Atypical empathic responses in adolescents with aggressive conduct disorder: A functional MRI investigation

Jean Decety, Kalina J. Michalska, Yuko Akitsu, Benjamin B. Lahey

Because youth with aggressive conduct disorder (CD) often inflict pain on others, it is important to determine if they exhibit atypical empathic responses to viewing others in pain. In this initial functional magnetic resonance imaging (fMRI) study, eight adolescents with aggressive CD and eight matched controls with no CD symptoms were scanned while watching animated visual stimuli depicting other people experiencing pain or not experiencing pain. Furthermore, these situations involved either an individual whose pain was caused by accident or an individual whose pain was inflicted on purpose by another person. After scanning, participants rated how painful the situations were. In both groups the perception of others in pain was associated with activation of the pain matrix, including the ACC, insula, somatosensory cortex, supplementary motor area and periaqueductal gray. The pain matrix was activated to a significantly greater extent in participants with CD, who also showed significantly greater amygdala, striatal, and temporal pole activation. When watching situations in which pain was intentionally inflicted, control youth exhibited signal increase in the medial prefrontal cortex, lateral orbitofrontal cortex, and right temporo-parietal junction, whereas youth with CD only exhibited activation in the insula and precentral gyrus. Furthermore, connectivity analyses demonstrated that youth with CD exhibited less amygdala/prefrontal coupling when watching pain inflicted by another than did control youth. These preliminary findings suggest that youth with aggressive CD exhibit an atypical pattern of neural response to viewing others in pain that should be explored in further studies.

1. Introduction

Conduct disorder (CD) is a serious mental disorder of childhood and adolescence that is characterized by a longstanding pattern of violations of rules and laws. Symptoms of CD include physical aggression, manipulative lying, theft, forced sex, bullying, running away from home overnight, and destruction of property. CD is a major public health problem because youth with conduct disorder not only inflict serious physical and psychological harm on others, but they are at greatly increased risk for incarceration, injury, depression, substance abuse, and death by homicide and suicide themselves (Loeber et al., 1998). Furthermore, CD is important because it is the major childhood precursor to antisocial personality disorder in adulthood (Lahey et al., 2005). Thus there is a pressing need to understand the biopsychological processes at multiple levels of analysis that give rise to CD. Biological studies of CD should lead to new approaches to its treatment, both by understanding the mechanisms underpinning CD and by matching treatments to specific deficits in different individuals with this heterogeneous disorder (Van Goorzen and Fairchild, 2008).

Empathy, the capacity to understand and appreciate the emotional states and needs of others in reference to oneself, has been one psychological characteristic repeatedly proposed as a core deficit in CD (Lovett and Sheffield, 2007 for a review). Here we consider empathy as a construct accounting for a sense of similarity in feelings experienced by the self and the other, without confusion between the two individuals (Batson et al., 1987; Decety and Batson, 2007; Decety and Jackson, 2004; Decety and Moriguchi, 2007; Eisenberg et al., 2006). The experience of empathy can lead to sympathy or empathetic concern for another based on the apprehension or comprehension of the other’s emotional state or condition, but empathy can also lead to personal distress, i.e., an aversive, self-focused emotional reaction to the
emotional state or condition of another (Batson et al., 1987; Decety and Lamm, in press; Eisenberg and Eggum, in press; Lamm et al., 2007a). Interestingly, some developmental psychologists have hypothesized that empathy and sympathetic concern for others are essential factors inhibiting aggression toward others (Eisenberg, 2005; Hoffman, 2000). Empathy may be regarded as a proximate motive motivating prosocial rather than antisocial behavior (Batson, 1991). It is commonly defined as an affective reaction that is appropriate to someone else’s situation rather than one's own. Some researchers have theorized that there should be a relation between aggressive behavior and a lack of empathy (e.g., Zahn-Waxler et al., 1995). Similarly, other scholars have proposed that lack of sympathy (callous disregard for the welfare of others) is an important risk factor for CD (Frick et al., 2005; Lahey and Waldman, 2003).

The propensity for aggressive behavior has been hypothesized to reflect a blunted empathic response to the suffering of others (Blair, 2005). Such a lack of empathy in aggressive individuals may be a consequence of a failure to be aroused by the distress of others (Raine et al., 1997). Similarly, it has been suggested that aggressive behavior arises from abnormal processing of affective information, resulting in a deficiency in experiencing fear, empathy, and guilt, which in normally developing individuals inhibits the acting out of violent impulses (Davidson et al., 2000; Herpertz and Sass, 2000). Consistent with this hypothesis, one functional MRI study found reduced left amygdala response in 13 adolescents with CD in response to the visual presentation of pictures with strong negative emotional valence compared to 14 control adolescents (Strezler et al., 2005).

However, an alternative hypothesis regarding the relation between affect and aggression also can be drawn from previous research that has shown that negative affect is generally positively associated with aggression (Anderson and Bushman, 2002; Berkowitz, 2003), suggesting that empathic mimicry in conjunction with poor emotion regulation might produce negative affect that increases aggression (Campbell, 1990; Gill and Calkins, 2003). For instance, there are many empirical studies that document that physical pain ofteninstigates aggressive inclinations (Berkowitz, 1983, 1993). This is particularly interesting in the light of recent work in cognitive neuroscience of empathy for pain.

