Neural Responses to Affective and Cognitive Theory of Mind in Children With Conduct Problems and Varying Levels of Callous-Unemotional Traits

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Context: Reduced neural responses to others’ distress is hypothesized to play a critical role in conduct problems coupled with callous-unemotional traits, whereas increased neural responses to affective stimuli may accompany conduct problems without callous-unemotional traits. Heterogeneity of affective profiles in conduct problems may account for inconsistent neuroimaging findings in this population.

Objectives: To broaden understanding of neural processing in conduct problems using an affective processing task including an empathy component as well as to explore dimensional contributions of conduct-problems symptoms and callous-unemotional traits to variance in affective neural responses.

Design: Case-control study.

Setting: On-campus neuroimaging facility.

Participants: Thirty-one boys with conduct problems (mean age, 14.34 years) and 16 typically developing control subjects (mean age, 13.51 years) matched for age (range, 10-16 years), IQ, socioeconomic status, handedness, and race/ethnicity. Participants were recruited using screening questionnaires in a community-based volunteer sample.

Main Outcome Measures: Functional magnetic resonance imaging of a task contrasting affective and cognitive theory of mind judgments.

Results: Relative to typically developing children, children with conduct problems showed reduced activation in right amygdala and anterior insula for affective vs cognitive theory of mind judgments. Furthermore, in the right amygdala, regression analysis within the conduct-problems group showed suppressor effects between ratings of conduct problems and callous-unemotional traits. Specifically, unique variance associated with conduct problems was positively correlated with amygdala reactivity, whereas unique variance associated with callous-unemotional traits was negatively correlated with amygdala reactivity. These associations were not explained by hyperactivity, depression/anxiety symptoms, or alcohol use ratings.

Conclusions: Childhood conduct problems are associated with amygdala and anterior insula hypoactivity during a complex affective processing task including an empathy component. Suppressor effects between conduct problems and callous-unemotional traits in the amygdala suggest a potential neural substrate for heterogeneity in affective profiles associated with conduct problems.

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Conduct problems are one of the most common reasons for a childhood referral to mental health and educational services, and they represent a substantial public health cost. Callous-unemotional traits (e.g., lack of guilt and empathy) distinguish a particularly problematic and severe group of children with conduct disorder. Twin studies have suggested that conduct problems coupled with CU traits are highly heritable, while conduct problems in children without CU traits appear to be driven primarily by environmental influences. Behavioral data suggest that children with conduct problems and CU traits have difficulties processing others’ fearful and sad facial expressions and vocal tones. In
contrast, conduct problems without CU traits are associated with an exaggerated affective response to perceived social threat (eg, anger) or in some cases, even ambiguous, neutral expressions. Functional magnetic resonance imaging (fMRI) studies of children/adolescents with conduct problems with and without CU traits have indicated a functional neural basis for these differing affective behavioral profiles. One region that is hypothesized to play a key role is the amygdala, a brain region commonly activated by stimuli indicating fear or threat. Amygdala hypoactivity in adult psychopaths has been suggested to at least partially underlie emotional dysfunction in this group. Children with conduct problems and CU traits have been found to show lower amygdala activity to others’ distress (eg, fearful facial expressions) compared with typically developing children and children with attention-deficit/hyperactivity disorder (ADHD) symptoms.

Functional magnetic resonance image studies focusing on children with conduct problems more generally, without subtyping participants on the basis of CU traits, have also found amygdala hypoactivity to sad faces and emotional scenes (relative to typically developing children). However, some studies have reported hyperactivity of the amygdala in response to neutral faces, during an empathy-for-pain task, and in response to emotional pictures. Sterzer and colleagues additionally found a reduced response in the dorsal anterior cingulate cortex in children with conduct problems relative to typically developing children. It may be that greater amygdala reactivity to emotional stimuli and reduced activity in emotion regulation regions of the brain (such as the dorsal anterior cingulate cortex) represent functional neural bases for why some children with conduct problems (perhaps those with low levels of CU traits) may react aggressively, even in the face of minimal provocation.

