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Rogers, Jack C; De Brito, Stéphane A

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RUNNING TITLE: GRAY MATTER IN YOUTHS WITH CONDUCT PROBLEMS

Cortical and subcortical gray matter volume in youths with conduct problems: A meta-analysis

Jack C. Rogers, PhD[1*], Stéphane A. De Brito, PhD[1*]

[1]School of Psychology, University of Birmingham, Birmingham, UK

*Address for correspondence:
Jack C. Rogers
School of Psychology
University of Birmingham
Edgbaston
Birmingham
B15 2TT, UK
Tel: +44(0)121 4147195
Email: j.rogers@bham.ac.uk/s.a.debrito@bham.ac.uk

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Abstract

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 CP that used VBM methods to facilitate replication and aid further analyses by researchers.

Data Sources: The PubMed, ScienceDirect, Scopus and Web-of-Science databases were searched identifying VBM studies published between 2007 and March 2015. Manual searches were conducted using title and citation information. Authors were contacted soliciting additional data.

Study Selection: A literature search revealed 28 studies, with 13 eligible for inclusion (394 youths with CP and 350 typically-developing [TD] youths).

Data Extraction and Synthesis: Anisotropic effect-size Signed Differential Mapping 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 Outcome(s) and Measure(s): Regional gray matter volume (GMV) differences in youths with CP compared to TD youths.

Results: Youths with CP had decreased GMV in left amygdala (SDM-estimate=-0.218;p=0.00002) (extending into anterior insula), right insula (SDM-estimate=-0.174;p=0.0004) (extending ventro-laterally into prefrontal cortex and inferiorly into superior temporal gyrus), left medial superior frontal gyrus (SDM-estimate=-0.163;p=0.001)

(extending into right anterior cingulate cortex) and left fusiform gyrus (SDM-estimate=-0.146;*p*=0.003). Sub-group meta-analysis assessing age-of-onset effects identified reduced GMV in the left amygdala (SDM-estimate=-0.232;*p*=0.0002) extending into anterior insula. Meta-regression analyses revealed that greater scores on measures of callous-unemotional traits were associated with a lower reduction in GMV in left putamen (SDM-estimate=-0.911;*p*=0.00006). The proportion of males and females in the sample related to decreased GMV in left amygdala (SDM-estimate=-0.31;*p*=0.000003) and increased GMV in right inferior temporal cortex (SDM-estimate=0.755;*p*=0.00001). Whilst there was no association with co-morbid ADHD or IQ, age-range did contribute to gray matter differences in left amygdala.

Conclusions and Relevance: We identified gray matter reductions within the insula, amygdala, frontal and temporal regions as the most consistent in CP as well as inconsistencies in sample characteristics across studies that should be addressed in future research.

Introduction

Youths with conduct problems (CP), such as conduct disorder (CD), oppositional defiant disorder (ODD) and disruptive behavior disorder (DBD), are characterized by aggressive, antisocial and oppositional/defiant behaviors during childhood and adolescence[1,2]. CP are one of the most prevalent child psychiatric disorders and among the most common reasons for a childhood referral to mental health services[3]. Crucially, CP in youths are not only predictive of antisocial and aggressive behaviors in adulthood, but also substance misuse, other mental health problems and poor physical health [4, 5], making them an important target for etiologic research and prevention efforts[6].

Youths with CP are a highly heterogeneous population incorporating different subgroups[7], potentially reflecting distinct etiological pathways to CP[8]. Several approaches have attempted to account for this heterogeneity[9], with two included within the Diagnostic and Statistical Manual of Mental Disorders (DSM-5[1]). The first is the age-based distinction between childhood-onset and adolescent-onset CD, introduced in DSM-IV[10]. This distinction is thought to identify two qualitatively and etiologically distinct subtypes and has been well supported for both females and males ([11]; but see[12]). The second subtyping approach distinguishes youths with CP as those displaying high (CP/HCU) versus low (CP/LCU) callous-unemotional (CU) traits[8, 13, 14]. CU 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 shown that youths with CP/HCU versus those with CP/LCU are characterized by different vulnerabilities[7]. This resulted in the inclusion of CU traits as the 'with Limited Prosocial Emotions' specifier for the diagnosis of CD in DSM-5[1].

