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<th>Abnormalities of cortical structures in adolescent-onset conduct disorder</th>
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<td><strong>Author(s)</strong></td>
<td>Jiang, Y; Guo, X; Zhang, J; Gao, J; Wang, X; Yao, S; Huang, B</td>
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Abnormalities of cortical structures in adolescent-onset conduct disorder

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9 Shenzhen Institute of Research and Innovation, University of Hong Kong, Shenzhen, Guangdong, People’s Republic of China

Abstract

Converging evidence has revealed both functional and structural abnormalities in adolescents with early-onset conduct disorder (EO-CD). The neurodevelopmental abnormalities underlying EO-CD may be different from those of adolescent-onset conduct disorder (AO-CD) patients. However, the cortical structure in AO-CD patients remains largely unknown. The aim of the present study was to investigate the cortical alterations in AO-CD patients.

Method. We investigated T1-weighted brain images from AO-CD patients and age-, gender- and intelligence quotient-matched controls. Cortical structures including thickness, folding and surface area were measured using the surface-based morphometric method. Furthermore, we assessed impulsivity and antisocial symptoms using the Barratt Impulsiveness Scale (BIS) and the Antisocial Process Screening Device (APSD).

Results. Compared with the controls, we found significant cortical thinning in the paralimbic system in AO-CD patients. For the first time, we observed cortical thinning in the precuneus/posterior cingulate cortex (PCC) in AO-CD patients which has not been reported in EO-CD patients. Prominent folding abnormalities were found in the paralimbic structures and frontal cortex while diminished surface areas were shown in the precentral and inferior temporal cortex. Furthermore, cortical thickness of the paralimbic structures was found to be negatively correlated with impulsivity and antisocial behaviors measured by the BIS and APSD, respectively.

Conclusions. The present study indicates that AO-CD is characterized by cortical structural abnormalities in the paralimbic system, and, in particular, we highlight the potential role of deficient structures including the precuneus and PCC in the etiology of AO-CD.
adulthood, AO individuals are more likely to have antisocial problems and are also expected to experience more health burden in later adult life than their control counterparts (Odgers et al. 2007; Roisman et al. 2010). Some recent evidence also suggests differentiated phenotypic findings as well as task performances, such as reward sensitivity and facial recognition, between AO-CD and EO-CD patients (Fairchild et al. 2009a, b; Passamonti et al. 2010; Silberg et al. 2014). In Fairchild et al. (2011), reduced volume of the right insula was only observed for AO-CD patients compared with healthy controls (HCs), while reduced volume of the amygdala was observed for both subtypes of CD relative to controls. Given the aforementioned findings, we expect to further explore the biological substrate of AO-CD, thereby providing conceivable evidence for the subtle distinction that may exist between the two subtypes. To date, several studies have compared the gray matter structure of normally developing youths and adolescents with CD, especially those with EO-CD (Kruesi et al. 2004; Sterzer et al. 2007; Huebner et al. 2008; Fairchild et al. 2011; Hyatt et al. 2012; Wallace et al. 2014). The abnormal structures identified most often included the orbitofrontal cortex (OFC) (Huebner et al. 2008), the amygdala (Huebner et al. 2008; Fairchild et al. 2011; Wallace et al. 2014), the insula (Sterzer et al. 2007; Fahim et al. 2011; Fairchild et al. 2011) and other temporal regions (Huebner et al. 2008; Hyatt et al. 2012). Moreover, gray matter volume in the frontal and temporal areas has often been found to be inversely related to the CD symptoms manifested by a subject (Sterzer et al. 2007; Huebner et al. 2008). It has been hypothesized that impairment of the aforementioned structures, which may affect emotional regulation and behavioral control (Blair, 2004), is associated with the inappropriate behaviors exhibited by CD subjects (Rubia et al. 2009). Correspondingly, aggressive, antisocial individuals were also found to have structural deficits in the prefrontal cortex, the anterior cingulate cortex (ACC) and several other interconnected regions of the brain (Yang & Raine, 2009). Although the structural findings regarding EO-CD have been largely studied in heterogeneous samples and with different study designs, structural alterations of AO-CD have been less investigated and the neural basis of different task performances between the two subtypes of CD remains unknown. In addition, it is important to note that almost all the work conducted before did not exclude attention-deficit/hyperactivity disorder (ADHD) which was characterized by a delay in cortical maturation (Shaw et al. 2007). It indicates that the contribution of co-morbid ADHD features to structural abnormalities observed for CD should be differentiated. Another concern is the use of voxel-based morphometry (VBM); while this method combines both thickness and surface features to calculate gray matter volume (Winkler et al. 2010), it may obscure the degree to which each factor contributes to volume differences since these measures were found to be globally and regionally independent and stemmed from different genetic and cellular mechanisms in the brain (Armstrong et al. 1995; Panizzon et al. 2009). While the surface-based method (surface-based morphometry; SBFM) enables separate measurement of cortical thickness and surface area as well as cortical folding based on the two-dimensional folded laminar structure of the cerebral cortex (Dale et al. 1999; Winkler et al. 2010), it aids in understanding neural abnormalities beyond the basic volumetric abnormalities and has the potential to elucidate the underlying causes of brain structural alterations and the cognitive processes affected by these abnormalities. In addition, surface-based registration provides significantly higher accuracy than any form of volume-based registration (Ghosh et al. 2010). Three SBFM studies in CD, however, recruited participants with an unspecified (Wallace et al. 2014) or wide age range, i.e. 12–18 years in Hyatt et al. (2012) and 16–21 years in Fairchild et al. (2015). Although they matched groups for age, the non-linear and region-specific manner of gray matter development from the ages of 4 to 20 years may confound group differences (Giedd et al. 1999). In the present study, we decided to set a cut-off of age 14 years for adolescence (Silberg et al. 2014), after the time when puberty has begun in most children and after the patterns of genetic influences have mainly stabilized (Silberg et al. 2001). Additionally, onset of CD after 16 years is rare (APA, 2013), so AO-CD patients aged 14–16 years were recruited along with age-, intelligence quotient (IQ)- and gender-matched HCs. Based on previous literature, we hypothesized that cortical deficits (including thickness, surface area and cortical folding) would be observed in AO-CD patients, especially in the paralimbic regions as has been postulated (Rubia, 2011). Second, the detected cortical deficits were assumed to be correlated with the high-level impulsive as well as antisocial problems in CD.

