Cortical and Subcortical Gray Matter Volume in Youths With Conduct Problems
A Meta-analysis

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**IMPORTANCE** A large number of structural neuroimaging studies have used voxel-based morphometry (VBM) to identify gray matter abnormalities in youths with conduct problems (CP), but the findings have been disparate and few have been replicated.

**OBJECTIVE** To conduct a meta-analysis of published whole-brain structural neuroimaging studies on youths with CP that used VBM methods to facilitate replication and aid further analyses by researchers.

**DATA SOURCES** The PubMed, ScienceDirect, Scopus, Google Scholar, and Web of Science databases were searched for VBM studies published from January 1, 2007, through March 31, 2015. Manual searches were conducted using title and citation information. Authors were contacted for additional data.

**STUDY SELECTION** A literature search identified 28 studies. Studies were excluded if they (1) failed to use VBM, (2) failed to report a voxelwise comparison between youths with CP and typically developing (TD) youths, (3) used different significance or extent thresholds throughout the brain, (4) included duplicated datasets, and (5) did not provide peak coordinates or parametric maps after contact with the authors. Thirteen studies were deemed eligible for inclusion (394 youths with CP and 350 TD youths).

**DATA EXTRACTION AND SYNTHESIS** Anisotropic effect-size signed differential mapping (SDM) was used for voxel-based meta-analyses. Statistical parametric maps comparing gray matter differences between youths with CP and TD youths were available for 11 of the studies, with peak coordinates available for the remaining studies.

**MAIN OUTCOMES AND MEASURES** Regional gray matter volume (GMV) differences in youths with CP compared with TD youths.

**RESULTS** Youths with CP had decreased GMV in the left amygdala (SDM estimate = −0.218; P < .001) (extending into anterior insula), right insula (SDM estimate = −0.174; P < .001) (extending ventrolaterally into the prefrontal cortex and inferiorly into the superior temporal gyrus), left medial superior frontal gyrus (SDM estimate = −0.163; P = .001) (extending into the right anterior cingulate cortex), and left fusiform gyrus (SDM estimate = −0.146; P = .003). Subgroup meta-analysis assessing age-at-onset effects identified reduced GMV in the left anterior insula (SDM estimate = −0.232; P < .001) (extending into amygdala).

Meta-regression analyses revealed that greater scores on measures of callous-unemotional traits were associated with a lower reduction in GMV in the left putamen (SDM estimate = −0.911; P < .001). The proportion of male and female youths in the sample was associated with decreased GMV in the left amygdala (SDM estimate = −0.31; P < .001) and increased GMV in the right inferior temporal cortex (SDM estimate = 0.755; P < .001). While there was no association with comorbid attention-deficit/hyperactivity disorder or IQ, age range was associated with gray matter differences in the left amygdala.

**CONCLUSIONS AND RELEVANCE** We identified gray matter reductions within the insula, amygdala, frontal and temporal regions in youths with CP as well as inconsistencies in sample characteristic analyses that should be addressed in future research.
Youths with conduct problems (CP), such as conduct disorder (CD), oppositional defiant disorder, and disruptive behavior disorder, are characterized by aggressive, antisocial, and oppositional or defiant behaviors during childhood and adolescence. Conduct problems are some of the most prevalent child psychiatric disorders and among the most common reasons for a childhood referral to mental health services. Crucially, CP are predictive of not only antisocial and aggressive behaviors in adulthood but also substance misuse, other mental health problems, and poor physical health, making them an important target for etiologic research and prevention efforts.

Youths with CP are a highly heterogeneous population that incorporates different subgroups, potentially reflecting distinct etiopathological pathways to CP. Several approaches have attempted to account for this heterogeneity, with two included within the DSM-5. The first is the age-based distinction between childhood-onset and adolescent-onset CD, introduced in DSM-IV. This distinction is thought to identify 2 qualitatively and etiologically distinct subtypes and has been well supported for both female and male youths. The second subtyping approach distinguishes youths with CP as those with high callous-unemotional (CU) vs low CU traits. Callous-unemotional traits reflect a lack of empathy and guilt combined with a shallow affect, the callous use of others for one’s own gain, and a lack of concern about own performance in important activities. Genetic, neuroimaging, and behavioral studies have found that youths with CP and high CU traits versus those with CP and low CU traits are characterized by different vulnerabilities. These findings resulted in the inclusion of CU traits as the “with limited prosocial emotions” specifier for the diagnosis of CD in DSM-5.

