Amygdala reactivity predicts adolescent antisocial behavior but not callous-unemotional traits

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\textbf{A B S T R A C T}

Recent neuroimaging studies have suggested divergent relationships between antisocial behavior (AB) and callous-unemotional (CU) traits and amygdala reactivity to fearful and angry facial expressions in adolescents. However, little work has examined if these findings extend to dimensional measures of behavior in ethnically diverse, non-clinical samples, or if participant sex, ethnicity, pubertal stage, and age moderate associations. We examined links between amygdala reactivity and dimensions of AB and CU traits in 220 Hispanic and non-Hispanic Caucasian adolescents (age 11–15; 49.5% female; 38.2% Hispanic), half of whom had a family history for depression and thus were at relatively elevated risk for late starting, emotionally dysregulated AB. We found that AB was significantly related to increased right amygdala reactivity to angry facial expressions independent of sex, ethnicity, pubertal stage, age, and familial risk status for depression. CU traits were not related to fear- or anger-related amygdala reactivity. The present study further demonstrates that AB is related to increased amygdala reactivity to interpersonal threat cues in adolescents, and that this relationship generalizes across sex, ethnicity, pubertal stage, age, and familial risk status for depression.

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\section{1. Introduction}

Antisocial behavior (AB) includes behaviors such as rule breaking, lying, and aggression. AB is a major public health concern because of its high prevalence and the negative impact of AB on perpetrators, victims, and their families (Foster and Jones, 2005; Nock et al., 2006; Ogderson et al., 2007). Recent research has suggested that youth with AB are a heterogeneous group (Frick and Viding, 2009), which may undermine intervention success. Thus, research that examines the divergent etiologies of specific dimensions within AB has the potential to inform more effective, personalized treatments (Frick and Nigg, 2012; Kahn et al., 2012; Moffitt et al., 2008).

\subsection{1.1. Divergent pathways of amygdala reactivity}

One recent approach to parsing AB into etiologically distinct subtypes is to measure the presence of callous-unemotional (CU) traits. CU traits were added as a subtyping specifier to the antisocial behavior diagnosis of Conduct Disorder in the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), titled “with limited prosocial behavior.” These traits are characterized by low empathy, lack of remorse, and shallow interpersonal affect (Frick and White, 2008; Viding et al., 2012). AB in the presence of CU traits is more highly heritable (Viding et al., 2005), and research is beginning to suggest that AB and CU traits may have divergent relationships with neural reactivity, particularly in the amygdala (Hyde et al., 2013).

The amygdala has been implicated in cognitive and affective processes believed to underlie behavioral deficits characteristic of youth AB, such as poor fear conditioning and impaired

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emotional regulation, potentially via two divergent pathways (Blair et al., 2014; Hyde et al., 2013). In one pathway, in those high on CU traits, relatively decreased amygdala reactivity to signals of interpersonal distress may prevent the processing of interpersonal distress cues, and disrupt important conditioning early in life that contributes to the development of empathy (Blair et al., 2014). In a second pathway, in those low on CU traits, but high on AB, relatively increased amygdala reactivity to cues of social threat may result in over-reactivity to threat and lead to emotional dysregulation, manifesting behaviorally as increased reactive aggression and AB (Hyde et al., 2013; Viding et al., 2012). Consistent with a dual pathway model, antisocial adolescents with high levels of CU traits (AB+/CU+) demonstrate relatively decreased amygdala reactivity to signals of interpersonal distress such as fearful facial expressions with directed eye gaze (Jones et al., 2009; Lozier et al., 2014; Marsh et al., 2008; Viding et al., 2012). In contrast, antisocial adolescents low on CU traits (AB-/CU- ) exhibit relatively increased reactivity of the amygdala to negative emotional stimuli, particularly interpersonal signals of threat, such as angry facial expressions with directed eye gaze (Herpertz et al., 2008; Sebastian et al., 2012; Sebastian et al., 2014; Viding et al., 2012).

Though a growing literature supports a dual pathway model for AB+/CU+ versus AB-/CU- adolescents, the majority of these studies have focused on small case-control samples of those extreme on AB and CU traits. Thus, beyond a few exceptions (e.g., Viding et al., 2014), studies of adolescents have been unable to separate the relative contribution of amygdala reactivity to AB versus CU traits. As evidence continues to accumulate emphasizing the dimensional nature of AB and CU traits (Blonigen et al., 2006; Krueger et al., 2007), research is needed to test these relationships across the distribution of AB and CU traits, particularly in samples with nonclinical levels of AB. Although recent studies have begun to examine AB dimensionally in healthy and at-risk adults (e.g., Carré et al., 2013; Hyde et al., 2014), it is important to examine this question in early adolescence at the cusp of the emergence of serious AB and other psychopathology. Thus, the primary goal of our study was to examine the relationships between AB, CU traits, and amygdala reactivity to fearful and angry facial expressions in a relatively large sample of teens with variability in AB and CU traits but without diagnosable levels of AB.

