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Commentary: Linking Cortical and Subcortical Developmental Trajectories to Behavioral Deficits in a Mouse Model of Prenatal Alcohol Exposure

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Fetal Alcohol Spectrum Disorder (FASD) refers to the broad range of adverse effects that can occur in children born to women who drink alcohol during pregnancy (Murawski et al, 2015). At the severe end of the spectrum is Fetal Alcohol Syndrome (FAS). Diagnostic criteria for FAS include pre- and postnatal growth retardation, a characteristic facial dysmorphology, and central nervous system neurodevelopmental abnormalities, such as microcephaly, neurological abnormalities, developmental delays and intellectual impairment. In addition to FAS, the full spectrum of alcohol effects can include: 1) partial FAS (pFAS), in which some but not all of the characteristic facial anomalies and CNS neurodevelopmental abnormalities are present, and significant behavioral and cognitive abnormalities are also observed; and 2) alcohol-related effects, which may be primarily physical (Alcohol-Related Birth Defects, ARBD) or primarily neurobehavioral (Alcohol-Related Neurodevelopmental Disorder, ARND) (Stratton et al, 1996). Importantly, similar cognitive, neuropsychological, and behavioral problems may be observed at all levels of alcohol exposure (Murawski et al., 2015). As well, one must be aware that numerous factors may influence both the short- and long-term effects of alcohol on the fetus, including: dose, timing, duration and pattern of alcohol exposure; maternal nutrition, health, and other drug use; a variety of environmental variables, including the social environment, life style issues, and socioeconomic variables; and both genetic variables, which affect sensitivity to alcohol's effects as well as absorption and metabolism of alcohol, among other things, and epigenetic alterations (Abel & Hannigan, 1995; Kobor & Weinberg, 2011; May & Gossage, 2011). Prenatal exposure to alcohol has been identified as a leading preventable cause of birth defects and intellectual and neurodevelopmental disabilities (Williams et al., 2015). Secondary disabilities are also common in children and adults with FASD compared to non-exposed individuals, including concurrent emotional, behavioral, and mental health problems, which can occur even with normal intelligence (Williams et al, 2015). FASD is often called the “invisible disability,” as facial dysmorphologies and growth deficiencies associated with FASD may not be present or may become less prominent with time, while perturbations to the CNS, with concomitant cognitive, behavioral, adaptive and self-

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regulatory deficits or abnormalities, occur and can persist long into adulthood (Chudley, 2008; Lynch et al., 2015; Moore & Riley, 2015; Streissguth et al., 1991).

Animal models of FASD have been critical in moving the field forward. They were first developed to address the skepticism that greeted the initial description of FAS by Jones and Smith (Jones & Smith, 1973) indicating that maternal alcohol consumption could cause major adverse effects. Studies using animal models demonstrated both biological and neurobehavioral effects that existed along a continuum and were consistent with clinical effects described. Moreover, these effects were shown to occur under conditions where environmental (eg., dose and timing of alcohol exposure, exclusion of other drugs, maternal health and nutrition) and genetic (eg., differences in vulnerability or sensitivity to alcohol, and absorption and metabolism of alcohol) variables could be controlled at a level not possible in humans, thus demonstrating that alcohol itself is indeed a teratogen. Studies with animal models are also important in providing insight into alcohol's mechanisms of action, as the brain and other tissues can be examined directly. An understanding of mechanisms underlying alcohol's adverse effects can inform the development of diagnostic, intervention and treatment strategies (Murawski et al., 2015).

The recent paper by Abbott et al (2016) in Alcoholism: Clinical and Experimental Research, entitled "The impact of prenatal ethanol exposure on neuroanatomical and behavioral development in mice," is a strong addition to the animal models literature on FASD. Building on their previous studies suggesting that abnormal gene expression and circuitry in the neocortex may underlie some reported disabilities of learning, memory, and behavior resulting from early exposure to alcohol (El Shawa et al., 2013), the present study utilized a mouse model of FASD to examine effects of prenatal alcohol (ethanol) exposure (PrEE) on body and brain growth and brain anatomy in newborn (P0), weanling (P20) and young adult (P50) mice. Importantly, abnormal cortical and subcortical anatomy was correlated with atypical behavior in the young adults. Their results demonstrate long-term alterations to cortical anatomy, including atypical developmental cortical thinning, and abnormal subcortical development, together with altered performance on behavioral tasks measuring sensorimotor integration and anxiety, in offspring exposed to alcohol *in utero*.

In terms of overall growth, Abbott et al (2016) reported that PrEE mice had lower birth weights and smaller brains than their age-matched counterparts, and these deficits persisted into early adulthood. In addition, brain/body weight ratios in PrEE mice were not altered at any age, suggesting overall deficits in growth rather than selective effects of alcohol on brain. Despite these deficits, however, average daily body and brain (whole brain) growth rates from birth to weaning age (P20) were similar in control and PrEE animals, whereas average growth rates from weaning to young adulthood (P50) were actually marginally *accelerated* in PrEE offspring compared to controls. The authors note that the period from weaning through adolescence is considered a sensitive developmental time period, as the body and brain undergo considerable maturation. In interpreting these findings, the authors suggest that although a growth spurt may represent a form of recovery in PrEE mice, there could be long-term adverse consequences of such accelerated growth rates, with negative impacts on programmed developmental mechanisms and unwanted consequences related to obesity later in life. This is a highly significant finding, and I would like to expand upon it