It is possible that different patterns of amygdala activity in children with conduct problems reflect different emotional vulnerabilities in those with and without CU traits. Only 1 fMRI study has looked at both conduct disorder symptoms and CU traits dimensionally. Comparing early-onset conduct disorder, late-onset conduct disorder, and typically developing children categorically, both conduct-disorder groups showed reduced responses to anger relative to neutral faces in regions including the amygdala, anterior insula, ventromedial prefrontal cortex, and orbitofrontal cortex. Neural responses to emotional faces (relative to neutral) within the conduct-disorder group did not correlate with either conduct disorder symptoms or CU traits, although unique contributions of conduct disorder symptoms and CU traits (controlling for the effects of the other variable) were not explored.

While several fMRI studies have looked at basic affective processing (emotional vs nonemotional scenes/facial expressions) in children with conduct problems, only 1 study has used fMRI to investigate neural correlates of more complex affect-laden processes including empathy for pain. This study found increased activation in the amygdala and striatum in boys with conduct disorder relative to control subjects when viewing accidental painful scenarios vs nonpainful situations. It was suggested that this may reflect increased enjoyment/arousal or reduced regulation of arousal in the face of others’ pain. Within the conduct-disorder group, there was a positive correlation between the amygdala’s response to pain and parent-reported scores of sadism, aggression, and daring.

Our study aimed to further elucidate neural correlates of conduct problems. First, we used a complex emotion processing task that included an empathy component to expand the currently small literature on neural processing of high-level socioaffective cognition in this group. A cartoon vignette paradigm was chosen contrasting affective theory of mind (ToM) (understanding emotions) with cognitive ToM (understanding intentions). An advantage of this task is that it indexes complex cognitive processing without relying on reading ability. Previous studies have found that children with conduct problems and adults with psychopathy show no impairment on tests of cognitive ToM. In contrast, adult psychopaths have shown impairment on tasks of affective ToM, a process thought to require the integration of cognitive ToM and empathy, which necessarily relies on the processing of basic affective cues. Because reduced empathy is a well-documented feature of childhood conduct problems, we predicted that children with conduct problems would show differential neural processing of affective ToM (relative to cognitive ToM) compared with typically developing children.

Second, we investigated the role of conduct problems and CU traits as dimensional variables within the conduct-problems group only. It was hypothesized that inconsistency characterizing previous studies of amygdala reactivity in children with conduct problems may be partly accounted for by differential independent contributions of conduct problems and CU traits. Suppressor effects occur when the inclusion of 2 correlated predictor variables in the same regression model increases the association between 1 or both of these variables and the dependent variable. In situations where suppressor effects occur, shared variance between predictors masks the unique association of each predictor with the dependent variable. When this shared variance between correlated predictors is suppressed, this leaves each enhanced variable (reflecting unique variance) as a more efficient predictor of the dependent variable. Behavioral studies have shown conduct problems to be positively correlated with emotional reactivity, and CU traits to be negatively correlated with emotional reactivity; however, these associations increase when the effect of the other variable (CU traits and conduct problems, respectively) is controlled for (ie, CU traits and conduct problems exert suppressor effects on one another). The neural basis of this effect has not been tested, but on the basis of previous behavioral studies, we predicted suppressor effects between conduct problems and CU traits, with unique variance associated with each of the 2 variables emerging as significant (and potentially opposing) predictors of neural response in regions commonly engaged in empathy processing including the amygdala and anterior insula.
PARTICIPANTS

Boys aged 10 to 16 years were recruited from the community via newspaper advertisements and local schools. Screening questionnaires were administered to parents and teachers of 176 boys whose families expressed an interest in taking part and provided informed consent; they were scored by a trained research assistant according to standard published guidelines. These yielded a research diagnosis of current conduct problems; dimensional assessment of CU traits; an overall psychopathology screen; demographic data for group-matching purposes (ie, socioeconomic status, parent-defined ethnicity, and handedness); and information regarding previous neurologic or psychiatric diagnoses. Current conduct problems were assessed using the Child and Adolescent Symptom Inventory–4R (CASI-4R)\(^23\) and Child and Adolescent Symptom Inventory–Conduct Disorder (CASI-CD) subscale, and CU traits were assessed using the Inventory of Callous-Unemotional Traits (ICU).\(^26\) Both were scored by taking the highest ratings from either the parent or the teacher questionnaire for any given item.\(^2\) The Strengths and Difficulties Questionnaire\(^28\) was used as a brief screening measure for psychopathology in the typically developing control group.