To characterize whole-brain and regional gray matter volume (GMV), recent structural magnetic resonance imaging (sMRI) studies on CP have used automated and unbiased methods such as voxel-based morphometry (VBM)[15, 16]. Two studies reported an overall reduction in GMV in youths with CP compared to TD youths[17, 18]. Youths with CP exhibit reduced GMV in a number of cortical and subcortical brain regions including anterior[12, 19, 20,21] and posterior[22] insula, temporal lobes bilaterally,[17,19, 22,23]right ventromedial prefrontal cortex (vmPFC)[12,23] incorporating orbitofrontal cortex (OFC),[12,17,19,24] right dorsolateral prefrontal cortex (dlPFC)[12,21,25], anterior cingulate cortex (ACC)[20,23,24], hippocampus[17,22], amygdala[17, 19, 20], and striatal regions[12, 20]. However, there are marked inconsistencies across studies regarding the foci of reduced gray matter, which encompass several fronto-temporal and striato-limbic structures. Two recent studies also failed to identify a significant difference in GMV between youths with CP and TD youths [26,27].

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[20, 27], studies could have resulted in low statistical power and increased risk of false-positive results[28]. Some studies failed to account for heterogeneity within CP in terms of age of onset of CD and levels of CU traits. Some studies have also included samples exhibiting high co-morbidity with other disorders, notably attention deficit hyperactivity disorder (ADHD)[12, 17, 19, 23, 26, 27] commonly co-morbid with CD [29, 30]. Controlling for ADHD as a potential confound can have a significant effect on reported results[12]. Finally, potential sex differences might also have contributed to the inconsistent findings, with recent VBM studies reporting divergent patterns of GMV abnormalities across sexes[12, 27].

Given this variability, we applied seed-based *d* mapping[31], a novel voxel-based meta-analytical method, on published whole-brain VBM studies in 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 (ROIs)[31]. To increase the accuracy and sensitivity of our analyses, we included the original statistical parametric maps from 85% of studies in our meta-analysis[31]. Reliability analyses were performed to assess robustness of findings. To examine the respective contribution of age of onset of CP on heterogeneity of CP and GMV differences, we conducted an additional subgroup meta-analysis including only studies that compared childhood-onset CP youths with TD youths. Given evidence of the differential etiology and neurobiology for CP youths displaying high versus low CU traits[7] and for CP in males versus females[32], meta-regressions were also conducted to examine the influence of CU traits and sex on GMV. Based on 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 were also examined given their influence on GMV[20,33].

Materials and methods

Search and Study Selection

A literature search of VBM studies published between 2007 – the year of the first VBM study in CP[19] – and March 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 (1) failed to use VBM, (2) to report a voxel-wise comparison between youths with CP and TD youths for GMV, (2) did not report whole-brain results (i.e., limited their analyses to specific ROIs), (3) used different significance or extent thresholds throughout the whole brain, (4) included duplicated data sets, and (5) 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 non-significant results, a Orwin's fail safe-analysis N[34] was performed to calculate the number of studies with an effect size of 0 needed to make the mean effect size non-significant (p > 0.05).

Comparison of regional gray matter volumes

Anisotropic effect-size Signed Differential Mapping (AES-SDM; v.4.21) software (http://www.sdmproject.com/software/) [31, 35] was used for voxel-based meta-analyses, comparing GMV differences in youths with CP and TD youths. AES-SDM enables original statistical parametric maps and peak coordinates to be combined with established meta-analytical statistics (eMethods 1 in the Supplement)[31]. 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[31]. The inclusion of the statistical parametric maps provides a more accurate representation of the results[31]. Statistical parametric maps for the group-wise comparison between youths with CP and TD youths were obtained for 11 (85%) of the 13 included studies (Table 1).

For two studies[17,21] 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 manuscripts. For one study[21] 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[36-38], statistical significance was determined using standard randomization tests (N=20) and a set of recommended thresholds optimizing sensitivity while adequately controlling for type 1 error (voxel p<0.005, peak

height SDM-Z=1, cluster extent=10 voxels)[31]. The full-width half-maximum (FWHM) was set to 20 mm[31,35] (eMethods 1 in the Supplement). Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines were followed[39].

