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Disorganized Amygdala Networks in Conduct-Disordered Juvenile Offenders With Callous-Unemotional Traits

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ABSTRACT

BACKGROUND: The developmental trajectory of psychopathy seemingly begins early in life and includes the presence of callous-unemotional (CU) traits (e.g., deficient emotional reactivity, callousness) in conduct-disordered (CD) youth. Though subregion-specific anomalies in amygdala function have been suggested in CU pathophysiology among antisocial populations, system-level studies of CU traits have typically examined the amygdala as a unitary structure. Hence, nothing is yet known of how amygdala subregional network function may contribute to callous-unemotionality in severely antisocial people.

METHODS: We addressed this important issue by uniquely examining the intrinsic functional connectivity of basolateral amygdala (BLA) and centromedial amygdala (CMA) networks across three matched groups of juveniles: CD offenders with CU traits (CD/CU+; $n = 25$), CD offenders without CU traits (CD/CU−; $n = 25$), and healthy control subjects ($n = 24$). We additionally examined whether perturbed amygdala subregional connectivity coincides with altered volume and shape of the amygdaloid complex.

RESULTS: Relative to CD/CU− and healthy control youths, CD/CU+ youths showed abnormally increased BLA connectivity with a cluster that included both dorsal and ventral portions of the anterior cingulate and medial prefrontal cortices, along with posterior cingulate, sensory associative, and striatal regions. In contrast, compared with CD/CU− and healthy control youths, CD/CU+ youths showed diminished CMA connectivity with ventromedial/orbitofrontal regions. Critically, these connectivity changes coincided with local hypotrophy of BLA and CMA subregions (without being statistically correlated) and were associated to more severe CU symptoms.

CONCLUSIONS: These findings provide unique insights into a putative mechanism for perturbed attention-emotion interactions, which could bias salience processing and associative learning in youth with CD/CU+.

Keywords: Amygdala, Callous-unemotional traits, Conduct disorder, Intrinsic functional connectivity, Morphometry, Psychopathy

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Psychopathy is a serious and difficult to treat personality disorder marked by affective and interpersonal deficits, along with impulsive and antisocial behaviors. The developmental trajectory of psychopathy seemingly begins early in life and includes the presence of callous-unemotional (CU) traits (e.g., deficient emotional reactivity and empathy, callous use of others) in youths with conduct disorder (CD) (1,2). These youngsters with nascent psychopathic traits showcase a disproportionate amount of violent and antisocial acts, respond less favorably to treatment, and as such place a substantial economic and emotional burden on society (1,2). Despite these pressing concerns, the pathophysiology of CD with CU traits remains poorly understood. Studying the neurocircuitry of CU traits in CD youth may provide crucial insights into the underlying pathophysiology, ultimately informing the development of reliable biomarkers and potential therapeutic targets.

Recent neurocircuitry models suggest amygdala-centered network dysfunction in the pathophysiology and symptomatology of CU traits in adult and adolescent antisocial populations (both incarcerated and nonincarcerated) (3,4). Within these models, the amygdala is supposedly hyporesponsive to negative affective stimuli and lacks optimal functional interactions with paralimbic brain regions, leading to deficient affective reactivity (particularly to fear), biased attention modulation, and poor associative learning (3,4). Remarkably, however, few studies have actually examined the functional integrity of major amygdalar networks in relation to callous-unemotionality, producing conflicting results of both enhanced and diminished network integrity (5–10). Additionally, despite recent postulates of amygdala subregional defects in CU pathophysiology among antisocial adults and adolescents (11), system-level studies of CU traits have typically examined the amygdala as a unitary structure, disregarding the

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separable functions and connectivity profiles of its different subregions. Hence, we lack a thorough understanding of how major amygdala subregions may contribute to the development and persistence of callous-unemotionality in antisocial people.

The amygdala comprises multiple structurally and functionally distinct subnuclei, commonly grouped into the basolateral amygdala (BLA) and centromedial amygdala (CMA) complexes (12). The BLA receives information from multiple brain systems and is a site of integration with cortical areas, including those that regulate socioemotional functions (12–14). It is heavily involved in the perception, evaluation, and memory formation of emotionally salient events (11,12). The CMA, in contrast, receives mostly modulatory inputs from the BLA and orbitofrontal cortex and is less heavily innervated by sensory and associative regions (12–14). It is the primary output site of the amygdala and orchestrates behavioral and physiological aspects of emotion processing and associative learning via its projections to the brainstem, cerebellum, and hypothalamus (11,12). Critically, recent models argue that the main cognitive and affective deficits related to CU traits are possibly driven by chronic BLA hypoactivity and exaggerated CMA function, which may speculatively be reflected in BLA and CMA functional connectivity (11). Despite these speculations, little is known of how these subregional connectivity profiles may actually contribute to CU pathophysiology.