**Method**

**Samples**

A total of 28 AO-CD participants aged 14–16 years (22 males and six females) were recruited from out-patient clinics affiliated with the Second Xiangya Hospital of Central South University (Changsha, Hunan, China). A diagnosis of CD was determined using the
Demographics and psychiatric characteristics of adolescents with CD and HCs

<table>
<thead>
<tr>
<th></th>
<th>HCs</th>
<th>CD patients</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age, years</td>
<td>15.1 (0.6)</td>
<td>14.8 (0.8)</td>
<td>0.13</td>
</tr>
<tr>
<td>Gender, n</td>
<td>21</td>
<td>22</td>
<td>0.46</td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>12.7 (6.9)</td>
<td>14.6 (6.6)</td>
<td>0.27</td>
</tr>
<tr>
<td>Subjective Socioeconomic Status Scale (SSS) (Hu et al., 1993)</td>
<td>6.2 (1.3)</td>
<td>6.1 (1.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>C-WISC</td>
<td>107.4 (6.9)</td>
<td>103.3 (9.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>MASC</td>
<td>38.3 (12.6)</td>
<td>44.6 (20.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>CES-D</td>
<td>12.7 (6.9)</td>
<td>14.6 (6.6)</td>
<td>0.27</td>
</tr>
<tr>
<td>APSD total</td>
<td>11.0 (2.8)</td>
<td>15.3 (4.3)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>APSD-callous-unemotional</td>
<td>4.5 (1.5)</td>
<td>6.4 (1.8)</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>SDQ total</td>
<td>12.5 (9.1)</td>
<td>15.5 (5.7)</td>
<td>0.04*</td>
</tr>
<tr>
<td>Gender</td>
<td>12.2 (5.1)</td>
<td>15.5 (5.7)</td>
<td>0.04*</td>
</tr>
<tr>
<td>CD patients</td>
<td>2.4 (1.3)</td>
<td>3.7 (1.8)</td>
<td>0.004**</td>
</tr>
</tbody>
</table>

Data are given as mean (standard deviation) unless otherwise indicated.

