received travel awards). In addition, two other trainees were selected to receive the Timothy A. Cudd and the Kenneth R. Warren Merit Awards. Representatives from the National Institute of Alcohol Abuse and Alcoholism (NIAAA), the Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD), Substance Abuse and Mental Health Services Administration (SAMHSA), and the Centers for Disease Control and Prevention (CDC) gave updates on FASD-related programs of these agencies. The trainees attending the meeting had the opportunity to interact with more senior researchers and clinicians in a networking lunch. The highlight of the meeting was the annual presentation of the Rosett Award, to recognize lifetime contributions, achievement, and service in FASD research.

The theme of the 2015 meeting was "Basic Mechanisms and Translational Implications." The first keynote presentation by Dr. Kazue Hashimoto-Torii, principal investigator at the Children's National Medical Center and assistant professor of pediatrics at George Washington University, was titled "The molecular defense mechanisms deployed by the developing brain against alcohol." Dr. Hashimoto-Torii began her talk by emphasizing that susceptibility to neuropsychiatric disorders is determined by both genetic and environmental factors. Disorders such as autism, schizophrenia, dyslexia, and bipolar disorders are polygenic, involving numerous genetic mutations, some of which overlap among these disorders (Fromer et al., 2014). In addition, these disorders involve multiple epigenetic alterations that can be the result of environmental influences (e.g., nutritional deficiencies, prenatal infections, maternal stress, and medication use). Multiple environmental risk factors may target a common intracellular signaling pathway. Manifestation of phenotypes will depend on the balance between the pathological insult and defense mechanisms. An important defense mechanism during development is the heat shock pathway. It involves translocation of heat shock factor 1 (HSF1) from the cytoplasm to the nucleus and induction of expression of heat shock proteins (HSPs), which function as molecular chaperones that act,

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in part, by facilitating refolding of proteins that were damaged by cellular stressors (e.g., exposure to changes in temperature or ultraviolet light). Drugs that promote heat shock signaling are currently being investigated for the treatment of cancer and neurodegenerative disorders.

Dr. Hashimoto-Torii then provided an overview of her work on the developmental effects of ethanol on cortical development. She used both human slice cultures from 15 to 18 gestational week fetuses exposed to ethanol *in vitro* for 24 h and fetal cerebral cortical samples obtained from pregnant mice (gestation days 14–16) injected with 2 g/kg of ethanol (Hashimoto-Torii, Kawasawa, Kuhn, & Rakic, 2011). Microarray analyses revealed that multiple HSPs were upregulated by ethanol exposure (e.g., heat shock 70 kDa proteins [HSP70] 1A and 1B). Similarly, exposure of pregnant mice at gestational day 14 to other environmental stressors (pentylenetetrazol-induced maternal kindling or methylmercury) also increased HSP70 expression in the fetal cerebral cortex (Hashimoto-Torii et al., 2014). In homozygous *Hsf1*KO mice, prenatal exposure to environmental stressors caused cortical heterotopias (at embryonic day 14), and reduced cortical layer thickness (at postnatal day 25), and these effects were not seen in heterozygous *Hsf1*KO mice (Hashimoto-Torii et al., 2014). Homozygous *Hsf1*KO mice prenatally exposed to pentylenetetrazol-induced maternal kindling, ethanol, or methylmercury also exhibited an increase in chemically induced seizure susceptibility at postnatal days 21–25 (Hashimoto-Torii et al., 2014). At embryonic day 15, these mice also exhibited greater reductions in neuronal cell proliferation and higher levels of cell death in response to ethanol exposure (Hashimoto-Torii et al., 2014). These disturbances in cortical development at embryonic stages may result in morphological abnormalities (i.e., heterotopia and the reduced cortical thickness) observed in adulthood. Using reporter mice that express red fluorescent protein driven by HSF1, it was determined that prenatal exposure to ethanol and other environmental stressors does not produce activation of the HSP pathway equally across all brain regions and also other organs (liver, heart, eye, limb bud, arteries, and spinal cord). Environmental stressors activate the HSP pathway at different levels even under conditions of identical cellular microenvironment and genetic background, suggesting that the heterogeneous effect of ethanol could be a consequence of a stochastic process. Computer simulation studies suggest that this process is indeed probabilistic. Overexpression of Hsf1 via *in utero* electroporation at embryonic day 14 inhibits cortical neuronal migration at postnatal day 14. Overall, these studies suggest that heterogeneous activation of the HSP pathway may lead to variable effects on brain development. For example, in cells exhibiting low activation of HSP, prenatal ethanol exposure may result in reduced cell proliferation and increased apoptosis. However, in cells with high HSP activation, ethanol exposure would result in arrested migration. Dr. Hashimoto-Torii concluded her talk by stating that stabilizers of the stress responses could play a role in the treatment of neurodevelopmental disorders (for example, the antipsychotic aripiprazole, which stabilizes dopamine signaling). She also pointed out that homogeneous up/down changes in gene expression may not account for the complex phenotypes observed in neurodevelopmental disorders. Since the pathological effects of ethanol can occur in a probabilistic manner, this supports the recommendation that there is no safe level of alcohol drinking during pregnancy.

