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Another Step Forward in Relating Facial and Brain Dysmorphologies Associated with Prenatal Alcohol Exposure

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The recent study by Yang and colleagues (2012) is a well-conducted, well-sampled neuroimaging investigation into fetal alcohol effects on corpus callosum structure, in relation to facial dysmorphology. Results of the study include observations of specific craniofacial malformations correlating with decrements in corpus callosum area and thickness in youth with prenatal alcohol exposure histories. Part of the value of this work rests on multisite sampling, which enabled data to be pooled across U.S. sites in Los Angeles and San Diego, as well as an international site in Capetown, South Africa. As part of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD), this study stems from a larger effort to combine cross-cultural assessment with novel methodologies and an interdisciplinary framework to advance understanding of fetal alcohol exposure-associated sequelae. A central CIFASD aim entails driving a research agenda to generate improved diagnostic criteria for the entire range of birth defects associated with prenatal alcohol exposure.

Craniofacial malformations (e.g., short palpebral fissures, smooth philtrum, thin vermilion border) are hallmark features of prenatal alcohol exposure, and along with growth deficiency and central nervous system (CNS) abnormalities, form a triad of characteristics required for the diagnosis of the fetal alcohol syndrome (FAS) (Bertrand et al., 2004). However, FAS falls at the severe end of the continuum of fetal alcohol effects, and many youth with cognitive and behavioral deficits believed to be attributable to prenatal alcohol exposure may not bear all, or any, of the facial dysmorphia necessary to meet FAS diagnostic criteria. Fetal alcohol-related pathologies other than FAS, including alcohol-related neurodevelopmental disorders, are estimated to occur at rates several-fold higher than FAS alone (Sampson et al., 1997). In recognition of the continuum of exposure-related effects, fetal alcohol spectrum disorders (FASD) is used as a nondiagnostic umbrella term (Bertrand et al., 2004). However, FASD is a descriptive term, not a clinical diagnosis. To date, there is no consensus on evidence-based diagnostic guidelines for fetal alcohol-related pathologies other than FAS. The diagnostic framework presently in place motivates concern that youth who exhibit a similar behavioral phenotype to individuals with FAS, but who lack the requisite craniofacial and/or growth characteristics required to meet FAS diagnostic criteria,

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may not qualify for treatment and social services (Bertrand et al., 2004). Accordingly, improving criteria related to early identification and diagnosis remains a major research priority in the field of fetal alcohol research. The Yang and colleagues study makes an important contribution to these goals by focusing on the relationship between alterations in the brain, face, and behavior in individuals with FASD. By relating measurements of brain structure with the assessment of facial morphology in a cross-cultural sample, this study identifies interrelated aspects of the complex pathology arising from prenatal alcohol exposure.

The corpus callosum has been a continued focus of FASD research, owing to both the commissure's functional significance as the brain's main conduit of interhemispheric transfer as well as an association between alcohol teratogenesis and callosal anomalies dating back to early autopsy reports and clinical magnetic resonance imaging (MRI) studies. Quantitative structural MRI studies of FASD have since confirmed earlier observations by reporting corpus callosal shape changes (Bookstein et al., 2002; Sowell et al., 2001) and subregional size reduction, adjusted (Riley et al., 1995; Sowell et al., 2001) and unadjusted (Astley et al., 2009) for total brain size. Additionally, diffusion tensor imaging (DTI) has revealed anomalous fiber integrity of the corpus callosum. Some, but not all, of these DTI studies report that individuals with FAS have poorer callosal white matter integrity than FASD individuals without FAS (Fryer et al., 2009; Li et al., 2009). Across neuroimaging modalities, the genu and splenium appear to be commonly affected subregions. Results of the Yang and colleagues study converge with these prior findings, in that individuals with FASD showed less callosal thickness and area in the anterior third and splenium, relative to typically developing peers. As discussed by the authors, these results implicate the disruption of fibers connecting homologous frontal and parieto-occipital regions. Such white matter alterations may relate to task-evoked brain activation abnormalities of frontal and parietal regions that have been observed via functional MRI of FASD samples (Fryer et al., 2007; Meintjes et al., 2010; Santhanam et al., 2009).

