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Commentary

Amygdala Response to Fear in Boys With Conduct Problems Following Parent Training: Considering Heterogeneity

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Conduct problems (CPs) in childhood, such as conduct disorder and oppositional defiant disorder, are among the most prevalent mental health disorders in childhood and a leading cause for referral to child and adolescent mental health services (1). The 2019 Global Burden of Disease Study found that for the 0- to 14-year-old age category, CPs have now become the leading cause of burden among mental disorders, in terms of both disability-adjusted life years and years lived with disability (2). Crucially, various prospective longitudinal studies have shown that the negative outcomes observed in youth persist into adulthood and cover a similar range of domains. Importantly, the worst outcomes in adulthood are experienced by those whose CP symptoms persist (1).

These data highlight the need for research on the treatment and prevention of childhood CPs and the potential benefit of treatment for the affected individuals, their families, and society. Current clinical guidelines and meta-analytic work drawing on high-quality randomized controlled trials conducted in different countries, both in real-world settings and in highly controlled conditions, identify behavioral parent training (or parent management training) as the most optimal and cost-effective treatment for CPs in early childhood (1). There is, however, evidence that up to 50% of children with CPs do not respond to this type of intervention, a variability that is likely to result partly from the heterogeneity in the clinical presentation and the neurocognitive characteristics of children with CPs (1). Even though the past decades have witnessed an intense focus on the study of parenting programs for CPs and an explosion of neuroimaging research on this population, there is a paucity of research combining these two strands. This situation hampers progress in the understanding of the neural mechanisms underpinning treatment outcomes in CPs.

In this context, a novel study by Sethi *et al.* (3) in the current issue of *Biological Psychiatry* is a welcome addition that represents an important contribution to the field. Sethi *et al.* conducted a case-control prospective study comparing 57 boys with CPs to 36 typically developing (TD) boys (5–10 years of age) who completed 2 functional magnetic resonance imaging (fMRI) sessions (18 weeks apart) and had their antisocial behavior (ASB) assessed at each visit. Boys with CPs had been referred to a parenting intervention group, and TD boys were recruited from the same schools and geographical regions. Importantly, the boys with CPs were subdivided into 2 groups based on whether their ASB improved (n = 27) or persisted (n = 30) after the intervention. Informed by a clearly articulated neurocognitive model of CPs (4) and meta-analyses (1,5) documenting reduced amygdala response to (mostly fearful) facial expressions, Sethi *et al.* focused on the amygdala as their main region of interest. Sethi *et al.* used an implicit emotional processing task in which the participants had to identify the sex of actors displaying fearful, happy, or neutral faces. Two hypotheses were tested. First, boys with CPs would display a preintervention amygdala hyporesponse to fear, which would normalize postintervention to the level of the TD group in boys with CPs whose ASB improves, but not in those whose ASB persists (reflecting a group × time interaction driven by the improving group). Second, only those boys with CPs who exhibited persistent ASB would show an amygdala hyporesponse to fear at baseline, and this would not change following the intervention (reflecting a main effect of group driven by the persistent group). Furthermore, to explore the influence of heterogeneity in the clinical presentation of the CP group, Sethi *et al.* assessed the influence of callous-unemotional (CU) traits on their behavioral and fMRI data given evidence that CU traits 1) are a well-established risk factor for persistent ASB across the lifespan, 2) are associated with continued impairment following parent training intervention, and 3) influence amygdala response to affective stimuli (5).

Results for the clinical data in the CP group as a whole indicated that ASB, CU traits, and attention-deficit/hyperactivity disorder symptoms were all reduced after intervention. However, except for the difference in ASB observed between the responder and the persistent groups, those two groups did not differ over time in CU traits, attention-deficit/hyperactivity disorder, and externalizing symptoms (i.e., no group × time interaction). Similarly, while the hypothesis of increased amygdala response (i.e., a group × time interaction) being associated with improvement in ASB was not supported, the second hypothesis was supported. Compared with the TD group, boys with CPs whose ASB persisted showed amygdala hyporesponse to fear both preintervention and postintervention (i.e., a main effect of group driven by the persistent group).