To characterize whole-brain and regional gray matter volume (GMV), recent structural magnetic resonance imaging (MRI) studies on CP have used automated and unbiased methods, such as voxel-based morphometry (VBM). Two studies reported an overall reduction in GMV in youths with CP compared with typically developing (TD) youths. Youths with CP exhibit reduced GMV in a number of cortical and subcortical brain regions, including anterior and posterior insula, temporal lobes bilaterally, right ventromedial prefrontal cortex (VMPFC), right dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), hippocampus, amygdala, and striatal regions. However, there are marked inconsistencies across studies regarding the foci of reduced gray matter, which encompass several frontotemporal and striatal structures. Two recent studies also failed to identify a significant difference in GMV between youths with CP and TD youths.

These inconsistent findings coupled with the low level of replication across studies likely reflect variations in data analytic strategy and sample characteristics within and across studies. The relatively small sample size for most, but not all, studies could have resulted in low statistical power and increased risk of false-positive results. Some studies failed to account for heterogeneity within CP in terms of age at onset of CD and levels of CU traits. Other studies have also included samples that exhibit high comorbidity with other disorders, notably attention-deficit/hyperactivity disorder (ADHD), which is commonly comorbid with CD. Controlling for ADHD as a potential confound can have a significant effect on reported results. Finally, potential sex differences might also have contributed to the inconsistent findings, with recent VBM studies reporting divergent patterns of GMV abnormalities across sexes.

Given this variability, we applied seed-based d mapping, a novel voxel-based meta-analytical method, on published whole-brain VBM studies in youths with CP. The inclusion of only whole-brain VBM studies means that the results were not biased or restricted by previous findings to a priori regions of interest. To increase the accuracy and sensitivity of our analyses, we included the original statistical parametric maps from 85% of studies in our meta-analysis. Reliability analyses were performed to assess robustness of findings. To examine the contribution of age at onset of CP on GMV differences, we conducted an additional subgroup meta-analysis including only studies that compared youths with childhood-onset CP and TD youths. Given evidence of the differential etiology and neurobiology for youths with CP displaying high vs low CU traits and for males vs females with CP, meta-regressions were also conducted to examine the influence of CU traits and sex on GMV. On the basis of the high comorbidity between CP and ADHD, we also conducted a meta-regression with ADHD included as a covariate of no interest. Finally, the influence of age, IQ, and CD symptom severity was also examined given their influence on GMV.

Methods

Search and Study Selection
A literature search of the PubMed, ScienceDirect, Scopus, Google Scholar, and Web of Science databases for VBM studies published from January 1, 2007 (the year of the first VBM study of CP) through March 31, 2015, was carried out. The study selection procedure is summarized in Figure 1. Titles, abstracts, citations, and reference lists of the outputted studies were assessed to determine relevance and to identify additional studies for inclusion. Studies were excluded if they failed to use VBM, failed to report a voxelwise comparison between youths with CP and TD youths for GMV, did not report whole-brain results (ie, limited their analyses to specific regions of interest), used different significance or extent thresholds throughout the whole brain, included duplicated data sets, and did not provide peak coordinates or parametric maps after contact with the authors. We contacted the corresponding authors to request the original statistical parametric maps and obtain additional details where necessary. To assess whether the available literature is biased toward excluding studies with nonsignificant results, an Orwin’s fail-safe analysis was performed to calculate the number of studies with an effect size of 0 needed to make the mean effect size nonsignificant (P > .05).
Figure 1. Inclusion of Studies in the Meta-analysis

28 Potentially relevant citations identified
Studies identified using the PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect databases

15 Excluded studies
7 Studies excluded because they used diffusion tensor imaging
3 Studies excluded because they used surface-based rather than voxel-based morphometry
2 Studies excluded because they did not include a comparison with a typically developing group and reported region of interest findings only
1 Study excluded because it used manual tracing methods
1 Study excluded because it reported structural changes in white matter concentration
1 Study excluded because it focused on patients at risk for alcohol dependence

13 Studies included in the meta-analysis

Keywords
Conduct disorder OR conduct problems OR disruptive behavior disorders OR oppositional defiant disorder OR callous-unemotional traits AND structural, gray matter, voxel-based OR VBM AND whole-brain