through the lens of Developmental Origins of Health and Disease (DOHaD). It is now recognized that the risk for adult diseases or disorders is markedly influenced by prenatal and early life environmental exposures or insults. This has been termed fetal or developmental programming. Beginning with seminal studies by David Barker and colleagues (reviewed in Barker and Thornburg, 2013), accumulating evidence provides support for the “fetal or developmental origins” hypothesis, indicating that low birth weight, together with accelerated infant catch-up growth, may be associated with a significant risk for adult obesity as well as adverse effects on cardiovascular, pulmonary, renal, and cerebral function (Lau et al., 2011). This association between low birth weight, accelerated postnatal growth, and later vulnerability was further elaborated with publication of the “thrifty phenotype hypothesis” (Hales & Barker, 1992) and subsequently, the “match-mismatch hypothesis” (Gluckman et al., 2005). These hypotheses suggest that a fetus growing under conditions of insufficient nutrition *in utero* makes adaptive changes in physiology and metabolism to prepare for survival postnatally under the “expected” condition of restricted nutrient availability (a match between pre and postnatal conditions, which makes the offspring best prepared to survive). However, a mismatch between the prenatal and postnatal environments, i.e., availability of adequate or abundant nutrition in postnatal life, would make these adaptations inappropriate. That is, the individual's physiological or metabolic processes, set to conserve nutrients in a deprived environment, would now be maladaptive, which could lead to increased risk for obesity and chronic diseases in later life. The thrifty phenotype and match-mismatch hypotheses have now been extended beyond their relevance to cardiovascular disease and metabolic syndrome, to include, as noted above, effects on lung function, immune function, learning ability, mental health, aging and menopause, polycystic ovaries, and cancer (as reviewed in Lau *et al.*, 2011). Furthermore, variables other than birth weight are now being used to provide a broader understanding of the quality of the intrauterine environment, and it is generally accepted that the window for programming or plasticity extends beyond fetal life to at least the early infancy period.

In addition to their important findings on body and brain weights and growth rates, Abbott *et al.* (2016) further report that alcohol exposure appears to disrupt the normal cortical developmental trajectory. Around weaning (P20), as the organism is maturing, normal developmental cortical thinning was generally observed in control mice across cortical areas. By contrast, in PrEE mice, all cortical areas examined, except V1, were thicker than those in controls, and there was a persistence of thickened frontal cortex in young adulthood. The authors note that thicker cortex (or delay/lack of thinning) at P20 suggests delayed development, while persistence of thickened frontal cortex is consistent with dysregulation of intra-neocortical connections, as demonstrated in their previous study (El Shawa et al., 2013). It was suggested that failure to prune these aberrant connections might be involved in the delayed cortical thinning observed. These findings have important clinical implications. The authors comment that the “...observation of reduced developmental cortical thinning during a time related to ‘middle childhood’ in children and a maintained perturbation during early adulthood is reminiscent of variation seen in humans with FASD,” and “...mark an alteration to an essential developmental process thought to be broadly driven by arealization, and in particular, the refinement of neuronal networks, white matter myelination and synaptic pruning (as supported by work by Sowell et al., 2004; Treit et al., 2014).”

In addition to these findings, PrEE was shown to alter the development of sensory areas in the neocortex, including the somatosensory, visual and auditory cortex, which would significantly impact sensory processing. Significant adverse effects of PrEE were also observed on development of the basal ganglia, hippocampus, and corpus callosum. Finally, performance on the Suok and platform apparatus at P50 revealed increased anxiety and reduced balance and sensorimotor integration in PrEE compared to control offspring.

By measuring functional outcome and linking it to altered neuroanatomical measures, the authors were able to suggest that impaired higher-order cortical processing and integration of auditory, somatosensory and visual information may contribute to balance and motor control impairments in their mouse model of FASD. In addition, the authors report that some anatomical measures showed recovery of PrEE-related phenotypes by young adulthood, without rescue of behavioral effects. Of relevance, their previous novel work on neocortical connectivity (El Shawa et al., 2013) provided evidence for the possibility that aberrant or ectopic intra-neocortical connectivity likely persisted into adulthood, and thus could contribute to maintenance of the behavioral phenotype.

The findings on neocortical and extra-neocortical brain changes are thoroughly discussed by the authors and links between their findings and findings in children with FASD support the importance of their work. The observation of reduced developmental cortical thinning was related to changes seen in individuals with FASD, as revealed by imaging studies (Sowell et al., 2004; Treit et al, 2014), which suggested critical alterations of the developmental trajectory. Importantly, their findings are also consistent with work demonstrating inhibited frontal cortex thinning in children with both attention deficit/hyperactivity disorder and FASD, compared to those with FASD alone, (Fernández- Jaén et al., 2011), which supports the suggestion of delayed or immature brain development.

In summary, the study by Abbott et al (2016) is an excellent example of how studies with animal models can support, extend, and provide unique insights into findings in clinical studies by examining the brain directly and demonstrating links between brain and behavior. Of particular note, by examining the developmental trajectory and demonstrating effects from birth to weaning and into young adulthood, the present study provides important information about persistence of brain abnormalities into adult life, which could inform the understanding of functional deficits in children, adolescents, and adults with FASD. Finally, the data obtained suggest possible biomarkers that could be investigated using standard imaging techniques in clinical populations, which could aid in clinical diagnosis of individuals with FASD.

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