Indeed, a growing number of functional magnetic resonance imaging (fMRI) studies have demonstrated striking similarities in the neural circuits involved in the processing of both the first-hand experience of pain and the experience of observing other individuals in pain (Jackson et al., 2006a). These studies have consistently shown that the perception of pain in others elicits activation of the neural circuit subserving the processing of the affective and motivational dimension of pain in oneself (Botvinick et al., 2005; Cheng et al., 2007; Gu and Han, 2007; Jackson et al., 2005, 2006b; Lamm et al., 2007a; Moriguchi et al., 2007; Morrison et al., 2004; Saarela et al., 2007; Singer et al., 2004; Zaki et al., 2007). This circuit includes the dorsal anterior cingulate cortex (ACC), the anterior midcingulate cortex (aMCC), the supplementary motor area (SMA), and anterior insula (Derbyshire, 2000; Price, 2000). In addition, somatosensory-evoked potentials (Bufali et al., 2007), magnetencephalography (Cheng et al., 2008) and fMRI studies (Cheng et al., 2007; Lamm et al., 2007b; Moriguchi et al., 2007a) have demonstrated that areas processing the sensory dimension of pain (posterior insula/somatosensory cortex) may also be elicited by the visual perception of pain in others.

Recently, one functional MRI study investigated empathy and intentionality in typically developing middle-school children (Decety et al., 2008) while they watched dynamic visual stimuli depicting either a person whose pain was accidentally caused or a person whose pain was intentionally inflicted by another individual. Interestingly, when watching a person inflicting pain on another, regions that are engaged in representing social interaction and moral behavior including the tempo-parietal junction, the paracingulate, orbital medial frontal cortices, and amygdala (Moll et al., 2003, 2007) were additionally recruited, and increased their connectivity with the frontoparietal attention network.

There also is evidence that specifically associates the amygdala with paralimbic prefrontal regions, including the dorsal and ventral/orbital medial prefrontal cortex (dMPFC and vMPFC/OFC, respectively), with human aggression (Coccaro et al., 2007; Davidson et al., 2000). In humans, amygdala atrophy and/or lesions have been associated with impulsively aggressive behaviors (van Elst et al., 2000). Specific damage to the OFC is associated with impulsive and aggressive behavior, and individuals with such damage show little control over their emotions as well as limited awareness of the moral implications of their actions (Anderson et al., 1999; Grafman et al., 1996). Since the amygdala and OFC are anatomically and functionally connected (Amaral and Price, 1984), their interactions may be critical for interpreting emotionally significant information and guiding goal directed behaviors (Saddoris et al., 2005). Furthermore, the OFC is hypothesized to play a key role in modulating limbic reactivity to threat (Davidson et al., 2000; Izquierdo et al., 2005), and in general is important for the interpretation of social cues.

Thus, there is evidence that perceiving others in pain triggers an automatic somatic and sensorimotor resonance between other and self, which activates almost the entire neural pain matrix including the periaqueductal gray (PAG) which is a major site in pain transmission and for processing fear and anxiety (Jenck et al., 1995), the SMA that programs defensive skeletalmotor impulses to avoid the stimulus in the context of nociceptive information (Morrison et al., 2006), and thalamus. Such a mechanism provides a functional bridge between first person and third person information, which allows for analogical reasoning, and offers a possible, yet partial, route to understanding others (Decety and Sommerville, 2003; Decety and Grèzes, 2006). It also provides a clear signal of the other’s distress that usually inhibits aggressive behavior.

So far, there is no published work on how youth with CD react to viewing others in pain. If the blunted empathic emotional response hypothesis is correct, adolescents with aggressive CD should react less to stimuli depicting others in pain than healthy controls. Furthermore, this lack of signal from the pain matrix and amygdala could account for impairment in recognizing information about the distress of others. If the pain-aggression hypothesis is correct, however, youth with aggressive CD should exhibit greater activation than healthy controls in the amygdala, PAG, and related areas in response to stimuli depicting others in pain. This strong activation of structures subserving negative emotion and less functional amygdala/OFC connectionedness could reflect a general tendency to experience personal distress that elicits aggression in some circumstances.

Including a condition in which pain is intentionally inflicted onto another allows us to examine the respective contribution of mechanisms that contribute to theory of mind and moral reasoning in the context of pain perception (Decety et al., 2008). This is particularly interesting to investigate with respect to antisocial behavior given that these individuals have been reported to lack guilt and empathic concern.

2. Methods and materials

2.1. Participants

Two groups of 16–18-year-old adolescents (exactly matched on age, sex, and race-ethnicity) were scanned. The participants were purposively selected from a 9-year longitudinal study of 127 adolescents with attention-deficit/hyperactivity disorder and a matched healthy comparison group of 125 youth (Lahey et al., 2005).
The study included eight structured diagnostic assessments of CD using the DSM-IV field trials version of the Diagnostic Interview Schedule for Children (Lahey et al., 1994; Shaffer et al., 1993) conducted over 9 years beginning at 4–6 years of age. Information on symptoms of the disruptive behavior disorders was obtained from teachers using the DSM-IV version of the DBD Checklist (Pelham et al., 1992). Beginning in the sixth annual assessment, the DISC was also administered to the youth. Youth were considered to exhibit each symptom if any informant reported it (Placeltini et al., 1992).

In the sixth annual assessment, parents also completed the Child and Adolescent Dispositions Scale (CADS, Lahey et al., 1998), which quantifies three socioemotional dispositions. Prosociality is defined by sympathetic concern for others, helping and sharing, respect for social rules, and guilt over misdeeds. It is similar to Eisenberg’s construct of dispositional sympathy (Eisenberg et al., 1989), which is inversely related to CD. Many prosociality items can also be viewed as the inverse of items defining the callous-unemotional trait (Frick et al., 2005). Daring is defined by the descriptors of daring, brave, and adventurous, and by enjoyment of risky and loud activities and rough games and sports. It is based on Farrington and West’s (1993) observation that parent ratings of the single item of ‘daring’ during childhood was a robust predictor of future criminal offending and is similar to the construct of sensation seeking, which is correlated with CD (Russo et al., 1993). Children rated high on negative emotionality are easily and intensely upset by frustrations, threats, and losses.