Comparison of Regional Gray Matter Volumes
Anisotropic effect-size signed differential mapping (SDM) software, version 4.21 (http://www.sdmproject.com/software), 32,36 was used for voxel-based meta-analyses, comparing GMV differences in youths with CP and TD youths. Anisotropic effect-size SDM enables original statistical parametric maps and peak coordinates to be combined with established meta-analytical statistics (eMethods 1 in the Supplement). 32 Statistical parametric maps used in this meta-analysis refer to group-level results for the comparison between youths with CP and TD youths. Both positive and negative effects are reconstructed within the same map, thus preventing a particular voxel from appearing in opposite directions. These negative effects are also included in the meta-analyses. 32 The inclusion of the statistical parametric maps provides a more accurate representation of the results. 32 Statistical parametric maps for the groupwise comparison between youths with CP and TD youths were obtained for 11 (85%) of the 13 included studies (Table 1).

For 2 studies, 17,22 raw statistical parametric maps were not available, but peak coordinates of significant group differences between youths with CP and TD youths from each contrast of interest were available in the reports. For one study, 22 that reported peak coordinates without statistical values, the threshold value was determined as the effect size of the coordinates. In line with previous meta-analyses, 38-40 statistical significance was determined using standard randomization tests (N = 20) and a set of recommended thresholds optimizing sensitivity while adequately controlling for type I error (voxel P < .005, peak height SDM z score = 1, cluster extent = 10 voxels). 32 The full-width half-maximum was set to 20 mm 32,36 (eMethods 1 in the Supplement). Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were followed. 41

Reliability Analysis, Subgroup Meta-analysis, and Meta-regressions
A jackknife analysis was used to establish the reliability of the results. 32,42 This sensitivity analysis consists of removing a single data set and repeating the analysis in sequence. If a previously significant brain region remains significant in all or most of the repeated analyses, it can be concluded that the effect is highly replicable. A subgroup meta-analysis was also carried out on studies that included only youths diagnosed as having childhood-onset CP.

Linear meta-regression analyses were used to examine the influence of (1) the mean CU traits score for youths with CP, (2) the ratio of males to females with CP across studies, and (3) the proportion of youths with CP comorbid for ADHD on GMV. The meta-regressions reported in this article should be treated as exploratory only, with a more strict threshold applied in all cases to control for false-positive results (P < .00017, Bonferroni corrected), 43 and results only considered when significant slopes were accompanied by significant differences at one extreme of the independent variable (eg, CU traits score for youths with CP) (eMethods 1 in the Supplement). Finally, because the assessment tools used to measure CU traits differed across studies (Table 1), mean CU scores for youths with CP were converted to the Percent of Maximum Possible scores, 44 which expresses raw scores in terms of the minimum and maximum. This established method of standardizing scores 44,45 allows comparisons across scoring methods, populations, and measures, overcoming problems associated with alternative standardization methods (eg, z scores) that do not allow comparison of scores across studies and samples. For 2 studies that used 2 different assessment tools to measure CU traits, 20,22 the average Percent of Maximum Possible score across measures of CU traits was calculated (eTable