Why are these novel findings important and how have they advanced the field? First, they provide the first evidence that amygdala hyporesponse to fear might be an important neural signature for treatment resistance in a subgroup of boys with CPs. In this respect, these findings provide further support to an important neurocognitive model of CP and its persistence (4). Second, they provide additional evidence for the neurocognitive heterogeneity within CPs in general, but particularly within those who exhibit high levels of CU traits. Indeed, recent neuropsychological data suggest that while youth with CPs as

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a group are impaired on emotion recognition, only a quarter of individuals with CPs show impaired performance (6), likely underpinned by how their brain processes facial expressions. In relation to CU traits, all 57 boys with CPs in this study had high levels of those traits (mean = 35.1) preintervention, yet nearly half of them did not show amygdala hyporesponse to fear and did respond to treatment. These fMRI and behavioral data are important for two reasons. First, the fMRI data support work indicating that there might be two distinct developmental routes (i.e., equifinality) and neurocognitive profiles leading to high CU traits in individuals with CPs, one of which might be characterized by high levels of anxiety and threat-related amygdala hyperresponse (5). Second, the fact that nearly half of the boys with high CU traits showed a significant reduction in their ASB is consistent with the findings of a recent meta-analysis of 60 studies showing that children with CPs and high CU traits do respond to treatment (7). Taken together, these data refute the belief among some researchers and clinicians that these children are resistant to treatment.

However, one important question remains: What might the mechanisms and neurocognitive correlates underpinning treatment response be? Sethi *et al.* (3) speculate that aspects of reinforcement learning targeted in parenting training might be a possible candidate, but the only other study combining fMRI and treatment data in this population did not find any association between pretreatment brain response to reward and punishment and treatment outcome (8). That study did not, however, include a posttreatment fMRI session.

There are three notable strengths of this study. First, the preintervention and postintervention scanning is necessary for identifying neural correlates of treatment outcome; this is the first study in CPs adopting this design. Second, the sample size of the CP group was large (n = 57) given the study population and the repeated assessments; the average sample size in similar studies on attention-deficit/hyperactivity disorder is n = 16 (9). Finally, the inclusion of a TD group allowed the authors to assess whether the brain response in both CP groups across time points differed in degree and nature from healthy responding. There were also limitations. First, fearful, happy, and neutral faces activate a network of regions, some of which (e.g., the insula) have been shown to be reliably associated with CP, both structurally and functionally (1,5). Therefore, while well-motivated by current theories and previous meta-analytical data, the exclusive focus on the amygdala as region of interest might be considered a missed opportunity to potentially identify other important regions for understanding socioaffiliative processes in CPs (5), which might also be associated with treatment outcome. Second, there is evidence of alteration to both functional and structural connectivity in CPs, particularly in circuits involving the amygdala and its connections to cortical regions (1). The lack of task-based functional connectivity analyses is therefore another limitation of this study. Finally, the heterogeneity within CPs in terms of clinical and neurocognitive profiles, as well as the evidence of structural and functional brain alterations in this population, means that future neuroimaging work examining predictors of treatment outcome might need to move away from the standard case-control group comparisons and instead combine multivariate statistics of multimodal neuroimaging data of individuals to understand interindividual differences (10).

CPs are associated with the highest burden in children 0 to 14 years of age and are predictive of poor outcomes in adulthood. Paradoxically, however, CPs are among the least widely recognized and studied psychiatric disorders and often go untreated, despite the availability of evidence-based treatments (1). In this context, the study by Sethi *et al.* (3) is important because it paves the way for future research examining the neural mechanisms of treatment outcome in CPs by providing preliminary data that amygdala hyporesponse to fear might partly explain why a subgroup of boys with CPs is resistant to parenting programs. Crucially, they highlight again the heterogeneity of this population, in terms of both neurocognitive profile and treatment response, with further evidence that those with high CU traits can be responsive to treatment.

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Article Information

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