CD, Conduct disorder; HCs, healthy controls; C-WISC, Chinese Wechsler Intelligence Scale for Children; SSS, Subjective Socioeconomic Status Scale; MASC, Multidimensional Anxiety Scale for Children; CES-D, Center for Epidemiologic Studies Depression Scale; APSD, Antisocial Process Screening Device; BIS, Barratt Impulsiveness Scale; SDQ, Strengths and Difficulties Questionnaire.

* p < 0.05, ** p < 0.01.

Self-report assessments

All participants underwent the Chinese versions of the Center for Epidemiologic Studies Depression Scale (Radloff, 1977) and the Multidimensional Anxiety Scale for Children (Yao et al., 2007b). These scales were used to assess depression and anxiety severity, respectively. In addition, the Chinese version of the Subjective Socioeconomics Status Scale (SSS) (Hu et al., 2012) was used to quantify each participant’s socio-economic status, the Strengths and Difficulties Questionnaire (SDQ) (Yao et al., 2009) was used to detect internalization and externalization of problems. Callous–unemotional (CU) traits were evaluated using the Antisocial Process Screening Device (APSD) (Frick, 2001), and the Barratt Impulsiveness Scale (BIS) (Yao et al., 2007a) was used to assess impulsiveness. All CD subjects were treatment-naive. Details regarding psychiatric assessments for the two groups are provided in Table 1.

Image acquisition

Three-dimensional (3D) T1-weighted images (Philips, Achieva, 3.0T, the Netherlands) for all participants were obtained using 3D turbo field echo sequence. Scan parameters are: repetition time = 8.5 ms, echo time = 3.743 ms, flip angle = 8°, matrix = 256 × 256 pixels, field of view = 256 × 256, number of slices = 180, slice thickness = 1 mm, image voxel size = 1.0 × 1.0 × 1.0 mm³, and acquisition time = 178 s.
**Image processing**

All participants' T1 images underwent a radiological evaluation performed by a specialist (W.S.) to assess the presence of abnormal radiological or structural features. No participants were excluded from further analysis because of motion artifacts. Anatomic reconstruction of the cortical surfaces was performed using the Freesurfer image analysis suite (stable release version 5.3.0; http://surfer.nmr.mgh.harvard.edu) as previously described (Dale et al. 1999; Fischl et al. 1999). Triangle meshes which represent the boundary of the white surface (the gray matter–white matter interface) and the boundary of the pial surface (the gray matter–cerebrospinal fluid interface) were generated using deformation algorithms based on local intensity values (Dale et al. 1999) and geometrical and topological constraints (Fischl et al. 2001). The estimated white and pial surfaces were manually corrected for inconsistencies by visual inspection by an operator blind to each subject’s diagnosis. The reconstruction procedure was repeated until accurate representations of white and pial surfaces were obtained. The reconstructed surfaces were used to calculate cortical thickness and surface area (Fischl et al. 1999), with the former estimated as the shortest distance in millimeters between the two surfaces. As a result, cortical thickness values with submillimeter accuracy were obtained from over 100,000 vertices per hemisphere.

Estimates of surface area (the total area of the surface encompassing a brain region) are quantified by assigning an area to each vertex equal to the average of its surrounding triangles (Winkler et al. 2012). The total vertex area is summed over all vertices, and it is equal to the sum of the areas of the triangles. The degree of cortical folding (assessed by local gyrification index; IGI) was measured using surface-based, 3D gyrification measurements according to Schaer et al. (2008), a validated method embedded in Freesurfer. The IGI at a given point on the cortical surface was computed as the ratio between the surface of a 25-mm radius circular region of interest (ROI) on the folded pial surface and the surface of the corresponding cortex’s outer perimeter (Schaer et al. 2008). The amount of cortical folding (IGI) at each pial surface location reflects the amount of cortex buried within the sulcal folds in the surrounding area. As correct IGI values are typically between 1 and 5, the greater the value of the IGI, the more surfaces are buried in sulcal folds (Schaer et al. 2012).