An ad hoc measure of sadism was created from items that did not factor onto the three main factors of the CADS. The sadism measure was composed of the items: enjoys bothering or hurting other children, thinks it’s funny when other children are upset; likes to scare other children, and thinks it would be fun to watch two dogs fight.

### 2.2. Experimental groups

The eight adolescents in aggressive CD group were recruited from the adolescents in the sample with the most persistent and aggressive histories of CD over the 9 years. In eight assessment over 9 years, they met criteria for DSM-IV CD 1–7 times (mean = 2.25) and exhibited a total of 2–18 aggression symptoms (fear of fights; bullying using a weapon; theft with confrontation of the victim; physical cruelty to people; cruelty to animals and forced sex) (mean = 7.2). All of the youth who met criteria for CD exhibited at least one CD symptom at age 4–6 years indicating that they all met DSM-IV criteria for childhood-onset CD. In contrast, the comparison group was selected to be eight adolescents who never exhibited any symptoms of CD or aggression during any of the eight assessments and who matched the CD youth in age, sex, and race-ethnicity.

There was a significantly greater prevalence of DSM-IV attention-deficit/hyperactivity disorder (ADHD), with the diagnosis requiring impairment in at least one setting, among the youth with CD (88%) than among the healthy controls (25%), $\chi^2 (d.f. = 1, n = 16) = 6.35, P > .05$. This is to be expected because the adolescents in this study all exhibited childhood-onset CD, which is almost always comorbid with ADHD (Lahey et al., 1998). Thus, when studying childhood-onset CD, it is always possible that any group differences actually reflect the nearly ubiquitous ADHD symptoms that accompany childhood-onset CD.

Parental written informed consent and adolescent oral assent (or consent if 18 years old) were obtained. Participants were paid for their participation. The study was approved by the University of Chicago Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

### 2.3. Stimuli preparation and validation

The task consisted of the successive presentation of animated visual images of hands and feet in blocks depicting painful and non-painful situations (NPSs). A series of 96 stimuli were created and validated for this study. Validation of the material was conducted with a group of 222 healthy male and female participants (age range 12–38 years; middle school to college educated) who were shown these dynamic stimuli and asked to estimate how painful these situations were and whether they believed that the pain was caused intentionally. Each animation consisted of three digital color pictures, which were edited to the same size (600 x 480 pixels). The durations of the first, second and third pictures in each animation were 1000 ms, 200 ms and 1000 ms, respectively. These animated stimuli contained scenes of various types of painful and non-painful everyday situations.

Each animation displayed one or two persons whose right hands or right feet were visible but not their faces (see Fig. 1). When presented, the two people were distinguished from another in clothing or shoe type. These 96 stimuli belonged to four categories (24 each) of pain and involved person types, including:

1. Only one person is in a painful situation caused by accident, e.g., a person dropping a heavy bowl on her hand (PCA, pain caused by accident).
2. Only one person is in a non-painful situation, e.g., opening a door (NPS, no pain situation).

![Fig. 1. Selective activation of the ACC, amCC and PAG overlaid on a sagittal MRI section of the MNI brain when control participants and participants with CD observed dynamic visual stimuli that depict painful situations caused by accident (a) compared with non painful situations (b).](https://biographies.gmodeljournal.org/)

3. One person is in a painful situation caused by another, e.g., stepping purposely on someone’s toe (PCO, pain caused by other).

4. One person is in a painful situation at first but this pain is alleviated by the other, e.g., helping another get his or her hand out of a door (APD, alleviated pain by other).

2.4. Training in the mock scanner

Prior to MRI scanning, adolescents were acclimated to the procedures in a mock scanner. The mock scanner was played (Jacques Cousteau’s Pacific Explorations). When the adolescents felt comfortable, they were presented with 24 stimuli (six per condition) depicting situations similar to, but not the same as, those they would watch in the actual scanning sessions. MRI noise was simulated through a recording played during the mock session, which lasted approximately 10–15 min with their parents in the room.

2.5. Scanning session

Stimuli were presented with E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA) and a back-projected system. A block-design paradigm was used with nine baseline blocks (duration 17.6 s each) during which a fixation cross was presented and eight active blocks (duration 19.8 s each) during which stimuli from one of the four categories were presented. The presentation order was counterbalanced across runs and across subjects. Each block consisted of six stimuli (2200 ms each) with five inter-stimulus intervals (1100 ms each) during which a black fixation cross was presented against a gray background. Adolescents were shown the stimuli in two short sessions (6 min each) to maintain their attention. To avoid confounding motor-related activations in the ACC and pre-SMA/SMA, no overt response was required. Instead, adolescents were instructed to watch the stimuli carefully.

Magnetic resonance imaging was performed on a GE 3 T magnet (Horizon LX). Functional images were obtained using T2*-weighted gradient echo spiral in/out pulse sequence (Glover and Lai, 2001). Thirty-six coronal slices of 5 mm slice thickness without spatial gap were obtained for 160 repetitions (including 16 discarded acquisitions at the onset of each of two runs) using the following parameters: TR = 2200 ms, TE = 26 ms, flip angle = 81°, FOV = 24 cm, matrix = 64 × 64, and in-plane resolution = 3.75 × 3.75 mm. The spiral-in/out sequence was shown to be effective in recovering blood oxygenation level-dependent (BOLD) signal in frontal regions important to this study (Preston et al., 2004). An axial T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (MP-RAGE) anatomical scan was also acquired for 3D localization (TR = 8 ms, TE = 3.2 ms, flip angle = 6°, FOV = 24 cm, matrix = 256 × 192, slice thickness = 1.5 mm, 124 slices).