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Table 1. Summary of Studies Included in the Meta-Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnosis</th>
<th>No. of Patients With CP (% Male)</th>
<th>Age at CP Onset, Mean (Range)</th>
<th>IQ of Patients With CP</th>
<th>No. of TD Patients (% Male)</th>
<th>Age of the TD Patients, Mean (Range)</th>
<th>IQ of the TD Patients</th>
<th>Sample</th>
<th>Measures of CU Traits</th>
<th>Comorbidity (% With ADHD)</th>
<th>Scanner Strength</th>
<th>FWHM, mm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterzer et al, 2007</td>
<td>CD</td>
<td>12 (100)</td>
<td>12.8 (9.0-15.0)</td>
<td>100.6</td>
<td>12 (100)</td>
<td>12.5 (9.0-15.0)</td>
<td>107.2</td>
<td>Clinical</td>
<td>None</td>
<td>ADHD (58)</td>
<td>1.5</td>
<td>8</td>
<td>&lt;.05 FWE corrected</td>
</tr>
<tr>
<td>Hubeiner et al, 2008</td>
<td>CD</td>
<td>23 (100)</td>
<td>14.5 (12.0-17.0)</td>
<td>96.7</td>
<td>23 (100)</td>
<td>14.2 (12.0-17.0)</td>
<td>98.9</td>
<td>Clinical</td>
<td>None</td>
<td>ADHD (74)</td>
<td>1.5</td>
<td>10</td>
<td>&lt;.05 corrected, cluster level</td>
</tr>
<tr>
<td>De Brito et al, 2011</td>
<td>CD and CU traits</td>
<td>23 (100)</td>
<td>11.6 (10.0-13.3)</td>
<td>95.4</td>
<td>25 (100)</td>
<td>11.8 (10.0-13.3)</td>
<td>106.9</td>
<td>Community</td>
<td>APSD</td>
<td>NA</td>
<td>3</td>
<td>8</td>
<td>&lt;.001 uncorrected</td>
</tr>
<tr>
<td>Dalwani et al, 2011</td>
<td>ASD</td>
<td>25 (100)</td>
<td>16.6 (14.0-18.0)</td>
<td>98.1</td>
<td>19 (100)</td>
<td>16.6 (14.0-18.0)</td>
<td>105.2</td>
<td>Clinical</td>
<td>None</td>
<td>ADHD (12)</td>
<td>3</td>
<td>8</td>
<td>&lt;.05 FWE corrected</td>
</tr>
<tr>
<td>Fahim et al, 2011</td>
<td>DBD</td>
<td>22 (100)</td>
<td>8.4 (8.0)</td>
<td>NA</td>
<td>25 (100)</td>
<td>8.4 (8.0)</td>
<td>NA</td>
<td>Community</td>
<td>None</td>
<td>NA</td>
<td>1.5</td>
<td>10</td>
<td>&lt;.05 FDR corrected</td>
</tr>
<tr>
<td>Fairchild et al, 2011</td>
<td>CD (childhood/adolescent onset)</td>
<td>63 (100)</td>
<td>17.8 (16.0-21.0)</td>
<td>99.3</td>
<td>27 (100)</td>
<td>18.5 (16.0-21.0)</td>
<td>101.4</td>
<td>Community</td>
<td>YPI and ICU</td>
<td>ADHD (24), substance abuse</td>
<td>3</td>
<td>8</td>
<td>&lt;.001 uncorrected</td>
</tr>
<tr>
<td>Stevens and Haney-Caron, 2012</td>
<td>CD</td>
<td>24 (67)</td>
<td>16.0 (15.0-16.0)</td>
<td>91.3</td>
<td>24 (67)</td>
<td>16 (15.0-16.0)</td>
<td>97.4</td>
<td>Community</td>
<td>None</td>
<td>ADHD (0), substance abuse</td>
<td>3</td>
<td>8</td>
<td>&lt;.05 corrected</td>
</tr>
<tr>
<td>Fairchild et al, 2013</td>
<td>CD (childhood/adolescent onset)</td>
<td>22 (0)</td>
<td>17.2 (14.0-20.0)</td>
<td>99.8</td>
<td>20 (0)</td>
<td>17.6 (14.0-20.0)</td>
<td>105.8</td>
<td>Community</td>
<td>YPI</td>
<td>ADHD (10), MDD</td>
<td>3</td>
<td>8</td>
<td>&lt;.001 uncorrected</td>
</tr>
<tr>
<td>Olvera et al, 2014</td>
<td>CD</td>
<td>24 (67)</td>
<td>15.8 (13.0-17.0)</td>
<td>91.9</td>
<td>24 (67)</td>
<td>15.3 (13.0-17.0)</td>
<td>98.6</td>
<td>Prison</td>
<td>None</td>
<td>ADHD (75), bipolar disorder</td>
<td>3</td>
<td>9.4</td>
<td>Equivalent to &lt;.05 FWE corrected</td>
</tr>
<tr>
<td>Cope et al, 2014</td>
<td>CD and OOD psychopathic traits</td>
<td>20 (100)</td>
<td>17.4 (14.9-19.0)</td>
<td>93</td>
<td>21 (100)</td>
<td>16.4 (12.8-19.0)</td>
<td>110.6</td>
<td>Prison/ community</td>
<td>PCL-YV</td>
<td>ADHD (5), substance abuse</td>
<td>1.5</td>
<td>10</td>
<td>&lt;.05 FWE corrected</td>
</tr>
<tr>
<td>Hummer et al, 2014</td>
<td>DBD</td>
<td>33 (73)</td>
<td>15.3 (13.0-17.0)</td>
<td>102.7</td>
<td>33 (73)</td>
<td>15.4 (13.0-17.0)</td>
<td>106.9</td>
<td>Community</td>
<td>None</td>
<td>ADHD (58)</td>
<td>3</td>
<td>8</td>
<td>&lt;.05 corrected</td>
</tr>
<tr>
<td>Michalska et al, 2015</td>
<td>CP and CU traits</td>
<td>43 (54)</td>
<td>10.1 (9.0-11.0)</td>
<td>NA</td>
<td>68 (52)</td>
<td>10 (9.0-11.0)</td>
<td>NA</td>
<td>Community</td>
<td>None</td>
<td>ADHD (NA), GAD, and MDD</td>
<td>3</td>
<td>NA</td>
<td>&lt;.001 uncorrected</td>
</tr>
<tr>
<td>Sebastian, et al, 2015</td>
<td>CP and CU traits</td>
<td>60 (100)</td>
<td>14.3 (10.0-16.0)</td>
<td>97.9</td>
<td>29 (100)</td>
<td>13.6 (10.0-16.0)</td>
<td>105.2</td>
<td>Community</td>
<td>ICU</td>
<td>NA</td>
<td>1.5</td>
<td>6</td>
<td>&lt;.001 uncorrected</td>
</tr>
</tbody>
</table>