**Statistical analysis**

Cortical thickness was smoothed with 10 mm while the IGI and surface area were smoothed using 5 mm full-width/half-maximum Gaussian kernels. To assess regional between-group differences in these cortical structural measures, surface-based group analyses were performed using the general linear model tools available in Freesurfer. Prior to the group comparisons, each participant’s data were resampled into an average spherical surface representation that optimally aligned the sulcal and gyral features across the subjects (Wismueller et al. 1999). Statistically significant differences between the cortical thickness, surface area and IGI of the two groups were identified using a Monte Carlo simulation (Hagler et al. 2006), a cluster-wise correction applied for multiple comparisons. Clusters were initially obtained using a $p < 0.05$ (two-tailed) vertex-wise threshold, and these were only reported if they met an additional cluster-wise probability ($P_{\text{cluster}}$) of $p < 0.05$ (two-tailed) at least. Statistically significant clusters with cortical thinning were defined as ROIs, then we mapped those ROIs to all of the individual subjects to extract statistical values for later correlation analyses.

**Post-hoc analysis**

To investigate gender and group effects, the two groups were compared using analysis of covariance with the structural thickness used as the dependent variable, and group and gender used as fixed factors. To determine whether potential confounders such as age, IQ, anxiety and depression level influenced the results obtained, a group comparison of thickness was performed by adding each of these factors as a covariate.

Pearson correlation analysis was applied to the BIS or ASPD total with ROI thickness in all participants and in AO-CD patients, while subscales of interest (including BIS-motor impulsivity, APSD-CU and APSD-impulsivity) were only used in patients. All correlation results were reported if they were associated with a $p$ value < 0.05, uncorrected.

**Results**

**Demographic and clinical data**

Table 1 lists the demographics and psychiatric characteristics for both groups. No significant differences in age, IQ, socio-economic status, anxiety or depression were observed between the two groups. However, CD patients had an overall higher total score and subscale scores for the APSD, BIS and SDQ compared with the HCs.

**Cortical thickness**

There were no group differences in mean cortical thickness in either the left or right hemisphere. In the left hemisphere, decreased cortical thickness was associated...
Table 2. Clusters of cortical thinning in adolescents in the two hemispheres (HCs > CD)

<table>
<thead>
<tr>
<th>Cluster number</th>
<th>Max</th>
<th>Size, mm²</th>
<th>TalX</th>
<th>TalY</th>
<th>TalZ</th>
<th>Number of vertices</th>
<th>Annotation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left hemisphere</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>−4.0</td>
<td>899.1</td>
<td>−13.9</td>
<td>−28.0</td>
<td>46.3</td>
<td>2113</td>
<td>PCC, precuneus, paracentral</td>
</tr>
<tr>
<td>2</td>
<td>−2.7</td>
<td>630.4</td>
<td>−18.1</td>
<td>35.4</td>
<td>−18.7</td>
<td>988</td>
<td>IOFC</td>
</tr>
<tr>
<td>3</td>
<td>−2.5</td>
<td>590.1</td>
<td>−12.9</td>
<td>−96.8</td>
<td>14.5</td>
<td>759</td>
<td>Lateral occipital</td>
</tr>
<tr>
<td>Right hemisphere</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>−4.0</td>
<td>1298.8</td>
<td>65.2</td>
<td>−17.0</td>
<td>3.0</td>
<td>3074</td>
<td>Superior temporal, supramarginal, insula</td>
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<tr>
<td>2</td>
<td>−3.7</td>
<td>839.1</td>
<td>31.0</td>
<td>−41.1</td>
<td>−9.0</td>
<td>1385</td>
<td>Parahippocampal, lingual, fusiform</td>
</tr>
</tbody>
</table>

HCs, Healthy controls; CD, conduct disorder; Max, log₁₀(p value); Tal (X, Y, Z), Talairach (X, Y, Z); PCC, posterior cingulate cortex; IOFC, lateral orbitofrontal cortex.

Potential confounders and correlation of ROIs with self-reported measurements

There was no evidence that gender influenced the results obtained (p > 0.2 in the five clusters). Group differences in cortical thickness for each cluster remained significant after controlling for age, IQ, anxiety and depression (p < 0.001).

For all the participants, four out of five clusters were negatively correlated with the APSD (except the right fusiform) and BIS (except the left precuneus) total scores, but only the left IOFC survived multiple comparisons (r = −0.44/−0.43, respectively, p < 0.01, Bonferroni, corrected).