The second keynote presentation was given by Dr. Julia Stephen, MEG/EEG Core Director, associate professor of translational neuroscience, The Mind Research Network, and was titled “Identifying atypical brain development based on altered timing: Insights from MEG.” Dr. Stephen focused on the effects of prenatal ethanol exposure in infants, preschool children, and adolescents. The overall goal of her research is to better identify individuals with atypical brain development. For her studies, she uses magnetoencephalography (MEG), a technique that measures electrical activity in the brain. In contrast to electroencephalography (EEG), which measures volume currents that are distorted when they pass through the skull, MEG measures magnetic fields that are not subjected to this type of distortion. Therefore, the area of the brain where signals originate can be better determined using MEG. MEG has several additional advantages, including that signals are measured at a distance using a helmet rather than sensors attached to the scalp, reducing the difficulties with acquiring data in children with sensory sensitivities. MEG and EEG detect responses in the millisecond range allowing for the detection of neuronal responses with excellent temporal resolution. In contrast, functional magnetic resonance imaging of blood flow changes in response to increases in neuronal activity occur over seconds as opposed to milliseconds, 3 orders of magnitude slower than MEG and EEG. However, MEG signals need to be corrected for head movement to avoid smearing of the signal and improving the signal-to-noise ratio. After correction for head movement, MEG’s spatial resolution has been shown to be 2–4 mm.

Dr. Stephen then presented an overview of her studies of visual pro-saccades in adolescents with FASD (Coffman et al., 2013). These studies evaluated the visual cortex response to central and peripheral stimuli. The latencies of M100 occipital cortex responses to both central and peripheral stimuli were significantly increased in the FASD group, and this effect was more pronounced for peripheral stimuli. Interestingly, saccade times were not altered in individuals with FASD in this study, suggesting that a mechanism had compensated for the deficits in visual cortical responses prior to the oculomotor response. An increase in gamma band (30–100 Hz range) oscillations were detected in subjects with FASD relative to controls, and it is hypothesized that this could perhaps explain the lack of behavioral alterations in these individuals (Stephen, Coffman, Stone, & Kodituwakku, 2013). Dr. Stephen has also characterized auditory sensory processing in preschoolers with and without prenatal alcohol exposure. In preschool children with FASD, an increase in the latency of auditory cortical responses was observed relative to controls (Stephen et al., 2012).

Dr. Stephen addressed the potential utility of MEG for early detection of alterations in brain development. Sensorimotor μ rhythm development can be evaluated in infants and preschoolers. The frequency of this rhythm increases linearly with age from approximately 4 Hz at 10 weeks of age to 8 Hz at 45 weeks (adult μ rhythm oscillation is in the 10-Hz range) (Berchicci et al., 2011). Therefore, this increase in μ rhythm frequency can be used to assess neurodevelopmental trajectory in a variety of conditions, including preterm birth; future studies should determine if it can also be useful in FASD cases. MEG and EEG are also being used to identify neurophysiological indices of sensorimotor deficits in 6- and 20-month-old infants prenatally exposed to opioids with and without alcohol co-exposure (ENRICH cohort). Preliminary results with 6-month-old infants suggest that there are alterations in theta band oscillations (associated with alertness) in alcohol-exposed infants.

Finally, Dr. Stephen discussed the use of joint individual component analysis linking MEG and diffusion tensor imaging (DTI) data (Stephen, Coffman, Jung, et al., 2013). Fractional anisotropy (FA) measured with DTI provides information on diffusion properties of water in white matter, reflecting overall tissue integrity. FA measures, which reflect myelination and other microstructural factors, can be correlated to alterations in neuronal responses in a brain region of interest. Ongoing studies are evaluating the relationship between structural changes in white matter and functional changes as measured by MEG to determine the interplay between the health of white matter networks and cortical functioning. Dr. Stephen concluded her talk by emphasizing that MEG provides good spatial resolution with high temporal resolution, which can be