Neurobiological Disturbances in Callous-Unemotional Youths

Disruptive behavior disorders, including conduct disorder, are found in a heterogeneous group of young people at varying risk of persistent antisocial behavior. Early attempts at delineating a more homogeneous subgroup of high-risk antisocial youths focused on identification of symptoms associated with attention deficit hyperactivity disorder (ADHD). Comorbidity between conduct disorder and ADHD is associated with more persistent antisocial behavior. However, this more persistent antisocial behavior is related to higher levels of conduct problems in this comorbid group rather than to the specific influence of ADHD symptoms (1). In addition, the presence of comorbid ADHD symptoms does not seem to designate a subgroup of conduct disorder youths with unique cognitive and affective deficits that result in their antisocial behavior (2).

Recently, there has been growing interest in the utility of the construct of psychopathy as an alternative to ADHD for subtyping antisocial youths (3, 4). Psychopathy is a complex personality disorder that includes interpersonal and affective traits, such as glibness and lack of empathy, guilt, and remorse, and behavioral characteristics, such as impulsivity and poor behavioral control. Despite debate on the number of dimensions needed to capture the construct of psychopathy in adults, research in antisocial youths has highlighted a potentially useful distinction between the impulsive-conduct problem dimension of psychopathy and callous-unemotional traits (e.g., lack of empathy, lack of guilt, and callous use of others for personal gain) (4, 5).

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Youths with high impulsive-conduct problem traits but low callous-unemotional traits tend to come from dysfunctional families, engage in reactive rather than instrumental aggression, and show high levels of emotional reactivity to threat or distress from others (5, 6). By contrast, those with prominent callous-unemotional traits seem to have a unique temperamental style characterized by fearlessness and thrill seeking. Their behavior is relatively stable and is associated with a more severe and persistent pattern of antisocial behavior, including instrumental aggression (5, 6). There is growing evidence from genetic, cognitive, and emotional information processing studies that callous-unemotional traits may be associated with a unique neurobiological developmental trajectory toward persistent antisocial behavior. Callous-unemotional traits are highly heritable compared with impulsive-conduct problem traits (7, 8) and are thought to be specifically associated with deficits in the processing of negative emotional stimuli, particularly fear and distress in others, which may impair socialization (9).

Because amygdala-ventromedial prefrontal cortical circuitry is implicated in emotional information processing, it has been suggested that amygdala dysfunction may be associated with callous-unemotional traits in psychopathy (9). A number of functional MRI (fMRI) studies in adult psychopaths confirm the amygdala dysfunction hypothesis

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(10), but there have been no similar studies in younger cohorts until the work of Marsh et al. in this issue of the *Journal* (11).

Marsh et al. used fMRI to investigate blood-oxygen-level-dependent (BOLD) responses during the performance of an implicit face processing task containing fearful, neutral, and angry faces in a sample of adolescents with callous-unemotional traits, adolescents with ADHD, and healthy comparison adolescents. Based on the adult literature, Marsh et al. hypothesized that callous-unemotional adolescents would show reduced amygdala activation in response to faces with fearful affect relative to the ADHD and comparison groups, and that no group differences would be seen in amygdala activity when participants viewed angry faces. Given reports that amygdala-ventromedial prefrontal cortex connectivity plays a role in fear affect processing, the authors also suggested that callous-unemotional traits would be associated with reduced functional connectivity between these regions.

The study sample consisted of 12 age-, gender-, and IQ-matched adolescents with callous-unemotional traits, 12 adolescents with ADHD, and 12 healthy comparison adolescents. There are no established cutoff scores for callous-unemotional traits on available measures of adolescent psychopathy; Marsh et al. used a cutoff score of ≥20 out of a maximum of 40 on the two primary psychopathy measures. They found that amygdala activation was reduced in the callous-unemotional group relative to the ADHD and comparison groups while processing fearful, but not neutral or angry, facial expressions. The finding that there were no brain regions where adolescents with callous-unemotional traits showed different BOLD responses to angry relative to neutral faces fits with behavioral data showing no deficits in anger recognition in those with psychopathic traits (9). By contrast, the investigators found that the ADHD group showed enhanced activation to angry faces in frontal regions but no evidence of amygdala dysfunction relative to healthy comparison subjects while viewing fearful faces. Although the enhanced ADHD activation in response to angry faces needs further exploration, these findings seem to add weight to the notion that ADHD is more associated with dysfunction in frontostriatal circuitry than in amygdala-ventromedial prefrontal cortical circuitry. A particularly novel aspect of this work is the data on amygdala-ventromedial prefrontal cortex functional connectivity and the finding that there is reduced connectivity in the callous-unemotional group relative to healthy subjects and those with ADHD. Given the authors' report that the reduction in amygdala-ventromedial prefrontal cortex connectivity was associated with callous-unemotional symptom severity, there is clearly a need for additional studies to look at the relationship between neural circuits of etiological interest and key psychopathological dimensions, such as callous-unemotional or impulsive-conduct problem traits.

Marsh et al. acknowledge some of the limitations in their work, including medication confounds and the restricted number of emotions under study. They did, however, conduct a secondary analysis that excluded subjects in whom medication may have had a confounding effect, and the results generally supported their primary findings. They can justify the choice of task based on the previous literature, and their sample sizes comply with the minimum recommended for studies of this nature. There have been new developments in the measurement of callous-unemotional traits (6) that will help with the standardization and comparison of measurements in future MRI studies—all of which should help in our understanding of the neural substrates of these traits.

This is the first fMRI report supporting the notion that amygdala dysfunction may be a key neurodevelopmental etiological factor in understanding callous-unemotional traits and that callous-unemotional symptom severity may reflect reduced amygdala-ventromedial prefrontal cortex connectivity. The work shows the potential utility of fMRI in advancing our neuroscientific knowledge about the developmental nature of disorders such as psychopathy and ADHD. By focusing on brain-behavior relationships rather than discrete psychiatric disorders, we can gain better insights into potential

symptom-targeted treatment interventions that may be applicable across a range of disorders. Because complex traits and behaviors are mediated by anatomically interconnected neural circuits with gray and white matter components, future studies need to look at both the structural and the functional neural correlates of key traits, symptoms, or behaviors in order to advance our neuroscientific knowledge. By studying callous-unemotional traits earlier in life, it is more likely that we can develop more effective prevention and intervention efforts based on a sound and coherent theoretical causal basis. Much more work is needed on the role of genetic-environmental influences on the development of callous-unemotional traits and antisocial behavior (8), and imaging genomics may offer promise. Given the societal burden of psychopathy across the lifespan and the suggestion that callous-unemotional traits may be a moderator of treatment outcome, it is important that future studies take a more dimensional approach to understanding the role of callous-unemotional traits in the maintenance of antisocial behavior.

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