Abbreviations: ADHD, attention-deficit/hyperactivity-disorder; APSD, antisocial process screening device; ASD, antisocial substance dependence; CD, conduct disorder; CP, conduct problems; CU, callous-unemotional; DBD, disruptive behavior disorder; FDR, false discovery rate; FWE, familywise error; FWHM, full-width half-maximum; GAD, generalized anxiety disorder; ICU, Inventory of Callous-Unemotional Traits; MDD, manic depressive disorder; NA, not available; ODD, oppositional defiant disorder; PCL-YV, Psychopathy Checklist; TD, typically developing; YPI, Youth Psychopathic Traits Inventory.

a Consistent with the diagnosis as included in the study.

b Studies for which raw statistical parametric maps were not available.

c After email communication with the lead author of that study (beginning January 30, 2015), it was made apparent that although the results did not yield any significant group differences at a significant threshold ($P < .05$, FWE corrected at whole-brain level), the group differences were present at a more lenient threshold (height threshold: $P < .001$ uncorrected; extend threshold: 0 voxels). For this study to be included in our meta-analysis, the authors were asked to provide the parametric maps produced at this lower, uncorrected threshold.
Results

Study Characteristics
Twenty-eight potential studies were identified for inclusion in the meta-analysis. Fifteen studies were excluded based on exclusion criteria (Figure 1 and eTable 5 in the Supplement). Thirteen eligible studies (Table 1) were identified that included a direct comparison of GMV between youths with CP and TD youths, 6 studies 17,20-22,28,37 includedyouthsdia
gnosed as having childhood-onset CP. Of the 13 studies that included a comparison between youths with CP and TD youths, 6 studies 17,20-22,28,37 indicated that a potential publication bias was unlikely because 302 studies with no effect would be needed to invalidate the reported findings.

Reliability Analysis
A jackknife sensitivity analysis revealed that the gray matter decrease in the left amygdala was preserved throughout all the 13 study combinations. The left insula and right inferior frontal gyrus GMV reduction failed to emerge in only one of the study combinations, with the right insula and left medial superior frontal gyrus GMV reductions failing to emerge in only 2 of the 13 study combinations. An additional cluster revealing reduced GMV in the left postcentral somatosensory cortex (Brodmann area 3) was observed in 27,21,22,27,28 of the 13 studies (eTable 6 in the Supplement). No additional significant clusters were found in either the positive or negative direction.

Subgroup Analysis: Effects of Age at Onset
A subgroup meta-analysis was carried out on studies that included only youths diagnosed as having childhood-onset CP. Of the 13 studies that included a comparison between youths with CP and TD youths, 6 studies 17,20-22,28,37 included youths diagnosed as having childhood-onset CP. This subsample included 159 youths with childhood-onset CP (40% of the total sample) and 180 TD youths (51% of the total sample). Youths with childhood-onset CP had decreased GMV in a large left-lateralized cluster that encompassed the insula and amygdala (Table 2 and Figure 2). The sensitivity analysis revealed that the gray matter decrease in the left amygdala and insula was broadly consistent across studies, with an additional cluster in the right insula observed in 4 of the 6 studies (eTable 7 in the Supplement).