For the AO-CD group only, APSD-CU was negatively correlated with thickness of the right superior temporal cortex (r = −0.4, p = 0.04) and the right fusiform (r = −0.63, p < 0.05, Bonferroni, corrected) while BIS-motor impulsivity was inversely correlated with the thickness of the right fusiform (r = −0.38, p < 0.05) and left IOFC (r = −0.35, p = 0.09). In addition, APSD-impulsivity was inversely correlated with IOFC thickness (r = −0.33, p = 0.07) with marginal significance. All correlation figures of CD patients are presented in the online Supplementary materials (Supplementary Figs S1–S5). We found no significant correlations between the total scores of BIS or APSD with ROI thickness.

Discussion

To our knowledge, this study is the first to document cortical abnormalities in a moderate cohort of AO-CD patients. The results clearly demonstrated that AO-CD was related to cortical thinning in multiple brain regions. As Rubia et al. (2011) previously postulated that abnormal activation of the ‘hot’ paralimbic system, which mediates the control of emotion and motivation (Blair, 2004), was specifically associated with CD (Rubia, 2011), cortical deficits in the left
Fig. 1. Differences in cerebral cortical thickness between adolescent-onset conduct disorder (AO-CD) patients ($n = 28$) and matched healthy controls (HCs; $n = 30$). Images of the left and right hemispheres for each group are presented. Medial (a), inferior (b) and posterior (c) views of the left inflated cerebral surfaces show differences in cortical thickness between the two groups. Lateral (d) and inferior (e) views of the right inflated cerebral surfaces show differences in cortical thickness between the two groups. Colored regions are used to indicate significant differences in cortical thickness between the two groups, with blue representing a greater thickness for the HC group compared with the AO-CD group. The value of the color bar is a log10 ($p$ value). Cluster labels correspond with those provided in Table 2. PCC, Posterior cingulate cortex; OFC, orbitofrontal cortex.
Although the structural imaging study in 441

439 EO-CD are more likely to be co-morbid with ADHD 438

437 which volume differences between the two subgroups 436

435 re 434 AO-CD.

433 re 432 Sterzer 431 not detect de 430 However, previous structural studies of EO-CD did 429 2009; Finger 428 avoidance learning and risky tasks (Rubia 427 normal activation during inhibitory tasks, passive 426 Wallace 425 studies of non-co-morbid CD (Hyatt 424 marginal gyri was in line with two recent structural 423 Cortical thinning of the precuneus, PCC and supra- 422 logical change in CD.

420 turbed due to AO-CD, although the parietal areas have 419 ation or processes related to these areas have been dis-

418 2011). The results indicated that gray matter matur-

417 Sterzer 2007; Huebner 416 (Kruesi 415 PCC, precuneus and supramarginal gyri which all 414 the left parietal regions with AO-CD, including the 413 gested that exceptional gray matter reductions occur in 412 and were consistent with volumetric reductions repeat-

411 also reported in previous studies on CD (Fairchild 410 paracentral cortex, fusiform and occipital areas were 409 types of CD. Moreover, thickness de 408 bic system may re 407 2008; Fairchild 406 (Kruesi 405 edly identi 404 and were consistent with volumetric reductions repeat-

403 closely matched the cortical topography of this system 402 Sterzer 401 OFC, right ACC, superior temporal and parahippo-

400 and the insula and parahip- 409 non-self/self-referential processes would be investi-

408 part of the PCC and precuneus has been primarily asso-

407 ocular abnormalities associated with CD subjects 406 however, previous structural studies of EO-CD did 405 non-self/self-referential processes would be investig-

404 2006). However, this assumption needs to be 403 2004; Sterzer 402 bermpohl, 2004); thus, abnormalities in these intercon-

401 2007; Wallace 400 tural reductions associated with CD subjects 409 and was also consistent with ab-

408 partially due to the dramatically dynamic changes that 407 of EO-CD failed to detect deficits in the parietal regions 406 to early adolescence (Giedd et al. 1999; Shaw et al. 405 these two alternative options could be exam-

404 Together, these results suggest that the deficits of the 403 cortical abnormalities in adolescent-onset conduct disorder 402 Cortical thinning of paralimbic structures, including 401 OFC, superior temporal gyrus, insula and parahippocampal gyrus, which were closely interconnected, 400 has been consistent with previously identified struc-