Participants were invited to take part in the fMRI phase of the study based on screening information. Child and Adolescent Symptom Inventory–Conduct Disorder subscale symptom severity scores were used to make the research diagnosis of current conduct problems. Symptom severity cutoff scores for inclusion in the conduct-problems group were 3 or higher (ages 10-14 years) and 6 or higher (ages 15-16 years). Scores of this magnitude and greater are associated with a clinical diagnosis of conduct disorder,\(^4\,9\) with an agreement between the screening cutoff scores for CASI-CD (completed by both parent and teacher) and clinical diagnoses of 0.95 for sensitivity and 0.56 for specificity. Further reliability and validity information for the CASI and ICU is provided in the eAppendix and eTable 1 (http://www.archgensychiatry.com). There were no restrictions on ICU score for the conduct-problems group. Typically developing control participants were matched to conduct problems participants on verbal/performance IQ, age, handedness, race/ethnicity, and socioeconomic status, but they were scored in the normal range for the CASI-CD and on each Strengths and Difficulties Questionnaire subscale. All control participants also scored less than the conduct-problems group median (45) on the ICU. For both groups, automatic exclusion criteria included a previous diagnosis of any neurologic or psychiatric disorder or a current prescription for psychiatric medication.\(^3\) To recruit a representative group of children with conduct problems, common comorbidities (ADHD, generalized anxiety disorder [GAD], depression, and substance/alcohol abuse) were not used as exclusion criteria, but current parent-reported symptom counts were obtained during MRI sessions using the CASI-4R so that their possible contribution to the findings could be systematically assessed.

After a complete description of the study was provided to participants, written informed consent from parents and written assent from participants were obtained. We scanned a total of 55 children (38 with conduct problems and 17 typically developing control participants), yielding a final sample of usable data from 31 boys with conduct problems and 16 control participants (there were exclusions owing to excessive motion [5 boys with conduct problems]; scanner refusal [1 with conduct problems]; technical problems [1 with conduct problems]; and task error rates >3 SDs more than group/condition means [1 control subject]); see Table 1 for participant demographics. All aspects of the study were approved by the University College London research ethics committee (project identifier: 0622/001).

EXPERIMENTAL TASK

Stimuli were 30 cartoons previously validated with adolescents in an fMRI setting:\(^2\) 10 each of affective ToM, cognitive ToM, and physical causality (PC). Each cartoon consisted of 3 frames telling a story and 1 final screen with 2 choices of ending (eFigure). Participants were asked to decide the appropriate ending. Each cartoon scenario portrayed 2 people to control for social content. For affective ToM cartoons, selection of the correct ending required participants to infer how 1 story character would react to their companion’s affective state. For cognitive ToM cartoons, selection of the correct ending required an inference based on the intentions or beliefs of 1 story character and their companion. For PC cartoons, an understanding of cause and effect (eg, sunshine melting snow) was required, but no understanding of mental states was required. Each trial (cartoon) lasted 15 seconds; after every sixth trial (2 cartoons from each condition, with the order of presentation randomized across participants), a fixation cross was presented for 15 seconds. Each trial consisted of an instruction screen for 3 seconds (“What happens next?”), followed by 3 story frames, each presented for 2 seconds (6 seconds in total). The choice of 2 endings was then displayed for 3 seconds. During this interval, the participant selected an ending using a key press response. There was then an interstimulus interval of 1 second.

PSYCHOMETRIC AND QUESTIONNAIRE MEASURES

Participants selected for fMRI scanning completed the Wechsler Abbreviated Scale of Intelligence\(^20\) 2-subtest version for group matching purposes, as well as the Alcohol Use Disorders Identification Test (AUDIT)\(^31\) and the Drug Use Disorders Identification Test,\(^32\) which are brief pen-and-pencil screening measures developed by the World Health Organization. A parent or guardian also completed the CASI-4R scales for ADHD, GAD, and major depressive episode (MDE) to ascertain symptom counts for disorders most commonly comorbid with conduct problems (Table 1).