2.6. Image processing and analysis

Image processing was carried out with SPM5 (Wellcome Department of Imaging Neuroscience, London, UK), implemented in MATLAB 7.0 (Mathworks Inc.). Sherborne, MA, USA, with multiple regression analysis of expected signal changes for each of the four block categories, which were constructed using the hemodynamic response function (HRF) provided by SPM5, was applied to the preprocessed images for each subject.

Individual subject data were analyzed using a fixed-effects model. Group data were analyzed using a random-effects model using one-sample t-tests. Condition effects at the subject level were modeled by box-car regressors representing the occurrence of each of the four block types. Except where noted, a voxel-level threshold of P < 0.005 for group contrasts, uncorrected for multiple comparisons (with an extent threshold of 10 contiguous voxels) was used to identify significant activations in pain-related regions and other regions of a priori interest. These included regions associated with theory of mind (TPJ, PCC), and emotion regulation activity changes in pain-related regions and other regions of a priori interest. These analyses is to assess whether the influence two neural networks exert over each other is modulated by certain psychological factors. The PPI analysis is used to compare the functional ‘coupling’ of different brain regions (physical component during different tasks (psychological component); it can capture the modulation of activity in one brain region by activity in another brain region dependent on specific active tasks. In a PPI analysis, a design matrix contains three columns of variables: (i) stimuli; (ii) a time-series ‘physiological’ variable that represents the time course of a seed region; and (iii) a variable that represents the interaction of psychological and physiological variables, (i) and (ii), respectively. In our case, we were interested in two-specific modulations: (1) whether the situation involved accidentally caused pain (PCA) or no pain (NPS) and (2) whether the pain was caused by another individual (PCO) or caused by accident (PCA). The regression coefficients for the interaction term (a measure of PPI) in activity between the seed region and the identified ‘coupled’ region (or regions) that is significantly different between tasks (i.e., pain caused by other vs. pain caused by accident) yields a significant PPI effect. As such, a PPI analysis examines differences in context-specific functional connectivity between regions of interest. Based upon a priori hypotheses, we were specifically interested in amygdala–PFC/OFC interactions while viewing painful situations. The left amygdala was selected as a seed region based on recent findings by Coccaro et al. (2007). This study reported less effective connectivity between the amygdala and PFC/OFC in a population of adults with intermittent explosive disorder (IED). To obtain data for the physiological variable, we extracted the individual time-series from a 6-mm spherical region centered on the coordinates of the PPI analysis. To perform an unbiased contrast analysis, we first performed a conjunction analysis with SPM5 to identify amygdala activation that was present across all subjects in both PCO and PCA blocks. The conjunction (i.e., PCO > Baseline and PCA > Baseline) analysis identified that the left amygdala cluster was active during both PCO and PCA conditions in the PPI analyses were performed in the following way: (1) extraction of the time-series data of the first eigenvalue of the seed VOI (2) generating a vector contrasting the time-series of the seed region (3) estimating neural response for the selected condition (the regressor), a second vector representing the main effect of the selected contrast (the psychological variable), and a third vector representing the VOI timecourse (the physiological variable); and (3) forward-convolving these regressors with the canonical hemodynamic response function in order to estimate the effects of the PPI regressor. The resulting statistical parametric maps (SPMs) showed clusters for which this activity differed across conditions.

As in the segmentation analyses, the two target contrasts were pain caused by accident > no pain situation, and pain caused by other > pain caused by accident. The resulting individual PPI-SPMs were then entered into a random-effects group analysis (two-sample t-tests) to look at group differences. Results were second-level rfx analyses, thresholded at P < 0.01 (corrected for areas with no a priori hypotheses, and P > 0.05, k = 10 uncorrected for areas with a priori hypotheses (i.e., areas of the pain matrix, dmPFC, OFC and tempo-parietal junction, which all have been associated with empathy for pain and mentalizing in previous studies (Cheng et al., 2007; Decety et al., 2008; Jackson et al., 2006b; Lamm et al., 2007a). To assess correlations between the youth’s post-scanning pain intensity ratings and their parameter estimates of the contrast between two tasks (i.e., the interaction variable that represents the interaction of physiological and psychological variables, (i) and (ii), respectively). Each individual’s average score for “pain caused by accident” on the VAS ratings was correlated with parameter estimates of the contrast “pain caused by accident” > Baseline. A significance threshold of P < 0.005 (uncorrected) and k > 10 was selected for these analyses. To reduce false positives associated with the multitude of possible analyses, significant correlations were only interpreted if they were located in a priori defined regions of the pain matrix (Derbyshire, 2000; Jackson et al., 2006a).