Reliability Analysis, Sub-Group Meta-Analysis and Meta-Regressions

A jack-knife analysis was used to establish the reliability of the results[31,40]. This sensitivity analysis consists of removing a single dataset 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 sub-group meta-analysis was also carried out on studies including only youths diagnosed with 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 co-morbid for ADHD on GMV. The meta-regressions reported here should be treated as exploratory only, with a more strict threshold applied in all cases to control for false-positives ($p < 0.00017$, Bonferroni-corrected)[40] and results only considered when significant slopes were accompanied by significant differences at one extreme of the independent variable (e.g. 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 (POMP)[41]. Scores which express raw scores in terms of the minimum and maximum score. This established method of standardizing scores[42,43] allows comparisons across scoring methods, populations and measures overcoming problems associated with alternative standardization methods (e.g. z-scores) that do not allow comparison of scores across studies and samples. For two studies that used two assessment

tools to measure CU traits,[20,22] the average POMP score across measures of CU traits was calculated (eTable 4 and eMethods 2 in the Supplement). In addition, the association between GMV and age, IQ and CD severity was examined (eFigure 2, 3 and 4; eTable 5, 6, and 7 and eMethods 3 and 4 in the Supplement).

Include Table 1 about here

Results

Study Characteristics

Twenty-eight potential studies were identified for inclusion in the meta-analysis. Fifteen studies were excluded based on inclusion criteria (Figure 1 and eTable 1 in the Supplement). Thirteen eligible studies (Table 1) were identified that included a direct comparison of GMV between youths with CP (N=394; M age=14.45; SD=2.94; age range=8 – 21 years) and TD youths (N=350; M age=14.33; SD=2.98; age range=8 – 21 years). Of the 394 youths with CP, 327 (83%) were males while 272 (78%) of the 350 TD youths were males. Eight of the 13 studies included only male participants, with four including male and female subjects and one including all female participants (Table 1).

Insert Figure 1 about here

Youths with CP vs. TD youths: Regional gray matter differences

AES-SDM analyses revealed decreased GMV for youths with CP compared to TD youths in the left amygdala and the insula bilaterally, with the cluster extent larger on the right, extending laterally into vlPFC/OFC and inferiorly into superior temporal gyrus (STG). Youths with CP also showed significantly reduced GMV in left medial superior frontal gyrus extending into right ACC, as well as reduced GMV in left fusiform gyrus (Table 2 and Figure 2). No significant GMV increases were observed for youths with CP compared to TD youths.

The Orwin's fail safe-analysis N[34] indicated that a potential publication bias was unlikely, as 302 studies showing no effect would be needed to invalidate the reported findings.

Insert Figure 2 about here

Insert Table 2 about here

Reliability Analysis

A jackknife sensitivity analysis showed that the gray matter decrease in the left amygdala was preserved throughout all the 14 study combinations. The left insula and right IFG 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 two of the study combinations. An additional cluster revealing reduced GMV in left postcentral somatosensory cortex (BA 3) was observed in five[17,20,21,26,27] out of the 13 studies (eTable 2 in the Supplement). No additional significant clusters were found in either the positive or negative direction.

Sub-group Analysis: Effects of age-of-onset

A sub-group meta-analysis was carried out on studies including only youths diagnosed with childhood-onset CP. Of the 13 studies that included a comparison between youths with CP and TD youths, six included youths diagnosed with childhood-onset CP[17,19-21,27,44]. This sub-sample comprised of 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 encompassing the insula and amygdala (Table 2 and Figure 2E). The sensitivity analysis revealed that the gray matter decrease in left amygdala and insula was broadly consistent across studies, with an additional cluster in right insula observed in three out of the six studies (eTable3 in the Supplement).

Meta-regression analyses: Effects of CU traits, sex differences and ADHD comorbidity

Higher CU trait severity in youths with CP was associated with a lower reduction in GMV in the left lentiform nucleus (putamen) ([-30, 0, -10], *P*=0.00006; SDM-*Z*=-3.62; k=14 voxels) (eFigure 1B in the Supplement)[1]. A higher proportion of males with CP in the sample was associated with decreased GMV in left amygdala ([-30, 0, -24], *P*=0.000003; SDM-*Z*=-3.31; k=165 voxels). However, only six out of the 13 studies revealed this negative correlation (eFigure 1A in the Supplement). A higher proportion of female youths with CP was associated with increased GMV in right inferior temporal gyrus ([54, -16, -24], *P*=0.00001; SDM-*Z*=2.99; k=115 voxels). However, this effect appeared to be driven by one study (eFigure 1A in the Supplement) that included only female participants with CD[12] and reported increased GMV for the CD group compared to TD youths in almost the same locus. The proportion of youths with CP currently co-morbid 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 2 and 3, eTable 5 and 6 and eMethods 3 and 4 in the Supplement). CD symptom severity was associated with GMV reduction in the right superior temporal gyrus (eFigure4 and eTable 7 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 to 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 vlPFC/OFC and inferiorly into STG. Reduced GMV was also observed for