IMRI DATA ACQUISITION

A Siemens Avanto 1.5-T MRI scanner was used to acquire a 5.5-minute 3-dimensional T1-weighted structural scan and 184 multislice T2-weighted echo planar volumes with blood oxygenation level–dependent contrast (1 run of 9 minutes). The echo-planar imaging sequence was designed to optimize signal detection and reduce dropout in the orbitofrontal cortex and amygdala,\(^33\) and it used the following acquisition parameters: 35 2-mm slices acquired in an ascending trajectory with a 1-mm gap; echo time = 50 milliseconds; repetition time = 2975 milliseconds; slice tilt = −30° (t > C); flip angle = 90°; field of view = 192 mm; matrix size = 64 × 64. Fieldmaps were also acquired for use in the unwarping stage of data preprocessing.

IMRI DATA ANALYSIS

Imaging data were analyzed using Statistical Parametric Mapping software (SPM version 8; http://www.fil.ion.ucl.ac.uk/spm). Data preprocessing followed a standard sequence: the first 5 volumes were discarded and data were realigned, unwarped using a fieldmap, normalized with a voxel size of 2 × 2 × 2 mm, and smoothed with an 8-mm Gaussian filter. A
RESULTS

TASK BEHAVIORAL DATA

Mean reaction time and error data are displayed in eTable 2. For reaction times, a group (conduct problems vs con-
However, there was no main effect of condition with marginally faster reaction times in the control group.

In the typically developing control group relative to the conduct-problems group (coordinates 24, −12, −10; coronal overlays show y coordinates) (A) and the right anterior insula (coordinates 32, 16, 10) (transversal overlays show z coordinates) (B). Error bars are plotted relative to baseline fixation for display and do not allow inference with respect to baseline fixation. Overlays are displayed for SVC (based on the procedure outlined in the “Methods” section) were 24, −5, −13 and 32, 16, 10 for the anterior insula. At the whole-brain level, comparing the conduct-problems group with the control group on this contrast yielded no significant responses at $P < .05$, FWE cluster-level corrected. None of the other contrasts of interest (cognitive ToM greater than affective ToM, affective ToM greater than PC, and cognitive ToM greater than PC) yielded any group differences, either at the whole-brain level or using SVC.

In regions showing a group difference for the affective ToM greater than cognitive ToM contrast (right amygdala and anterior insula), regression analyses within the conduct-problems group were conducted to investigate the degree of association between dimensional measures of conduct problems (CASI-CD scores), CU traits (ICU scores), and peak voxel contrast estimates for affective ToM greater than cognitive ToM. Variables of interest (CASI-CD and ICU scores) were entered together at the first stage. Also, CASI-ADHD, CASI-GAD, CASI-MDE, and AUDIT scores were entered at the second stage to assess whether these variables influenced the association between CASI-CD or ICU and variance in neural responses.

Within the amygdala, suppressor effects were found between CASI-CD and ICU scores (Figure 2). In line with the literature on CU traits and in keeping with the accepted definition of suppressor effects, CASI-CD and ICU scores were correlated with each other ($r = 0.49$, $P = .006$). Bivariate correlations between each of these variables and amygdala response were not significant (for CASI-CD: $r = 0.21$, $P = .25$; for ICU: $r = -0.32$, $P = .08$). However, unique variance associated with CASI-CD after controlling for ICU positively predicted amygdala response ($P = .02$; see Table 2 for model results), while unique variance associated with ICU after controlling for CASI-CD negatively predicted amygdala response ($P = .008$). Including CASI-ADHD, CASI-
GAD, CASI-MDE, and AUDIT could not explain these effects (for CASI-CD, \( P = .04 \); for ICU, \( P = .08 \) [marginal]), and none of these variables made a significant independent contribution to variance in amygdala response (all \( P > .10 \)). Neither bivariate correlations or regression analyses showed significant associations between any independent variable and anterior insula response.