Parametric analyses were also performed to determine the regions whose activity varied with the eight CD youths’ mean number of aggression symptoms over all trials. Each individual’s mean number of aggressive symptoms, and mean score on each of the three CADS scores, negative emotionality, daring/sensation seeking and prosociality, as well as adolescents’ average for the sadism score were correlated with parameter estimates of the contrast PCO > PCA. A significance threshold of P < 0.005 (uncorrected) and k = 10 was selected for these analyses. Correlation analyses between participants’ HRV measures and their mean post-scan pain ratings

After the fMRI sessions, the same stimuli that had been shown during scanning were presented to the adolescents on a computer screen. They were asked to rate how painful the each situation was using a computer-based visual analogue scale (VAS) ranging from “no pain” to “extreme pain.” Adolescents were also asked to report what they felt when watching the stimuli in the scanner. Mean ratings for each of the four conditions were assessed by repeated measures ANOVA. A significance threshold of P < 0.05 was used for all comparisons.
aggression and sadism scores on the CADS were not performed on the control sample, as, befitting the selection of these individuals as controls, there was no variation in their scores on these items (mean = 0, S.D. = 0).

3. Results

3.1. Post-scanning pain ratings

A repeated-measures ANOVA on the pain ratings indicated that both healthy adolescents and adolescents with CD rated the painful situations as depicting significantly greater pain (F1,14 > 98.9, P < 0.001) (PCA: 57 ± 7, and PCO: 59 ± 7 for healthy adolescents; PCA: 61 ± 5 and PCO: 62 ± 4 for adolescents with CD) than the neutral situations (APO: 27 ± 8, and NPS: 0.4 ± 0.2 for healthy adolescents; APO: 29 ± 7 and NPS: 2 ± 1 for adolescents with CD). There was not a significant difference between the PCO and the PCA conditions (P > 0.26).

3.2. Functional MRI results

When watching others in pain caused by accident (PCA) versus others in NPSs, the pain matrix (including the anterior insula, dmCC, somatosensory cortex, and PAG) was selectively activated in both groups (see Tables 1 and 2). In addition, in adolescents with CD only, significant signal increase was detected bilaterally in the amygdala, striatum, medial orbitofrontal cortex, and temporal pole. A two-sample t-test for this contrast (PCA > NPS) showed a significant group effect (CD vs. controls) in anterior cingulate cortex, left amygdala, right caudate, and temporal pole bilaterally (see Table 3).

Watching painful situations intentionally caused by another individual (PCO) versus pain caused by accident (PCA) was associated with different patterns of activation in the CD and the control groups. The anterior paracingulate cortex, lateral OFC, right TPJ, the right amygdala, and superior frontal and medial prefrontal gyrus were activated in the control group. A different pattern of activation was observed in the CD group, which activated the left temporal pole, medial OFC and middle temporal gyrus and precuneus.

Direct comparisons (two-sample t-tests) between the control and CD groups when viewing situations depicting an individual intentionally inflicting harm (PCO) versus pain caused by accident (PCA) showed greater activation in adolescents with CD than controls in the left anterior insula, SMA, and precentral gyrus (see Table 4). Conversely, activation of the left DLPFC [42, 42, 22, t = 4.79] and right superior frontal gyrus [18,66, 3, t = 4.79] was greater in controls than CD subjects. Participants with CD showed

<table>
<thead>
<tr>
<th>Regions of interest</th>
<th>MNI coordinates</th>
<th>t-Value</th>
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<tbody>
<tr>
<td>Pain caused by accident versus no pain situation</td>
<td>X Y Z</td>
<td></td>
</tr>
<tr>
<td>R: anterior insula</td>
<td>32 32 4</td>
<td>11.65</td>
</tr>
<tr>
<td>L: middle insula</td>
<td>–40 –2 8</td>
<td>5.30</td>
</tr>
<tr>
<td>L: anterior cingulate cortex</td>
<td>–2 12 24</td>
<td>10.95</td>
</tr>
<tr>
<td>R: middle cingulate cortex</td>
<td>6 42 9.30</td>
<td></td>
</tr>
<tr>
<td>R: pre-supplementary motor area</td>
<td>4 48 7.69</td>
<td></td>
</tr>
<tr>
<td>L: supplementary motor area</td>
<td>–4 52 5.68</td>
<td></td>
</tr>
<tr>
<td>R: somatosensory cortex</td>
<td>–58 –29 36 4.70</td>
<td></td>
</tr>
<tr>
<td>L: medial orbital gyrus</td>
<td>10 46 –14 8.05</td>
<td></td>
</tr>
<tr>
<td>L: medial orbital gyrus</td>
<td>–6 54 –6 8.75</td>
<td></td>
</tr>
<tr>
<td>L: temporal pole</td>
<td>–56 10 –2 7.71</td>
<td></td>
</tr>
<tr>
<td>R: temporal pole</td>
<td>38 66 4 2.65</td>
<td></td>
</tr>
<tr>
<td>R: ventral striatum [putamen]</td>
<td>26 12 –4 8.12</td>
<td></td>
</tr>
<tr>
<td>L: ventral striatum (head of caudate)</td>
<td>8 4 10 4.88</td>
<td></td>
</tr>
<tr>
<td>R: periaqueductal gray</td>
<td>2 –30 7 3.09</td>
<td></td>
</tr>
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<td>L: periaqueductal gray</td>
<td>–2 –30 –7 4.17</td>
<td></td>
</tr>
<tr>
<td>L: amygdala</td>
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<td></td>
</tr>
<tr>
<td>R: amygdala</td>
<td>15 –8 9 9.42</td>
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</table>

Pain caused by other versus pain caused by accident

<table>
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<tr>
<th>Regions of interest</th>
<th>MNI coordinates</th>
<th>t-Value</th>
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<tbody>
<tr>
<td>Pain caused by accident &gt; no pain situation</td>
<td>X Y Z</td>
<td></td>
</tr>
<tr>
<td>L: temporal pole</td>
<td>–34 16 –28</td>
<td>6.64</td>
</tr>
<tr>
<td>L: middle temporal gyrus</td>
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</tr>
<tr>
<td>R: middle temporal gyrus</td>
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</tr>
<tr>
<td>R: precuneus</td>
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</tr>
<tr>
<td>L: inferior temporal gyrus</td>
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<td></td>
</tr>
<tr>
<td>R: superior frontal gyrus</td>
<td>16 42 34 5.97</td>
<td></td>
</tr>
<tr>
<td>L: medial orbitofrontal cortex</td>
<td>–4 30 –17 4.79</td>
<td></td>
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3.3. Brain regions showing greater activation in adolescents with CD compared with controls in response to the PCO > NPS contrast. Whole-brain voxel-wise analysis (P < 0.005, uncorrected).