1.2. Moderators of the links between AB, CU traits, and amygdala reactivity

Beyond this first goal, recent work has highlighted that several factors may moderate the relationship between AB and amygdala reactivity to interpersonal threat and distress, at least in adults. For example, in a recent study of young men, we found that participant race moderated the associations between AB, CU traits, and amygdala reactivity (Hyde et al., 2016). This study demonstrated that amygdala reactivity was related to AB in response to fearful facial expressions but only in African Americans (versus European Americans). Though these results were intriguing, the study focused exclusively on African and European American young men, and thus could not examine the extent to which sex or ethnicity (i.e., Hispanic versus non-Hispanic) may also moderate these relationships. Moreover, these recent studies have often focused on adults (e.g., Carré et al., 2013; Hyde et al., 2014) with little attention to how age or stage of puberty may also moderate these pathways, which is particularly important during adolescence. Rapid pubertal development occurs in early adolescence and results in hormonal changes that affect neural correlates of social and affective processing (Crone and Dahl, 2012), which likely result in changes in amygdala reactivity to emotional facial expressions (Hare et al., 2008). Thus, a second goal of the current study was to examine the ways in which the relationship between amygdala reactivity to emotional facial expressions and AB and CU traits may vary based on participant sex, ethnicity, pubertal timing, and age.

Finally, previous studies have focused on relationships between AB, CU traits and amygdala reactivity in adolescents with extreme, early-starting, diagnosable levels of AB. Yet, in contrast to this extreme group, many adolescents will show subclinical and/or late onset AB during adolescence (up to 25% of teens show late onset AB; Moffitt, 1993; Moffitt et al., 2002). Many of these subclinical and “late starting” adolescents will be at risk for AB because of comorbid diagnoses associated with emotional dysregulation (e.g., depression). Two factors may contribute to subclinical and later onset of AB: First, adolescence is a period in which teens are learning to control their emotions and are more impulsive (Hinshaw, 2003) and second, internalizing disorders rapidly increase in prevalence during adolescence, which can lead to AB as a result of underlying premorbid or comorbid internalizing symptoms (e.g., depression, anxiety; Hinshaw et al., 1993). However, little research has examined neural pathways to subclinical AB in adolescents at higher risk for depression, even though these youths comprise a substantial portion of the population. To address this significant gap in the literature, in the present study we also sought to examine our aims in a unique sample for this research: adolescents without diagnosable levels of AB, but with enrichment for familial risk for depression that could lead to the emergence of later AB.

1.3. Present study

The goal of the present study was to investigate relationships between amygdala reactivity and dimensional measures of AB and CU traits in a sample of adolescents with nonclinical levels of AB at the start of adolescence. We examined reactivity to fearful and angry facial expressions compared to a non-face control condition to evaluate the differential contribution of reactivity to interpersonal distress or threat, respectively. Consistent with prominent theories of AB and CU traits (Blair et al., 2014), we expected that AB would be related to increased amygdala reactivity to angry facial expressions, whereas CU traits would be uniquely related to decreased amygdala reactivity to fearful facial expressions. Finally, given previous research suggesting differential neural correlates for AB between men and women (Carré et al., 2013), as well as across race/ethnicity (Hyde et al., 2016), and research suggesting that pubertal onset may influence amygdala reactivity (Crone and Dahl, 2012), we examined these relationships in an early adolescent sample containing substantial proportions of Hispanic participants and girls during early to middle adolescence to analyze potential moderation of findings based on sex, ethnicity, pubertal timing, and age. Though sex, ethnicity and puberty based analyses were exploratory, we expected that relationships between AB, CU traits, and amygdala reactivity would be strongest in male participants and Caucasians in early stages of puberty, given that prior research in this area has focused on Caucasian boys during early adolescence (Jones et al., 2009; Sebastian et al., 2014; Viding et al., 2012). Finally, though we focused on the amygdala globally, given the different roles in fear learning, potential implications for the development of later psychopathy (Moul et al., 2012), as well as the different afferent and efferent connections of the centro-medial (CM) versus the basolateral (BL) regions (Amunts et al., 2005), we also conducted exploratory analyses within the CM versus BL sub-regions. We examined these questions in a large sample of psychiatrically healthy participants, in a sample that was enriched with adolescents with familial risk for depression (50% of the sample) and thus potentially at risk for later comorbid and emotionally dysregulated late onset AB.
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