Table 2. Meta-analysis Results Comparing Gray Matter Volume in 394 Youths With CP vs 350 TD Youths and 159 Youths With Childhood-Onset CP vs 180 TD Youths

<table>
<thead>
<tr>
<th>Anatomical Locationa</th>
<th>Hemisphere</th>
<th>MNICoordinates (x, y, z)</th>
<th>SDMz Value</th>
<th>P Valueb</th>
<th>Effect Size (SDM Estimate)c</th>
<th>No. of Voxels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Youths with CP less than TD youths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amygdala</td>
<td>Left</td>
<td>−32, 2, −20</td>
<td>−2.837</td>
<td>.0002</td>
<td>−0.218</td>
<td>114</td>
</tr>
<tr>
<td>Insula (BA 48)</td>
<td></td>
<td>−42, 8, −8</td>
<td>−2.235</td>
<td>.0006</td>
<td></td>
<td>277</td>
</tr>
<tr>
<td>Insula (BA 38)</td>
<td>Right</td>
<td>36, 20, −16</td>
<td>−2.302</td>
<td>.0004</td>
<td>−0.174</td>
<td>105</td>
</tr>
<tr>
<td>IFG (triangularis) (BA 45)</td>
<td>Left</td>
<td>48, 20, 2</td>
<td>−2.252</td>
<td>.0006</td>
<td></td>
<td>107</td>
</tr>
<tr>
<td>IFG (orbitalis) (BA 47)</td>
<td></td>
<td>46, 24, −6</td>
<td>−2.203</td>
<td>.0008</td>
<td></td>
<td>85</td>
</tr>
<tr>
<td>IFG (opercularis) (BA 48)</td>
<td>Left</td>
<td>54, 20, 10</td>
<td>−2.162</td>
<td>.001</td>
<td></td>
<td>36</td>
</tr>
<tr>
<td>Insula (BA 48)</td>
<td></td>
<td>30, 14, −18</td>
<td>−2.089</td>
<td>.001</td>
<td></td>
<td>48</td>
</tr>
<tr>
<td>STG/Temporal Pole</td>
<td></td>
<td>38, 14, −22</td>
<td>−2.046</td>
<td>.002</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Superior frontal gyrus (medial) (BA 10)</td>
<td>Left</td>
<td>−6, 54, 28</td>
<td>−2.164</td>
<td>.001</td>
<td>−0.163</td>
<td>77</td>
</tr>
<tr>
<td>ACC (BA 32)</td>
<td>Right</td>
<td>6, 50, 14</td>
<td>−1.979</td>
<td>.002</td>
<td></td>
<td>49</td>
</tr>
<tr>
<td>Fusiform gyrus (BA 19)</td>
<td>Left</td>
<td>−34, −78, −16</td>
<td>−1.940</td>
<td>.003</td>
<td>−0.146</td>
<td>43</td>
</tr>
<tr>
<td>Youths with childhood-onset CP less than TD youths</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insula (BA 48)</td>
<td>Left</td>
<td>−40, 12, −12</td>
<td>−2.102</td>
<td>.0002</td>
<td>−0.232</td>
<td>274</td>
</tr>
<tr>
<td>Amygdala</td>
<td>Left</td>
<td>−26, 0, −12</td>
<td>−1.923</td>
<td>.0005</td>
<td></td>
<td>132</td>
</tr>
</tbody>
</table>

Abbreviations: ACC, anterior cingulate cortex; BA, Brodmann area; CP, conduct problems; IFG, inferior frontal gyrus; MNI, Montreal Neurological Institute; SDM, signed differential mapping; STG, superior temporal gyrus; TD, typically developing.

* Areas shown in boldface reflect the peak anatomical location with the breakdown of local peaks within this cluster also shown.
Voxel-probability threshold: P = .005; cluster extent threshold: 10 voxels. Corrected using gaussian random fields theory cluster-based correction for multiple comparisons (P < .001).

The SDM estimate values, equivalent to the effect size, are reported for the cluster peaks.