<table>
<thead>
<tr>
<th>Regions of interest</th>
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<th>t-Value</th>
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<tbody>
<tr>
<td>Pain caused by accident &gt; no pain situation</td>
<td>X Y Z</td>
<td></td>
</tr>
<tr>
<td>L: middle insula</td>
<td>–37 6 10</td>
<td>3.30</td>
</tr>
<tr>
<td>R: anterior cingulate cortex</td>
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</tr>
<tr>
<td>R: middle cingulate cortex</td>
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<td></td>
</tr>
<tr>
<td>R: supplementary motor area</td>
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<td></td>
</tr>
<tr>
<td>R: medial orbital gyrus</td>
<td>2 54 10 3.41</td>
<td></td>
</tr>
<tr>
<td>L: medial orbital gyrus</td>
<td>–4 56 –8 3.57</td>
<td></td>
</tr>
<tr>
<td>L: temporal pole</td>
<td>–50 –4 0 3.37</td>
<td></td>
</tr>
<tr>
<td>R: temporal pole</td>
<td>62 –2 6 3.34</td>
<td></td>
</tr>
<tr>
<td>R: amygdala</td>
<td>–18 –8 10 3.10</td>
<td></td>
</tr>
<tr>
<td>L: caudate (striatum)</td>
<td>12 18 4 3.74</td>
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</tbody>
</table>

Table 2 Brain regions showing significant signal increase (P < 0.005, uncorrected) in the CD participants for both pain caused by accident and pain caused by other conditions.

<table>
<thead>
<tr>
<th>Regions of interest</th>
<th>MNI coordinates</th>
<th>t-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain caused by accident &gt; no pain situation</td>
<td>X Y Z</td>
<td></td>
</tr>
<tr>
<td>L: anterior insula</td>
<td>–26 24 –4</td>
<td>3.48</td>
</tr>
<tr>
<td>R: supplementary motor area</td>
<td>12 –10 60 3.83</td>
<td></td>
</tr>
<tr>
<td>R: precentral gyrus</td>
<td>–30 –16 54 3.47</td>
<td></td>
</tr>
</tbody>
</table>

Table 3 Brain regions showing greater activation in participants with CD compared with healthy control participants in response to the PCA > NPS contrast. Whole-brain voxel-wise analysis (P < 0.005, uncorrected).

Table 4 Brain regions showing greater activation in participants with CD compared with healthy control participants in response to the PCA > NPS contrast.
diminished BOLD response in the anterior PCC, TPJ and the lateral orbitofrontal cortex. The degree of activation in the anterior TP in the CD group was linearly correlated with the post-scanning VAS ratings of the pain experienced by the persons in the stimuli ($r = 0.91, P < 0.001$). Furthermore, similar and high correlations were found between VAS ratings and hemodynamic activity in the aMCC ($r = 0.93, P < 0.001$) and right anterior and middle insula ($r = 0.89, P < 0.001$).

### 3.3. Effective connectivity analysis

The PPI analysis indicated that the CD group differed from the controls in the extent to which activity in the amygdala covaried with frontal cortical regions and the insula during the PCO condition compared to the PCA condition. For the healthy adolescents, PPI analyses showed that activity in the left amygdala was accompanied by condition-dependent (pain caused by other > pain caused by accident) functional interaction with a number of areas in the prefrontal cortex (see Table 5). The pattern of coupling was observed only in the pain caused by other > pain caused by accident contrast. In contrast, the CD group showed no significant effective connectivity between amygdala and these frontal and parietal regions. However, in this group, the PCO condition did modulate the effective connectivity between the amygdala and the left insula [−32, 12, −18], which was not the case for the healthy controls. Direct comparisons (two sample t-tests) confirmed the above differences between these two groups ($P < 0.005$). Interestingly, the effective connectivity between the left amygdala and the temporal pole was stronger for PCA > NPS in participants with CD. No significant modulation was detected with frontal regions.

### 3.4. Correlation analyses between hemodynamic response and traits related to psychopathy

Mean number of aggressive CD symptoms and ratings on the CADS during dimension both correlated with amygdala, inferior frontal gyrus, right PAG and right middle cingulate cortex [12, 38, 32] activations but prosociality did not. Interestingly, adolescents’ sadism scores were highly correlated with activity in right amygdala [28, −12, −8], bilateral precuneus [0, −56, 46; 4, −60, 64], and left fusiform gyrus [−24, −52, −14] ($P < 0.0001$).