To explore the specificity of these effects, whole-brain regression analyses were conducted within the conduct-problems group; first including CASI-CD and ICU scores as individual regressors and then including both within the same model. When entered as individual regressors, no region showed a positive or negative relationship with either CASI-CD or ICU scores at a cluster-corrected threshold or in a priori predicted regions. When both were included in the model, the only region showing a positive relationship with CASI-CD scores and a negative relationship with ICU scores (the pattern of suppressor effects seen in the peak voxel analyses) was a single voxel in the right amygdala/parahippocampal gyrus border that survived SVC at \( P < .05 \), FWE (coordinates 24, \(-12\), \(-10\); adjacent to the peak voxel used above). No regions showed the reverse pattern (ie, a negative relationship with CASI-CD scores and a positive relationship with ICU scores).

**COMMENT**

Our study extends our understanding of neural processing in conduct problems. First, we replicated the finding of low amygdala reactivity to affective compared with nonaffective stimuli in children with conduct problems\(^{11,12,14}\) using a more complex affective task than has been used previously. Reduced activation during affective ToM in the conduct-problems group relative to the typically developing control group was also seen in the right anterior insula, a region commonly activated during tasks requiring empathy\(^{20}\) and also previously implicated in the functional pathophysiology of conduct problems.\(^{17}\) Second, we explored conduct problem symptoms and CU traits as dimensional variables within our conduct-problems group, and we demonstrated independent and contrasting contributions of conduct problems symp-

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**Table 2. Multiple Regression Results Showing Conduct Problem Symptoms and CU Traits as Unique Predictors of Amygdala Response to Affective Greater Than Cognitive ToM in the Conduct-Problems Group**

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>Standard Error of B</th>
<th>( \beta )</th>
<th>t</th>
<th>( P ) Value</th>
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<tr>
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<td></td>
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<tr>
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<td>0.50</td>
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<tr>
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<td>0.16</td>
<td>0.72</td>
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</table>

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AUDIT, Alcohol Use Disorders Identification Test; CASI, Child and Adolescent Symptom Inventory; CD, conduct disorder; CU, callous-unemotional; GAD, generalized anxiety disorder; ICU, Inventory of Callous-Unemotional Traits; MDE, major depressive episode; ToM, theory of mind.

\(^a\) \( P < .05 \).
toms and CU traits on amygdala response. The finding of suppressor effects between conduct problems and CU traits at the neural level may go some way toward explaining previously inconsistent findings of both hypoactivation and hyperactivation of the amygdala in children with conduct problems.

Affective ToM (understanding others’ emotions) is hypothesized to require cognitive ToM (understanding intentions and beliefs) and empathy (which relies on the processing of basic affective cues).19 Compared with typically developing control children, children with conduct problems showed reduced right amygdala and anterior insula activity to affective ToM relative to cognitive ToM, despite there being no differences in behavioral performance between groups. In both regions, this was driven by a significantly greater neural response to affective vs cognitive ToM in typically developing control children, but no difference between conditions in the conduct-problems group. The amygdala data are consistent with previous observations of hypoactivation of this structure in response to visually salient stimuli (emotional faces and scenes) in children with conduct problems.11,12,14 However, our findings suggest that this atypical response pattern is also evident when children with conduct problems process more abstract affective information requiring narrative inference. This could reflect failure to appropriately process emotionally salient cues present in these scenarios, such as facial expressions of distress and concern or comforting body postures signifying empathy.