404 controls (Kruesi et al. 2004; Sterzer et al. 2007; 403 Among these studies, there has been consistent 402 both structural and functional neuroimaging data with 401 Thus, this assumption needs to be 400 children and adolescents 409 off the use of the term ‘autistic’ in diagnostic manuals 408 did not detect deficits in these areas (Kruesi et al. 2004; 407 it might reflect that these deficits are specific features of 406 and it might 405 2006). However, this assumption needs to be 404 influence of B, C and D within the VBM analysis 403 Although the functional imaging study in adolescent-onset conduct disorder 402 Consideration of results that were derived from the 401 taken together, these results suggest that the deficits of the 400 results: the OFC demonstrates decreased gray matter 403 Q5

434 433 of AO-CD. Although the structural imaging study in 432 (Fairchild et al. 2011), perhaps due to the co-morbidity 431 which volume differences between the two subgroups 430 were compared did not detect parietal differences 429 (Fairchild et al. 2011), perhaps due to the co-morbidity 428 of ADHD in their CD samples, adolescents with 427 EO-CD are more likely to be co-morbid with ADHD 426 than their AO-CD counterparts (APA, 2013). 425 Otherwise, differences can be attributed to different 424 methods adopted (VBM v. SBM). Indeed, activation 423 of the PCC and precuneus has been primarily associ- 422 with various self-referential processes through 421 its interconnection with other midline structures in 420 the brain, including the ACC and OFC (Northoff & 419 hyatt et al. 2012), However, our study sug-

418 also suggested that exceptional gray matter reductions occur in 417 the left parietal regions with AO-CD, including the 416 PCC, precuneus and supramarginal gyri which all 415 have not been observed in EO-CD (Kruesi et al. 2004; 414 Sterzer et al. 2007; Huebner et al. 413 2008; Fairchild et al. 2011). Thus, deficits in the paralim-

410 p-value), the positive value (4.0) of cluster 2 represents a converse result of the contrast; Tal (X, Y, Z), Talairach (X, Y, Z); HCs, healthy controls; CD, conduct disorder; rACC, rostral anterior cingulate cortex; mOFC, medial orbito-frontal cortex.

Table 3. Clusters of gyrification deficits in adolescents in the right hemisphere

<table>
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<tr>
<th>Cluster number</th>
<th>Max</th>
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<th>TalZ</th>
<th>Number of vertices</th>
<th>Annotation</th>
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<tr>
<td>(HCs &gt; CD)</td>
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<td></td>
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</tr>
<tr>
<td>1</td>
<td>−3.7</td>
<td>3622.4</td>
<td>8.3</td>
<td>37.0</td>
<td>−3.9</td>
<td>5927</td>
<td>rACC, mOFC, superior frontal</td>
</tr>
<tr>
<td>(CD &gt; HC)</td>
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</tr>
<tr>
<td>2</td>
<td>4.0</td>
<td>4765.7</td>
<td>27.7</td>
<td>−14.4</td>
<td>60.2</td>
<td>11 449</td>
<td>Precentral, postcentral, supramarginal</td>
</tr>
</tbody>
</table>

427 OFC, right ACC, superior temporal and parahippocampal gyri and the insula in our AO-CD patients 426 closely matched the cortical topography of this system 425 and were consistent with volumetric reductions repeated-

424 Sterzer 2009; Finger et al. 2011; Dalwani et al. 2014). However, previous structural studies of EO-CD did 423 However, previous structural studies of EO-CD did 422 an age-related increase in gray matter from childhood 421 to early adolescence (Giedd et al. 1999; Shaw et al. 420 These two alternative options could be exam-

419 Cortical thinning of the precuneus, PCC and supra-

418 marginal gyri was in line with two recent structural 417 studies of non-co-morbid CD (Hyatt et al. 2012; 416 Wallace et al. 2014), and was also consistent with ab-