### 4. Discussion

The goal of this study was to explore differences in neural response to empathy- and sympathy-eliciting stimuli between adolescents with childhood-onset aggressive CD and adolescents with no history of CD symptoms over 9 years. As predicted, when the control participants observed painful situations accidentally caused (PCA condition), regions of the pain matrix were selectively activated, including the insula, aMCC, dorsal ACC, SMA, PAG and somatosensory cortex. This result fits well with previous functional neuroimaging studies on pain empathy in adults (Jackson et al., 2006a, for a review) as well as in typically developing children (Decety et al., 2008) that consistently showed that attending to the other people’s pain triggers an automatic somatic sensorimotor resonance mechanism between other and self, which activates almost the entire neural pain matrix in the observer including the PAG and the SMA.

Interestingly, the pattern of activation in the adolescents with CD showed both similarities as well as striking differences from the control youth when observing accidentally caused painful situations (PCA > NPS). In the CD group, hemodynamic signal increase was detected in the insula, aMCC, SMA, PAG, and somatosensory cortex (see Fig. 1). In addition, strong activation was observed bilaterally in the amygdala, striatum, and temporal poles. The dorsal portion of the TP projects to the hypothalamus, a neuromodulatory region important for autonomic regulation. Electrical stimulation of the TP produces changes in heart rate, respiration, and blood pressure (Gloor et al., 1982). In contrast, these regions (i.e., amygdala, ventral striatum and TP) were not activated in the control participants. Most importantly, as reported in Table 3, direct comparison of the two groups indicated that participants with CD have a significantly stronger signal response in the aMCC, striatum and left amygdala than the control participants when viewing painful situations that have been accidentally caused. This result suggests that individuals with CD actually react to viewing pain in others to a greater extent in some important brain regions than youth without CD.

The finding that aggressive adolescents with CD exhibit greater response in the pain matrix when viewing accidentally inflicted pain than controls is interesting given the finding of previous fMRI studies that reported reduced amygdala response in youth with CD during the viewing of pictures with negative emotional valence (Marsh et al., 2008; Sterzer et al., 2005), as well as reduced amygdala volume (Sterzer et al., 2007). The present findings suggest that youth with CD do not exhibit reduced amygdala response to all negatively valenced stimuli; indeed, they appear to exhibit enhanced response to images of people in pain, including a specific activation of the striatum.

Our results suggest that there may be no deficit in neural response to pain in others (as reflected by the strong activation in the amygdala, temporal poles, and other structures in the pain matrix) in youth with CD. In fact, this somatic sensorimotor resonance was significantly greater ($P < 0.005$) in participants with CD than without CD. We also observed that, in participants with CD, the extent of amygdala activation to viewing pain in others was significantly correlated in a positive direction to their number of aggressive acts and their ratings of daring and sadism score on the CADS.

The present findings are consistent with at least two hypotheses that should be tested in future studies. The first hypothesis is that highly aggressive antisocial youth enjoy seeing their victims in pain and, because of their diminished PFC/amygdala connectivity, may not effectively regulate positively reinforced aggressive behavior. The amygdala is involved in the processing of more than just negative affect. Numerous studies point to a role for the amygdala in positive affect, and its coupling with the striatum enables a general arousing effect of reward (Murray, 2007). It is possible, therefore, that the robust hemodynamic response in the amygdala to viewing others in pain in youth with aggressive CD reflects a positive affective response (e.g.,...
“enjoyment” or “excitement”). The finding that CADS ratings of daring items (which reflect enjoyment of novel and risky situations) and sadism items (which reflect enjoyment of hurting others or viewing people or animals being hurt) correlated positively with amygdala response in youth with CD is consistent with this hypothesis. In addition, this interpretation is consistent with the significant activation among youth with aggressive CD of the striatum, which is part of the system implicated in reward and pleasure, among other things.

There are important reasons to be cautious when interpreting the activation of the striatum as indicating a positive affect response to viewing others in pain, however. The striatum is located at the head of the caudate nucleus and anterior portion of the putamen and receives major input (excitatory fibers) from the amygdala and the hippocampal formation. It can be viewed as a functional interface between the limbic and motor systems (Mogenson et al., 1980). In humans, the striatum is activated by stimuli associated with reward, but also by salient aversive, novel, and intense stimuli. A common property linking these stimuli is saliency (Groenewegen, 2007). The instrumental aspects of avoidance unlike the Pavlovian elicited responses require connections between the amygdala and the ventral striatum for their acquisition and/or expression. In particular, the nucleus accumbens of the striatum may be a crucial area for the initiation and control of instrumental responses triggered by either appetitive or aversive responses, resulting from its innervation by dopaminergic pathways (LeDoux et al., 2002).

Thus, it is not easy to determine if the amygdala/striatum response in CD participants is associated with positive or negative affect when watching the pain of others. Although this hypothesis requires more extensive testing, the fact that this view others in pain also was associated with strong activation of the PAG may argue against it. This region of the midbrain receives input from the amygdala and its stimulation triggers aversive or defensive responses and anxiety. It is also worth noting that lesion to the striatum is associated with selective impairment of anger processing, both in the recognition of signals of anger and the experience of this emotion (Calder et al., 2004).