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[1] 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 < 0.0005).

youths with CP in left medial superior frontal gyrus, extending into 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 sub-group meta-analysis of studies that only included youths with childhood-onset CP revealed reduced GMV in the left amygdala and insula when compared to 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 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 grey 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[45-49]. The GMV reduction in the amygdala observed in youths with CP supports previous behavioral and fMRI evidence of impairments and atypical amygdala response in tasks probing those processes[12,50,51]. Youths with CP also exhibited reduced GMV in the anterior insula bilaterally, a region forming part of a network related to empathic concern for others[52,53], and also critical for behavioral adjustment during risky decision-making[54]. This result fits well with fMRI studies reporting atypical anterior insula response in youths with CP while watching others in distress or pain[52,55,56] and during decision-making[57,58], suggesting that abnormality within this structure might partly underlie impaired empathy and poor decision-making that in turn increases risk for violence seen in CP[8,59]. This interpretation is supported by evidence that anterior insula GMV in male adolescents with CP

correlated positively with empathy scores[19] and negatively with the number of lifetime CD symptoms[20] and aggressive behavior[19].

We also observed decreased GMV in the right vlPFC/OFC, implicated in decision-making, response inhibition, and emotion regulation.[60-62], all of which have been shown to be impaired in youths with CP[63]. There is also evidence that antisocial personality disorder, for which a diagnosis of CD by age 15 is required[1], is associated with GMV reduction in the OFC whose volume is negatively correlated with symptoms of antisocial personality disorder in adults.[64] Therefore, decreased vlPFC/OFC GMV could compromise self-regulation in youths with CP and increase the risk for antisocial and aggressive behavior[64]. Finally, youths with CP exhibited reduced GMV in left medial superior frontal gyrus, extending into right ACC. GMV reduction in the medial superior frontal gyrus has not been commonly reported in previous sMRI 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[51]. The reduced GMV observed in superior frontal gyrus also extended into right rostral ACC, a region where atypical response has been reported in previous studies on CP investigating empathy for pain[52,56,65] and processing of negative pictures[66].

The sub-group meta-analysis of studies that only included youths with childhood-onset CP and TD youths revealed reduced GMV in the left amygdala extending into anterior insula 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. Out of the six studies included in our sub meta-analysis, only one[19] reported decreased GMV in both the amygdala and the insula while two reported decreased GMV in the amygdala only[17,20] and three did not report group differences in those regions[21,27,44]. Therefore, our results may help

clarify this disparity and, in line with previous fMRI studies reporting atypical amygdala and anterior insula response in youths with childhood-onset CP in tasks probing affective processing and decision-making[50], 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 left putamen, which forms part of the striatum, a region critical for reinforcement learning and decision-making[67]. The effect in the putamen is consistent with previous sMRI studies that reported a positive association between striatal volume and CU traits in youths with CP[20] and psychopathy scores in psychopathic adults[68]. 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 males with CP and reduced GMV in left amygdala, which contrasts with a recent VBM study where both males and females with CD showed similar reductions in GMV in the amygdala compared to TD youths[12]. We also observed a positive association between the proportion of females with CP and GMV in right inferior temporal cortex, but we consider this association as spurious given that it was driven by the one study that include females participants only[12]. Finally, ADHD comorbidity did not influence our main results, consistent with evidence from two recent SDM meta-analyses of sMRI 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[69,70].