One particularly powerful method for examining BLA and CMA functional connectivity is intrinsic functional connectivity (iFC) analysis, which delineates the functional architecture of intrinsically (i.e., spontaneously) coupled brain networks (15). As such, dissociable BLA and CMA connectivity profiles were recently demonstrated in healthy adults and adolescents (16–18), consistent with earlier observations in rodents and primates (12,13). Importantly, these iFC profiles were severely disorganized in both adult and adolescent psychiatric patients with emotion-regulation deficits, suggesting impairments in various amygdala-mediated functions (19–21). Despite the reputed amygdala dysfunction in CU etiology (3,4), no study has tested whether BLA and CMA iFC profiles may similarly be disorganized in clinically antisocial people with CU traits. To date, only one study has examined BLA and CMA connectivity in relation to CU, showing increased task-based coupling of BLA with frontal and parietal systems, accompanied by decreased CMA coupling with regulatory prefrontal regions (7). This was, however, in a healthy nonforensic group of adults without marked antisocial behaviors, and the investigators used a task-based effective connectivity approach rather than iFC analysis. Hence, nothing is yet known of how the iFC of BLA and CMA networks may relate to CU traits in clinically antisocial youth.

We addressed this important issue by examining BLA and CMA iFC in a carefully selected sample of CD juvenile offenders with high levels of CU traits (CD/CU+), relative to matched control subjects. To elucidate unique contributions of CU traits, we also included a matched group of CD juvenile offenders with low levels of CU (CD/CU−). Additionally, we employed structural analyses to examine whether perturbed iFC of BLA and CMA networks coincides with altered volume and shape of the amygdaloid complex. Psychopathology seemingly involves coinciding changes in iFC and structure of amygdala subregions (20–22), as network communication and information processing depend heavily on structural properties of neurons (e.g., size, configuration, arrangement) (23). As such, conjoint examination of amygdala connectivity and structure seems crucial for a deeper understanding of CU pathophysiology in clinically antisocial populations.

Given earlier reports of subregion-specific anomalies in amygdala functionality and connectivity in relation to CU traits (7,11), one might tentatively speculate that BLA hypoactivity could result from excessive top-down control, whereas the opposite may account for exaggerated CMA function. As such, we cautiously hypothesized CD/CU+ youth to show BLA hyperconnectivity with frontal and parietal control systems, accompanied by CMA hypoconnectivity with regulatory frontal regions. Given the separable connectivity profiles of BLA and CMA with frontal areas (14), BLA hyperconnectivity was expected in both dorsal and ventral portions of the frontal cortex, whereas CMA hypoconnectivity would be limited to ventral/orbitofrontal regions. As abnormal connectivity and structure of amygdala subregions tend to accompany each other (20–22), and given earlier reports of amygdala subregional hypotrophy in relation to psychopathic traits (24,25), we also hypothesized that abnormal BLA and CMA connectivity in CD/CU+ would coincide with local hypotrophy within the amygdaloid complex. Finally, we expected that more perturbed amygdalar connectivity in CD/CU+ youth would relate to more severe CU symptoms.

METHODS AND MATERIALS

Participants

Fifty severely antisocial male juvenile offenders with a DSM-IV diagnosis of CD (mean age = 16.83 ±1.32 years) and 24 age-, IQ-, and socioeconomic status-matched healthy control male adolescents (mean age = 16.96 ± 1.29 years) were included. All participants were 15 to 19 years old and were medication free. Juvenile offenders with CD were recruited from a juvenile detention center and a forensic psychiatric facility and had all been convicted for crimes such as assault, murder, and armed robbery. Healthy control adolescents were carefully recruited through local advertisement. More details regarding participant inclusion are provided in the Supplement.

Clinical Assessment

For all juvenile offenders, DSM-IV diagnoses of CD were confirmed using the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-PL) (26). All juvenile offenders had to fulfill criteria for CD with at least one aggressive symptom (e.g., used a weapon, has been physically cruel to people). Following this, and in line with previous work (27,28), CD boys were divided into high (CD/CU+; $n = 25$) and low (CD/CU−; $n = 25$) CU traits groups, based on a median split of CD youths' total scores on the Inventory of Callous-Unemotional Traits (29) (median = 28). All CD/CU+ youths scored above, whereas CD/CU− and healthy comparison youths scored below the median. Typically, normative Inventory of Callous-Unemotional Traits total scores tend to hover around 20 to 26, with scores above 28 to 30 signaling potentially severe CU and antisocial traits (30–35). Additional