The right amygdala gray matter volume reduction was also observed but at a cluster extent of only 9 voxels (below cluster extent threshold).
Higher CU trait severity in youths with CP was also associated with a lower reduction in GMV in the right amygdala at a more liberal significance threshold ($P < .0005$). A higher proportion of male youths with CP in the sample was associated with decreased GMV in the left amygdala (coordinates, $−30, 0, −10; P < .001; SDM z \text{ score} = −3.62; k = 14 \text{ voxels}$) (eFigure 4B in the Supplement). Higher CU trait severity in youths with CP was also associated with a lower reduction in GMV in the right amygdala at a more liberal significance threshold ($P < .0005$). A higher proportion of male youths with CP in the sample was associated with decreased GMV in the left amygdala (coordinates, $−30, 0, −24; P < .001; SDM z \text{ score} = −3.31; k = 165 \text{ voxels}$). However, only 6 of the 13 studies revealed this negative correlation (eFigure 4A in the Supplement). A higher proportion of female youths with CP was associated with increased GMV in the right inferior temporal gyrus (coordinates, $54, −16, −24; P < .001; SDM z \text{ score} = 2.99; k = 115 \text{ voxels}$). However, this effect appeared to be driven by one study (eFigure 4A in the Supplement) that included only female participants with CD and reported increased GMV for the CD group compared with TD youths in almost the same locus. The proportion of youths with CP currently comorbid for ADHD (Table 1) was not associated with significant suprathreshold clusters. The main meta-analysis results were not significantly influenced by IQ, but studies using samples with a larger age range were associated with greater GMV reduction in the left amygdala (eFigure 1, eFigure 2, eTable 2, eTable 3, eMethods 3, and eMethods 4 in the Supplement). Conduct disorder symptom severity was associated with GMV reduction in the right superior temporal gyrus (eFigure 3 and eTable 4 in the Supplement).
Discussion

To our knowledge, this is the first image-based meta-analysis of VBM studies of GMV examining differences between youths with CP and TD youths. The main findings were that, compared with TD youths, those with CP exhibited significantly reduced GMV in the left amygdala, extending into the left anterior insula, as well as the right insula, extending laterally into right vIPFC/OFC and inferiorly into the STG. Reduced GMV was also observed for youths with CP in the left medial superior frontal gyrus, extending into the right ACC, as well as in the left fusiform gyrus. Across the 13 studies, gray matter reduction in the left amygdala was the most reliable finding. A subgroup meta-analysis of studies that only included youths with childhood-onset CP revealed reduced GMV in the left amygdala and insula when compared with TD youths, broadly consistent with the main meta-results. The meta-regression analysis also revealed that higher levels of CU traits were associated with a lower reduction in GMV in the left putamen. The proportion of male youths with CP was associated with decreased GMV in the left amygdala, while the proportion of female youths with CP was related to an increase in GMV in the right inferior temporal gyrus. Finally, while age range and CD severity were associated with some of the gray matter differences observed in the left amygdala and right STG, respectively, ADHD comorbidity and IQ did not contribute to the reported GMV differences.

The amygdala is involved in a host of different processes, including, but not limited to, classical aversive conditioning, decision-making, face processing, emotional empathy, and response to threat through the initiation of the hypothalamic-pituitary-adrenal axis stress response. The GMV reduction in the amygdala observed in youths with CP supports previous behavioral and functional MRI evidence of impairments and atypical amygdala response in tasks probing those processes. Youths with CP also exhibited reduced GMV in the anterior insula bilaterally, a region that forms part of a network related to empathic concern for others and also critical for behavioral adjustment during risky decision-making. This result fits well with functional MRI studies reporting atypical anterior insula response in youths with CP while watching others in distress or pain and during decision-making, suggesting that abnormality within this structure might partly underlie impaired empathy and poor decision-making that in turn increase the risk of violence seen in youths with CP. This interpretation is supported by evidence that anterior insula GMV in male adolescents with CP correlated positively with empathy scores and negatively with the number of lifetime CD symptoms and aggressive behavior.

We also observed decreased GMV in the right vIPFC/OFC, implicated in decision-making, response inhibition, and emotion regulation, all of which are impaired in youths with CP. There is also evidence that antisocial personality disorder, for which a diagnosis of CD by the age of 15 years is required, is associated with GMV reduction in the OFC whose volume is negatively correlated with symptoms of antisocial personality disorder in adults. Therefore, decreased vIPFC/OFC GMV could compromise self-regulation in youths with CP and increase the risk of antisocial and aggressive behavior.