This study is also significant because it supports a small, but growing, body of literature relating features of facial dysmorphology to brain alterations in youth with FASD. Specifically, Yang and colleagues report that measurements of palpebral fissure length (PFL) in FASD participants correlate with callosal thickness and area in the anterior third, isthmus, and splenium. These findings associating brain and facial dysmorphology may reflect concurrent disruption of the developing callosum and facial features. The relationship between morphology of the anterior third and PFL scores withstood statistical control of age, gender, site, and total white matter volume, suggesting that fibers interconnecting frontal regions may have a particularly robust relationship with facial dysmorphology in FASD. Interestingly, no associations in this large sample were observed between corpus callosum morphology and lipometer-based measurements of the philtrum. Future research is needed to understand why some aspects of facial dysmorphology appear more related to callosal development than others, and whether this finding generalizes to other samples.

While the current study makes progress in relating facial and brain dysmorphologies, it also raises a number of questions that require further inquiry. The 3 study sites show considerable variation across within-site results comparing callosal thickness of individuals

with FASD relative to the control group (shown in Yang et al., 2012, figure 1). Addressing questions regarding what site-specific factors may drive these divergent patterns is undoubtedly an important direction for future research. Improved understanding of factors in FASD that are potentially associated with variation in structural and functional brain alterations (e.g., alcohol exposure patterns, psychiatric comorbidities, IQ, age, co-occurring prenatal exposures) may contribute to diagnostic refinement, and/or identify risk and protective factors essential for informed outreach efforts. For example, the authors note in discussion of their work that varying degrees of FASD-associated cognitive deficits might relate to observed variation among the 3 sites in corpus callosum morphology. Previous research has identified distinct corpus callosum shape profiles associated with different patterns of neuropsychological detriment in FASD (Bookstein et al., 2002), as well as correlations between callosal shape displacements and verbal learning impairments in FASD (Sowell et al., 2001). These prior findings underscore the importance of including examination of cognitive ability in characterizing callosal effects in FASD. In addition, quantity, frequency, and timing of prenatal alcohol exposure may explain variation in observed brain alterations. Inverse relationships have been reported between regional brain size measurements, including corpus callosum length, and number of days per week of maternal drinking (Astley et al., 2009). In the Yang and colleagues study, quantification of maternal alcohol exposure was unavailable for the majority of subjects studied, and thus, as the authors note, the study was underpowered to examine exposure relationships. Last, limitations inherent in correlational observations necessarily preclude inference of a causal relationship between prenatal alcohol exposure and CNS effects. Callosal damage may arise from etiological sources other than, or in addition to, prenatal alcohol exposure, and the authors specifically cite a lack of assessment for concomitant teratogenic exposures as a study limitation. There are, of course, many other pre- and postnatal factors that might impact brain development in this population, which are unaccounted for in this and the majority of other FASD neuroimaging studies published to date.

Future research is needed to establish the functional significance of the relationships between facial and callosal alterations reported by the Yang and colleagues study. Other questions to be addressed include the extent to which face– brain relationships have implications for diagnostic criteria refinement, as well as identifying factors that explain site-specific variations. The relationship between severity of dysmorphic features and cognitive deficits in FASD has been shown to be mediated by task-associated regional brain volumes (Coles et al., 2011), supporting the relevance of examining facial dysmorphology in seeking to understand brain–behavior relationships in FASD. The Yang and colleagues study provides support to an existing literature that the developing corpus callosum may be especially sensitive to the teratogenic effects of prenatal alcohol exposure. Furthermore, the observed link between callosal structure and PFL measurements underscores the utility of facial signs in FAS to signal underlying brain alterations.

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