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Commentary

Developmental Considerations of Comorbidity in Autism Spectrum Disorder: The Need for Science Across Multiple Units of Analysis

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In the last 2 decades, we have seen heightened interest in comorbidity in autism spectrum disorder (ASD). Research in this area has spanned clinical studies, intervention trials, and neurobiological models. Difficulty with emotion regulation (ER) and cognitive control are pervasive problems in individuals with ASD. It is possible that some of the core diagnostic features of ASD may underlie these issues. Examining the circuitry primarily involved in the regulation of emotional behavior in the context of functional connectivity models of autism is indeed a new direction. In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Ibrahim *et al.* (1) report an interesting neuroimaging study examining functional connectivity of the amygdala–prefrontal cortex (AMY–PFC) circuitry in children with ASD with the goal of examining potential patterns of association between neurobiological function and comorbidity. The PFC and AMY are important components of a well-established network that supports socioemotional processing in healthy individuals. The AMY controls expression of the emotional response via projections to other subcortical brain regions, and the PFC regulates emotional expression through projections to the AMY (2). While connectivity models of ASD have largely focused on corticocortical connectivity, this study's focus on AMY–PFC connectivity is a novel and much-needed approach. Approximately 4 out of 5 children with ASD are diagnosed with comorbid psychiatric disorders (3), with a rate of anxiety disorders as high as 84% (4) and a rate of major depressive disorder as high as 70% (5). There are also higher rates of mood and anxiety disorders in the first-degree family members of children with ASD (6). Thus, comorbid conditions that impact the processing of affect play a significant role in the emotional and social behavior of individuals with ASD. Although replication with a larger sample size is needed in the future, the current study (1) is a fresh new direction in considering comorbid conditions and their underlying neurobiology as important factors in autism symptomology.

Ibrahim *et al.*'s findings (1) are intriguing but not necessarily surprising when viewed through the lens of developmental psychopathology. We specifically refer to two tenets of developmental psychopathology: 1) that comorbidity among children is the rule rather than the exception, and 2) that there often exist multiple paths to the same outcome (pathology, in this case disruptive behavior [DB]), termed "equifinality." Herein, we expand on these points to support our view that perhaps a developmental "building up" approach to the science of comorbidity in ASD will prove fruitful. In other words, most research in this area has (we believe, by necessity) carved groups and samples based on diagnosis [in the case of Ibrahim *et al.* (1), ASD, ASD plus DB, and typically developing groups]. This study's findings suggest, among other things, that patterns of AMY–PFC functional connectivity and emotional reactivity in ASD plus DB are similar to what is frequently seen in youths with DB (without ASD).

Impaired ER is extremely common in ASD but is not part of the diagnostic criteria according to the DSM-5 or the ICD-9. Many scientists, ourselves included, want to understand why this is the case and how, when ER is impaired, it might be related to co-occurring psychiatric problems. There is indeed a substantial body of research showing an association between ER impairment and pathology, in both ASD samples and non-ASD samples. Given the early biological roots of ASD and its genetic basis, it is logical to infer that ER impairment—both behaviorally and at the neurobiological level—emerges later in development and after the onset of ASD. The same argument holds for most forms of psychiatric comorbidity in ASD. To truly understand the role that ER impairment plays in psychopathology, we must understand its developmental course. To do this, longitudinal research with large and well-characterized samples is needed. If ER (or a neuromarker of ER impairment) is shown to developmentally precede the onset of secondary pathology, this will be extremely informative to improving targeted prevention and personalized medicine (point 1).

The results of the Ibrahim *et al.* study (1) are consistent with other research (7) in indicating that the comorbidity (e.g., aggression and social anxiety) is what drives differences in neural or behavioral indicators, more so than the ASD diagnosis per se. We argue that this is especially true when using older, clinically referred, or cognitively unimpaired samples. In other words, ASD may be so heterogeneous that the diagnosis, as an entity, is of limited utility in trying to understand neuromarkers of ER impairment. The identification of neuromarkers of dysregulated emotion/reactivity or specific behavior problems does not lend itself to diagnostic boundaries. The diagnoses capture only the outcome of behaviors, not their developmental roots (point 2).

Although AMY–PFC connectivity has been characterized relatively well, it has not received similar levels of attention in the ASD literature. The results of this study extend previous work in ASD that indicate reduced AMY connectivity by targeting AMY–PFC circuitry in relation to behavioral phenotype. While most neuroimaging studies use a dichotomous comparison between ASD and neurotypical groups, this study

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specifically targeted a third group of children with ASD who have comorbid DB problems. The selective recruitment and inclusion of two different ASD groups may be helpful in identifying the circuitry that is unique to ASD as well as to comorbid conditions like DB. In closing, we urge further scientific investigation of the roots of ER impairment in ASD, across units of analysis and over the course of development.

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