The group difference in the anterior insula is consistent with previous observations of an empathy deficit in conduct problems (particularly in the presence of high CU traits).18 The present finding is also in line with a previous fMRI study,13 which found a reduced response in the left anterior insula in adolescents with conduct disorder in response to angry faces relative to neutral faces, as well as another study that observed an association between anterior insula volume and empathy in conduct problems.37 Findings are also consistent with behavioral reports of spared cognitive ToM abilities in conduct problems despite affective-processing deficits.18,19

On the basis of inconsistent findings with regard to amygdala activity in previous studies11,12,15,16 and suppressor effects between conduct problem symptoms and CU traits at the behavioral level,22,23 our second aim was to investigate dimensional contributions of conduct problem symptoms and CU traits to variance in the neural processing of affective stimuli in children with conduct problems. We found that unique variance associated with conduct problems was positively related to amygdala response to affective ToM scenarios after controlling for CU traits, while unique variance associated with CU traits was negatively related to amygdala response after controlling for conduct problem symptoms. Because neither conduct problems nor CU traits were significantly related to amygdala activity in zero-order correlation analyses, this is suggestive of suppressor effects between conduct problems and CU traits at the neural level. Other indicators of psychopathology commonly comorbid with conduct problems did not drive these relationships. Interestingly, the dimensional associations found in the amygdala did not hold for the anterior insula.

Although 4 task contrasts of interest were conducted at the second level, only 1 (affective ToM greater than cognitive ToM) yielded group differences at the corrected whole-brain level or in small-volume–corrected regions of interest. Given previous evidence suggesting spared cognitive ToM abilities in children with conduct problems and high levels of CU traits,18 it is perhaps unsurprising that group differences were not found for cognitive ToM greater than affective ToM. However, it might be predicted that affective ToM greater than PC should yield similar group differences as affective ToM greater than cognitive ToM. Indeed, at a lower threshold, activations in the amygdala and anterior insula were seen for both contrasts. However, the PC condition is not as well matched a control condition for affective ToM and may have provided a more noisy contrast than cognitive ToM. However, the PC condition demonstrated that both cognitive and affective ToM cartoons reliably engage the ToM network.

There were some limitations to our study. Our sample was recruited from a community setting and had a research diagnosis of conduct problems. It would be important to replicate these findings with children who have a clinical diagnosis of conduct disorder. This study also focused only on boys; it will clearly be important to systematically investigate neural correlates associated with conduct problems in girls. Additionally, 5 participants in the conduct-problems group were excluded owing to excessive motion in the scanner, while no typically developing children were excluded for this reason. Inspection of demographic and behavioral data revealed no obvious differences between the excluded participants and the experimental sample of conduct-problems participants. Therefore, it is unlikely that these exclusions systematically biased our collected data. In terms of the experimental task, our study cannot disambiguate which component (or components) of empathy processing might be driving the group differences in the amygdala and insula (eg, basic processing of affective cues, emotional contagion, more conscious affect sharing, or speed of habituation to distress cues). Future studies should aim to disambiguate these processes. Importantly however, we have established that affective-processing abnormalities in the conduct-problems population, previously demonstrated with only basic stimuli (eg, cropped faces), are also elicited by a more ecologically valid task representing the type of complex affective scenario encountered on a daily basis. Finally, it is unclear why anterior insula response to affective ToM scenarios was not related to CU traits or conduct problem symptoms within the conduct-problems group, despite the observed group difference. Further study is needed to determine the relationship between CU traits, conduct problems, empathy, and anterior insula response in individuals with conduct problems.

This study also had a number of strengths. Our findings consolidate and extend previous studies, demonstrating that conduct problems in children are associated with amygdala and anterior insula hypoactivity during a complex affective-processing task including an
empathy component. In addition, suppressor effects were found between CU traits and conduct problem symptoms in relation to amygdala activity, suggesting a potential neural substrate for the heterogeneity in affective profiles associated with conduct problems. From a theoretical perspective, this may help account for inconsistency in amygdala reactivity reported in previous studies of children with conduct problems. From a clinical perspective, this finding adds further weight to the view that the conduct-problems population is heterogeneous, comprising distinct subgroups characterized by different neurocognitive vulnerabilities. Preliminary evidence indicates that levels of CU traits may have implications for treatment response.38 Our data suggest that variance unique to CU traits is associated with reduced affective responding to affective social scenarios. Therefore, it is possible that high CU traits could influence response to standard components of treatment for conduct disorder, particularly victim empathy work and social skills training. In our view, more routine evaluation of CU traits population is heteroge-

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Online-Only Material: The eAppendix, eTables, and eFigure are available at http://www.archgenpsychiatry.com.

REFERENCES