The second hypothesis is that youth with CD have a lower threshold for responding to many situations with negative affect, including viewing pain in others, and are less able to regulate these negative emotions through cortical processes. Many studies indicate that individuals with CD tend to respond to aversive stimuli with greater negative affect than most other youth (Lahey and Waldman, 2003). This is potentially important as their negative affect may increase the likelihood of aggression, especially in the absence of effective emotion regulation (Berkwitz, 1993, 2003). This interpretation fits well with the hypothesis of a dysfunction in the neural circuitry of emotion regulation (Davidson et al., 2000) and is consistent with our analyses of effective PFC/amygdala connectivity. Aggression may be related to instability of negative affect and poor impulse control (Raine, 2002). Children with aggressive behavior problems have difficulties regulating negative emotions, which may result in harmful patterns of interpersonal behavior (Lewis et al., 2006). Often triggered by hypersensitivity to specific stimuli, aggressive adults experience escalating agitation followed by an abrupt outburst of aggressive and threatening behavior (Gollan et al., 2005). Failure to discriminate between pain to others and to oneself may further lead to negative emotion when viewing others in pain. The fact that the anterior TP was specifically and highly activated in youth with CD provides support for the distress interpretation. It has been suggested that the TP is part of a system that modulates visceral functions in response to emotionally evocative stimuli based on its anatomical connectivity (Kondo et al., 2003). A number of neuroimaging studies have reported activation in the left anterior TP in response to negative visual and auditory stimuli, such as aversive sounds (Olson et al., 2007). Importantly, one fMRI study found that TP activation correlates with personal distress scores, a measure of how much one personally feels upset when viewing another’s negative emotions (Moriguchi et al., 2006).

Stimuli that depicted pain intentionally caused by another individual (PCO vs. PCA) were associated, in the control group (but not in the CD group), with additional activation of right temporoparietal junction, anterior PCC, medial prefrontal cortex, and left lateral OFC. The same pattern of activity in response to viewing painful situations intentionally inflicted on another individual was recently reported in a functional MRI study with typically developing children, and interpreted with relation to the perception of social interaction and intentionality (Decety et al., 2008). Functional neuroimaging studies have consistently supported the existence of a distributed neural network underlying the ability to understand other people as intentional and emotional agents (theory of mind mechanism). This network comprises the superior temporal sulcus, the TPJ, and the medial prefrontal/anterior paracingulate cortex (e.g., Caramazza et al., 2007; Decety and Lamm, 2007). Specifically, research indicates that the anterior PCC is implicated in understanding the mental states of an agent involved in social interaction, regardless of whether this interaction is observed, taking place online or even imagined (e.g., Walter et al., 2004).

Different patterns of response were detected in the orbitofrontal cortex across the two groups. While the lateral OFC was selectively activated in the control participants when observing pain inflicted by another, activation of the medial OFC was found in the participants with CD, direct comparison between the groups confirmed this finding. The OFC/MPFC has been specifically implicated in a variety of areas relevant to CD and aggression, including the regulation of negative affect (Phan et al., 2005).

Importantly, as reported in Table 5, PPI analyses demonstrated significantly greater amygdala/PFC coupling when watching pain being intentionally caused by another individual in the control group than the CD group. In particular, in healthy adolescents, left amygdala activity covaried with activity in the prefrontal cortex to a greater extent while watching situations of pain being intentionally caused compared to viewing of pain caused by accident. Adolescents with CD showed no significant functional connectivity between frontal regions and amygdala, which is in line with a recent study that demonstrated greater functional connectivity between the amygdala and PFC in comparison subjects than a group of aggressive youth (Marsh et al., 2008).

We posit that the condition in which another individual is inflicting pain intentionally on another elicits in the normal controls a certain degree of regulation/inhibition. Such regulatory process depends upon the posterior superior temporal sulcus and medial prefrontal cortex (Hareniski and Hamann, 2006). A meta-analysis shows that frontal regions become active when subjects engage in cognitive strategies (such as reappraisal or detachment) to modulate negative affect (Ochsner and Gross, 2005). This is consistent with the role of the prefrontal cortex in cognitive inhibition and executive function, processes that are important for the regulation of affect (Fuster, 2001).

Overall, our results suggest a complex relation between the neural correlates of empathy and CD. The functional MRI data seem to indicate that adolescents with CD are at least as responsive to the pain of others as the adolescents without CD. The fact that activation of the posterior insula, somatosensory cortex, and PAG were involved in the observation of others in painful situations supports such an interpretation. However, when observing pain intentionally caused by another there was no activation in...
adolescents with CD, in the neural regions that contribute to self-regulation and metacognition (including moral reasoning), such as the DLPC, PCC, TPJ, dorsal and medial ACC and lateral OFC. This pattern stands in contrast with that of the control group and a previous study with typically developing children (Decety et al., 2008).

Research with non-humans demonstrates that physical pain often elicits aggression (Berkowitz, 2003). It has been hypothesized that aggressive persons are disposed to experience negative affect (Anderson and Bushman, 2002; Lahey and Waldman, 2003). This suggests that, in certain situations, empathic mimicry might produce high levels of distress in youth predisposed to be aggressive that, ironically, increases their aggression. It is possible that strong activation of neural circuits that underpin actual pain processing is associated with negative affect in youth with CD. This, in conjunction with reduced activation in areas associated with emotion regulation, could result in a dysregulated negative affective state, which may instigate aggression under some circumstances (Berkowitz, 1983). For example, youth with CD who see an injured friend (or fellow member of a gang) may be more likely to respond aggressively than other youth for this reason.

Finally, the strong and specific activation of the amygdala and ventral striatum in the aggressive adolescents with CD during the perception of pain in others is an important and intriguing finding, which necessitates additional research in order to understand the relative roles of negative and positive affect when viewing others in pain in aggression and empathic dysfunction.

4.1. Conclusion

This study is to our knowledge the first functional neuroimaging investigation of brain response to pain empathy-eliciting stimuli in aggressive adolescents with CD. In the future it will be important, given the limited size of our sample, to examine whether these findings replicate with larger samples. We believe that such investigations are critical to move beyond self-report measures of empathy. They will also provide a better understanding of the computational and neural mechanisms underpinning empathy as well as their dysfunction in high-risk juvenile populations.

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References