Finally, youths with CP exhibited reduced GMV in the left medial superior frontal gyrus, extending into the right ACC. The GMV reduction in the medial superior frontal gyrus has not been commonly reported in previous structural MRI studies on CP, illustrating the advantage of the meta-analytic approach adopted here. Given its central role in social cognition in general and perspective taking in particular, this finding could partly explain data indicating impaired perspective taking in youths with CP. The reduced GMV observed in the superior frontal gyrus also extended into the right rostral ACC, a region where atypical response has been reported in previous studies on CP investigating empathy for pain and processing of negative pictures. The subgroup meta-analysis of studies that only included youths with childhood-onset CP and TD youths revealed reduced GMV in the left anterior insula, extending into the amygdala in the CP group. Prior to our meta-analysis, it was unclear which brain regions could be consistently considered as structurally abnormal in childhood-onset CP. Of the 6 studies included in our subgroup meta-analysis, only 1 study reported decreased GMV in both the amygdala and insula, whereas 2 studies reported decreased GMV in the amygdala only, and 3 studies did not report group differences in those regions. Therefore, our results may help clarify this disparity and, in line with previous functional MRI studies reporting atypical amygdala and anterior insula response in youths with childhood-onset CP in tasks probing affective processing and decision-making, support the view that structural and functional abnormalities within those regions are associated with childhood-onset CP.

Higher CU traits were associated with a lower reduction in GMV in the left putamen, which forms part of the striatum, a region critical for reinforcement learning and decision-making. The effect in the putamen is consistent with previous structural MRI studies that reported a positive association between striatal volume and CU traits in youths with CP and psychopathy scores in adults. Interestingly, however, our exploratory meta-regression results suggest that higher levels of CU traits are associated with more similar GMV in youths with CP and TD youths within this region. Subsequent meta-regression analyses revealed a negative association between the proportion of male youths with CP and reduced GMV in the left amygdala, which contrasts with a previous VBM study in which both male and female youths with CD showed similar reductions in GMV in the amygdala compared with TD youths. We also observed a positive association between the proportion of female youths with CP and GMV in the right inferior temporal cortex, but we consider this association spurious given that it was driven by the one study that includes female participants only. Finally, ADHD comorbidity did not influence our main results, consistent with evidence from 2 recent SDM meta-analyses of structural MRI studies in youths with ADHD that identified GMV reduction in the basal ganglia and, to a lesser extent, larger GMV in the left posterior cingulate cortex.
This study has several limitations. First, we did not include unpublished studies, but the Orwin’s fail-safe N analysis indicated that a potential publication bias was unlikely. Second, our results are inherently tied to the limitation of VBM that cannot detect spatially complex and subtle group differences in other brain metrics, such as cortical thickness and surface area. However, our results of decreased gray matter in the vIPFC/OFC and the insula are broadly consistent with those of 3 surface-based morphometry studies that examined cortical thickness and surface area. Third, given a lack of data, we were unable to conduct a direct comparison between youths with adolescent-onset CP and TD youths. Fourth, a measure of CU traits in youths with CP was only available for 5 of the 13 studies, further limiting any strong conclusions drawn from the meta-regression analyses. Finally, the 13 included studies differed in sample size as well as several comorbid psychopathologies, which might have influenced our results.

Conclusions

The results of this meta-analysis suggest that youths with CP present with significantly reduced GMV in the left amygdala and insula bilaterally, extending ventrolaterally into the vIPFC/OFC and inferiorly into the STG on the right. Youths with CP also showed reduced GMV in the left medial superior frontal gyrus, incorporating the right rostral ACC, and the left fusiform gyrus. These findings help build a more coherent account of structural abnormalities in youths with CP. The subgroup and meta-regression analyses provided additional information about how heterogeneity within CP might influence GMV abnormalities in this population. There is a pressing need for larger and prospective longitudinal structural MRI studies of CP to examine the associations between those variables and GMV in the same study.


34. Giedd JN, Rapoport JL. Structural MRI of pediatric brain development: what have we learned and where are we going? Neuro. 2010;67(5):728-734.