415 normal activation during inhibitory tasks, passive 414 avoidance learning and risky tasks (Rubia et al. 2008, 413 2009; Finger et al. 2011; Dalwani et al. 2014), 412 However, previous structural studies of EO-CD did 411 not detect deficits in these areas (Kruesi et al. 2004; 410 Sterzer et al. 2007; Huebner et al. 2008), and it might 409 reflect that these deficits are specific features of 408 AO-CD. Although the structural imaging study in 407 which volume differences between the two subgroups 406 were compared did not detect parietal differences 405 (Fairchild et al. 2011), perhaps due to the co-morbidity 404 of ADHD in their CD samples, adolescents with 403 EO-CD are more likely to be co-morbid with ADHD 402 than their AO-CD counterparts (APA, 2013). 401 Otherwise, differences can be attributed to different
Fig. 2. Cerebral cortical folding differences in the right hemisphere between adolescent-onset conduct disorder (AO-CD) patients ($n = 28$) and matched healthy controls (HCs; $n = 30$). Lateral (a) and medial (b) views of the right cerebral surfaces show differences in the gyrification index between the two groups. Colored regions are used to indicate significant differences in the gyrification index values for the two groups, with blue representing greater values for the HC group compared with the AO-CD group. Conversely, red/yellow coloring represents greater values for the AO-CD group compared with the HC group. The value of the color bar is a $\log_{10}$ ($p$ value). Cluster labels correspond with those provided in Table 3. mOFC, Medial orbitofrontal cortex; rACC, rostral anterior cingulate cortex.
cognition (Blair & Cipolotti, 2000), reward and punishment processing (O’Doherty et al. 2001; O’Doherty, 2004); abnormalities in these processes have been closely related to aggression, which is a major characteristic of CD (Blair, 2004). Convergent evidence from functional MRI has also suggested lower activation of the OFC in response to reward task and emotional stimuli processing in CD adolescents compared with controls (Herpertz et al. 2008; Rubia et al. 2009). Abnormalities in the insula (Sterzer et al. 2007; Fairchild et al. 2011, 2015) have been associated with lack of empathy, and may contribute to abnormal emotional processing among CD subjects. Cortical deficits in the right superior temporal cortex and fusiform gyri found in our and previous studies (De Brito et al. 2009; Fairchild et al. 2011; Hyatt et al. 2012; Wallace et al. 2014) have the potential to explain why facial expression recognition was impaired in both EO-CD and AO-CD subjects (Fairchild et al. 2009a). The right fusiform gyrus maintains facial expression recognition probably through its communication with the superior temporal cortex (Winston et al. 2004) and OFC (Hornak et al. 2003). Thus, cortical thinning of these structures may compromise the understanding of others’ feelings and intentions, leading to a perception of ambiguous social cues as threatening (Fairchild et al. 2008). Together, we speculated that deficits in these paralimbic structures reflect a non-specific effect of CD and play a crucial role in the development of CD.

Abnormal IGI values detected in the right ACC were in line with IGI and volume alterations in CD (De Brito et al. 2009; Hyatt et al. 2012). The ACC plays an essential role in controlling responses (Bush et al. 2000) since the structural and functional organization of the ACC ideally enables it to participate in willed motor control via its extensive connections with the prefrontal cortex (Paus et al. 1993) and the precentral cortex (Dum & Strick, 1991). Deficits in the ACC have been found in CD and aggressive adolescents (Sterzer et al. 2005; Stadler et al. 2007; Gavita et al. 2012; Hyatt et al. 2012), especially on the right side (Boes et al. 2008).

However, the increased IGI of the precentral cortex seems inconsistent with the results of Hyatt et al. (2012) and Wallace et al. (2014), and the discrepancies could be attributed to the heterogeneity of the subjects (AO-CD only v. CD, and age distribution) or the interactions between genes and environment, since gryrification which was largely determined genetically has also been shown to experience developmental alterations that occur from childhood to adolescence (White et al. 2010), as the microstructure of neuronal sheets (Richman et al. 1975) and axonal connectivity (Van Essen, 1997) have all been shown to affect cortical folding. Aberrant higher-order structures, like the ACC and OFC, together with lower-order motor regions, like the precentral cortex, may undermine the control–motor circuit, thereby resulting in poor regulation of impulsive behavior.

In general, gryrification is also thought to be intrinsically related to surface area (Eyler et al. 2011), but the diminished surface areas detected in the right inferior temporal and the precentral cortex in the present study were only partly overlapped with areas with folding alterations. Of note, the reduction of surface area (p < 0.05, corrected) was not as robust as alterations of gryrification (p < 0.01, corrected). Surface area is known to be associated with both number of cortical folds (i.e. local gryrification) and separation between cortical folds (i.e. sulci) (Fry et al. 2010). A discrepancy between alterations in surface area and folding in CD patients, for example (Wallace et al. 2014), may be due to an illness-related disproportional development of the brain gyri and sulci (Casanova et al. 2010; Shokouhi et al. 2012), and this assumption needs to be addressed in future.