Limitations

First, we did not include unpublished studies, but the Orwins fail-safe N[34] 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[71]. However, our results of

decreased gray matter in the vlPFC/OFC and the insula are broadly consistent with those of three surface-based morphometry studies that examined cortical folding and surface area[71-73]. 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 five 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 from this meta-analysis suggest that youths with CP present significantly reduced GMV in the left amygdala and insula bilaterally, extending ventro-laterally into vlPFC/OFC and inferiorly into STG on the right, left medial superior frontal gyrus incorporating right rostral ACC and left fusiform gyrus compared to TD youths. These findings help build a more coherent account of structural abnormalities in youths with CP. The sub-group 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 sMRI studies of CP to examine the associations between those variables and GMV in the same study.

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Figure 1 Title. Inclusion of studies in the meta-analysis

Figure 2 Title. Decreased GMV for youths with CP (N=394) compared to TD youths (N=350)(**A – D**) and for childhood-onset CP youths (N=159) compared to TD youths (N=180)(**E**; dashed line).

Figure 2 Legend.

Slices are shown in the sagittal, axial and coronal planes with MNI coordinates of the selected slices representing the peak in the x,y,z direction. A. Peak in left amygdala extending into left insula. B. Peak in right insula extending ventro-laterally into right inferior frontal gyrus and inferiorly into superior temporal gyrus. C. Peak in left medial superior frontal gyrus. D. Peak in left fusiform gyrus (circled). E. Peak in left amygdala extending into insula for CO-CP youths compared to TD youths only. See Table 2 for further details.

Table 1. Summary of studies included in the meta-analysis

Study	Diagnosis[a]	N of DBD (male %)	Mean age DBD (range)	IQ DBD	N of TD (male %)	Mean age TD (range)	IQ TD	Sample Characteristics	Measures of CU traits	Co-morbidity (ADHD %)	Scanner Strength	FWHM (mm)	Significance
Sterzer et al.[19]2007	CD	12 (100%)	12.8 (9-15 yrs)	100.6	12 (100%)	12.5 (9-15 yrs)	107.2	Clinical	None	ADHD (58%)	1.5	8	p<0.05, FWE-corrected
De Brito et al.[44]2009	CP/CU traits	23(100%)	11.6 (10-13.3 yrs)	95.4	25(100%)	11.8 (10-13.3 yrs)	106.9	Community	APSD	NA	3	8	p<0.001, uncorrected
Dalwani et al.[25]2011	ASD	25(100%)	16.6 (14-18 yrs)	98.1	19(100%)	16.6 (14-18 yrs)	105.2	Clinical	None	ADHD (12%)	3	8	p<0.05, FWE-corrected
Fairchild et al.[20]2011	CD (childhood/ adolescent onset)	63 (100%)	17.8 (16-21 yrs)	99.3	27 (100%)	18.5 (16-21 yrs)	101.4	Community	YPI & ICU	ADHD (24%), Substance abuse	3	8	p<0.001, uncorrected
Stevens & Haney-Caron[18]2012	CD	24(67%)	16 (15-16 yrs)	91.3	24(67%)	16 (15-16 yrs)	97.4	Community	None	ADHD (0%), Substance abuse	3	8	p<0.05, corrected
Fairchild et al.[12]2013	CD (childhood/ adolescent onset)	22(0%)	17.2 (14-20 yrs)	99.8	20(0%)	17.6 (14-20 yrs)	105.8	Community	YPI	ADHD (10%), MDD	3	8	p<0.001, uncorrected
Olvera et al.[23]2014	CD	24(67%)	15.8 (13-17 yrs)	91.9	24(67%)	15.3 (13-17 yrs)	98.6	Prison	None	ADHD (75%), Bipolar disorder	3	9.4	Equivalent to p<0.05, FWE-corrected
Cope, Ermer, Gaudet et al.[22]2014	CD/ODD Psychopathic traits	20(100%)	17.4 (14.9-19 yrs	93	21(100%)	16.4 (12.8-19 yrs)	110.6	Prison/ Community	PCL-YV	ADHD (5%), Substance abuse	1.5	10	p<0,05, FWE-corrected
Hummer et al.[26]2014	DBD	33(73%)	15.3 (13-17 yrs)	102.7	33(73%)	15.4 (13-17 yrs)	106.9	Community	None	ADHD (58%)	3	8	p<0.05, corrected
Michalska et al.[27]2015[b]	DBD	43(54%)	10.1 (9-11 yrs)	NA	68(51.5%)	10 (9-11 yrs)	NA	Community	None	ADHD (NA), GAD & MDD	3	NA	p<0.001, uncorrected
Sebastian, et al.[24] 2015	CP/CU traits	60(100%)	14.3 (10-16 yrs)	97.9	29(100%)	13.6 (10-16 yrs)	105.2	Community	ICU	NA	1.5	6	p<0.001, uncorrected
Huebner et al.[17]2008	CD	23(100%)	14.5 (12-17 yrs)	96.7	23(100%)	14.2 (12-17 yrs)	98.9	Clinical	None	ADHD (74%)	1.5	10	p<0.05, corrected, cluster level
Fahim et al.[21]2011	DBD	22(100%)	8.4 (8 yrs)	NA	25(100%)	8.4 (8 yrs)	NA	Community	None	NA	1.5	10	p<0.05, FDR-corrected

Abbreviations: IQ = Intelligence Quotient; TD = typically developing; yrs = Years; CU-traits = callous-unemotional traits; FWHM = full-width half-maximum; CD = conduct disorder; DBD = disruptive behaviour disorder; ASD = antisocial substance dependence; VBM = voxel-based morphometry; ADHD = Attention-deficit hyperactivity-disorder; APSD = Antisocial Process Screening Device; CP = conduct problems; ICU = Inventory of Callous-Unemotional Traits; ODD = oppositional defiant disorder; MDD = manic depressive disorder; GAD = generalised anxiety disorder; PCL-YV = Psychopathy Checklist: YPI = Youth Psychopathic Traits Inventory; FWE = family-wise error; FDR = false-discovery rate; NA = not available. Gray: Studies for which raw statistical parametric maps were not available.

[a] Consistent with the diagnosis as included in the study.

[b] Following personal communication with the lead author (beginning 30/01/2015) it was made apparent that whilst 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). In order 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.

Table 2: Meta-analysis results comparing GMV in youths with CP (N=394) versus TD youths (N=350) (*top*) and childhood-onset CP youths (N=159) versus TD youths (N=180) (*bottom*)

Anatomical location[a] (Brodmann area; BA)	Hemisphere	MNI-coordinate (x,y,z)	SDM Z value	*p* value[b]	Effect size (SDM-Estimate)[c]	No. of voxels
CP < TD						
Amygdala[d]	**Left**	**-32, 2, -20**	**-2.837**	**0.00002**	**-0.218**	**114**
Insula (BA 48)		-42, 8, -8	-2.235	0.0006		277
Insula (BA 38)	**Right**	**36, 20, -16**	**-2.302**	**0.0004**	**-0.174**	**105**
IFG (*triangularis*) (BA 45)		48, 20, 2	-2.252	0.0006		107
IFG (*orbitalis*) (BA 47)		46, 24, -6	-2.203	0.0008		85
IFG (*opercularis*) (BA 48)		54, 20, 10	-2.162	0.001		36
Insula (BA 48)		30, 14, -18	-2.089	0.001		48
STG/Temporal Pole		38, 14, -22	-2.046	0.002		20
Superior frontal gyrus (*medial*) (BA 10)	**Left**	**-6, 54, 28**	**-2.164**	**0.001**	-0.163	**77**
ACC (BA 32)	Right	6, 50, 14	-1.979	0.002		49
Fusiform gyrus (BA 19)	**Left**	**-34, -78, -16**	**-1.940**	**0.003**	**-0.146**	**43**
CO-CP < TD						
Insula (BA 48)	**Left**	**-40, 12, -12**	**-2.102**	**0.0002**	**-0.232**	**274**
Amygdala		-26, 0, -12	-1.923	0.0005		132

Abbreviations: MNI = Montreal Neurological Institute; SDM = signed differential mapping; CP = conduct problems; TD = typically developing; CO = childhood-onset.

Anatomical abbreviations: IFG = inferior frontal gyrus; STG = superior temporal gyrus; ACC = anterior cingulate cortex.

[a] Areas shown in **BOLD** reflect the peak anatomical location with the breakdown of local peaks within this cluster also shown.

[b] Voxel-probability threshold: p = 0.005, cluster extent threshold: 10 voxels. Corrected using Gaussian Random Fields theory cluster-based correction for multiple comparisons (p < 0.001).

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

[d] Right amygdala GMV reduction was also observed but at a cluster extent of only 9 voxels (below cluster extent threshold).