The robust negative relationship between impulsive or antisocial symptoms and the thickness of the IOFC irrespective of diagnosis implies that impulsive and antisocial behavior is closely associated with cortical thinning in this region. The IOFC plays a pivotal role in top-down control (Elliott & Deakin, 2005), and deficits of the IOFC might be a shared neural substrate underlying impulsivity and antisocial behaviors (Blair, 2004), rather than a specific feature of a certain mental disorder.

While in AO-CD patients only the negative correlations between CU and the thickness of the fusiform, including the lingual and parahippocampal gyri came out with significance, which was consistent with Fairchild et al. (2015). This implies the close relationship between the CU traits and processes maintained by the above structures, such as facial expression recognition (Winston et al. 2004). We found no statistically significant correlations between BIS-motor impulsivity (or APSD-impulsivity) and cortical thickness, but both of them indicated a similar negative trend. Thus, our results demonstrated that cortical thinning in these areas, such as the OFC, fusiform and parahippocampal gyrus, was associated with a higher level of impulsivity.

Interestingly, although we ruled out co-morbidity such as ADHD, ODD, etc., the results of the present study are largely consistent with those of previous studies. This is not uncommon in brain imaging studies, since a meta-analysis (on more than 20 000 subjects and 26 different brain disorders) showing that MRI lesions that were common across all brain disorders were more likely to be located in hubs of the normal brain connectome (Crossley et al. 2014). According to ‘graph theory’ (van den Heuvel & Sporns, 2011), structural deficiencies, including the OFC, ACC, superior temporal cortex, and fusiform gyri, should reflect an intrinsic brain network dysfunction, as opposed to a primary area dysfunction.
temporal cortex, insula, PCC, and precuneus in the present study, match well with the ‘hubs’ of cerebral cortex which play a pivotal role in attracting and integrating neuronal information across the whole brain. It may lead to a conclusion that the high-value hubs of human brain networks are more likely to be anatomically abnormal than non-hubs in many (if not all) brain disorders. However, the triggering of a certain brain disorder may rely on complex relationships of the whole brain, including the architecture, neurotransmitters of the brain and so on, and this needs to be investigated in future studies.

Limitations

There were potential limitations in the present study. First, the cross-sectional nature of the present study constrained us from inferring whether the structural abnormalities observed in the present AO-CD cohort are caused by latter triggering of multiple structures, or represent an abnormal developmental trajectory of these structures, and, as DSM-5 pointed out, AO-CD individuals are less likely to persist into adulthood compared with those with EO-CD (APA, 2013); so, whether the observed deficits were limited in adolescence also needs to be answered. Longitudinal observation will enable us to uncover the developmental emergence of cortical markers of AO-CD, thereby helping us to identify those who are at high risk of developing such disorder and seeking protective factors that can delay or even prevent the onset of CD. Second, we did not include EO-CD samples in the present study, and so it remains unknown whether the observed AO-CD specific deficits reflect distinct pathophysiological processes or the heterogeneity of potential confounding variables in our samples compared with previous EO-CD samples. Nevertheless, given the relative abundance of evidence on EO-CD, it is still reasonable to conclude that our study initiated a valuable insight into this question. Therefore, to better understand the neural basis of CD with respect to age of onset, future work examining the brain structural features of both subtypes of CD in multi-center and larger samples is needed.

Conclusion

In summary, structural abnormalities identified in this AO-CD cohort are similar to those previously observed for EO-CD, except for the parietal cortex. Thus it is possible that the PCC/precuneus deficits identified in the present AO-CD cohort provide valuable insight into a potential distinction between the two subtypes of CD, despite their shared features. Importantly, in contrary to Moffitt’s original notion, these and previous results suggest that the etiology of both subtypes share a biological vulnerability (Silberg et al., 2014), and they reinforce a possibly quantitative, rather than qualitative, distinction between the etiology of the different onset of CD (Fairchild et al., 2013). Following this line of reasoning, our study provides supportive evidence for the revision of this theory. However, further studies are needed to better address this issue.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715001361

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Declaration of Interest

None.

References


Cortical abnormalities in adolescent-onset conduct disorder


