City Research Online

City St George's, University of London

Citation: Smaragdi, A., Cornwell, H., Toschi, N., Riccelli, R., Gonzalez-Madruga, K., Wells, A., Clanton, R., Baker, R., Rogers, J., Martin-Key, N., et al (2017). Sex Differences in the Relationship Between Conduct Disorder and Cortical Structure in Adolescents. Journal of the American Academy of Child & Adolescent Psychiatry, 56(8), pp. 703-712. doi: 10.1016/j.jaac.2017.05.015

This is the published version of the paper.

This version of the publication may differ from the final published version. To cite this item please consult the publisher's version.

Permanent repository link: https://openaccess.city.ac.uk/id/eprint/20627/

Link to published version: https://doi.org/10.1016/j.jaac.2017.05.015

Copyright and Reuse: Copyright and Moral Rights remain with the author(s) and/or copyright holders. Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge, unless otherwise indicated, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way. For full details of reuse please refer to City Research Online policy.

City Research Online: http://openaccess.city.ac.uk/ publications@citystgeorges.ac.uk

Sex Differences in the Relationship Between Conduct Disorder and Cortical Structure in Adolescents

Areti Smaragdi, PhD, Harriet Cornwell, BSc, Nicola Toschi, PhD, Roberta Riccelli, PhD, Karen Gonzalez-Madruga, MSc, Amy Wells, BSc, Roberta Clanton, BSc, Rosalind Baker, PhD, Jack Rogers, PhD, Nayra Martin-Key, PhD, Ignazio Puzzo, PhD, Molly Batchelor, BSc, Justina Sidlauskaite, PhD, Anka Bernhard, MSc, Anne Martinelli, MSc, Gregor Kohls, PhD, Kerstin Konrad, PhD, Sarah Baumann, MSc, Nora Raschle, PhD, Christina Stadler, PhD, Christine Freitag, MD (Habilitation), PhD, Edmund J.S. Sonuga-Barke, PhD, Stephane De Brito, PhD, Graeme Fairchild, PhD

Objective: Previous studies have reported reduced cortical thickness and surface area and altered gyrification in frontal and temporal regions in adolescents with conduct disorder (CD). Although there is evidence that the clinical phenotype of CD differs between males and females, no studies have examined whether such sex differences extend to cortical and subcortical structure.

Method: As part of a European multisite study (FemNAT-CD), structural magnetic resonance imaging (MRI) data were collected from 48 female and 48 male participants with CD and from 104 sex-, age-, and pubertal-status–matched controls (14–18 years of age). Data were analyzed using surface-based morphometry, testing for effects of sex, diagnosis, and sex-by-diagnosis interactions, while controlling for age, IQ, scan site, and total gray matter volume.

Results: CD was associated with cortical thinning and higher gyrification in ventromedial prefrontal cortex in both sexes. Males with CD showed lower, and females with CD showed higher, supramarginal gyrus cortical thickness compared with controls. Relative to controls, males with CD showed higher gyrification and surface area in superior frontal gyrus, whereas the opposite pattern was seen in females. There were no effects of diagnosis or sex-by-diagnosis interactions on subcortical volumes. Results are discussed with regard to attention-deficit/hyperactivity disorder, depression, and substance abuse comorbidity, medication use, handedness, and CD age of onset.

Conclusion: We found both similarities and differences between males and females in CD–cortical structure associations. This initial evidence that the pathophysiological basis of CD may be partly sex-specific highlights the need to consider sex in future neuroimaging studies and suggests that males and females may require different treatments.

Key words: conduct disorder, antisocial behavior, sex differences, brain structure, surface-based morphometry

J Am Acad Child Adolesc Psychiatry 2017;56(8):703–712.

Conduct disorder (CD) is a psychiatric disorder that emerges in childhood or adolescence and is characterized by aggressive and antisocial behavior.[1] It incurs major costs for affected individuals, their families, and society in general.[2] Neurodevelopmental theories of CD propose that dysfunction in a set of cortical and subcortical brain regions causes increased vulnerability to antisocial behavior and aggression.[3] The regions that have received most attention are those implicated in emotion processing, empathy, decision making, and reinforcement learning, such as the amygdala, anterior insula, ventromedial prefrontal cortex (vmPFC), and striatum.[3] Amygdala dysfunction is argued to lead to impairments in stimulus-reinforcement learning, which may be particularly influential during socialization because the individual fails to learn the connection between their aggressive acts and the distress cues (e.g., sad expressions) displayed by others.[4] The anterior insula is implicated in processing aversive stimuli as well as awareness of one's own and others' affective and physiological states[5-6]; consequently, insula dysfunction may lead to empathy[7] and interoception deficits. Striatal dysfunction is thought to cause deficits in prediction error signaling, which would mean that the individual is less sensitive to discrepancies between the predicted and actual outcomes of their actions, thereby disrupting their ability to learn from reinforcement.[3] Finally, vmPFC dysfunction could lead to difficulties in representing the value of stimuli, which may impair effective decision making.[3,8]

In addition to these regions, there is increasing evidence that CD is associated with superior temporal and anterior and posterior cingulate cortex dysfunction, which may disrupt social cognitive and self-referential processing.[9,10]

Supplemental material cited in this article is available online.

Recent structural magnetic resonance imaging (MRI) meta-analyses have supported these neurodevelopmental models by confirming that individuals with CD have lower gray matter volume (GMV) in many of these regions, including the amygdala, anterior insula, vmPFC, and superior temporal cortex.[11]

Although the lifetime prevalence of CD is up to 10 times higher in males than in females,[12-14] it is nevertheless one of the most common disorders in adolescent females,[15] and one of the main reasons for referral to child and adolescent mental health services.[16,17] CD presents in different ways in males and females; males with CD display higher levels of aggression[18] but lower levels of comorbid disorders, such as depression,[19] and are more likely to develop antisocial personality disorder in adulthood.[13] Furthermore, there seem to be quantitative differences between males and females in vulnerability to risk factors.[20] It has been suggested that females may require a higher loading of genetic or environmental risk in order to develop CD.[21] Relating this differential threshold theory to the neuroimaging context, one prediction is that females who do surpass the threshold for a CD diagnosis may show more pronounced brain abnormalities than their male counterparts, which would be reflected in sex-by-diagnosis interactions.

Very few imaging studies have investigated sex differences in CD, and such studies have yielded inconsistent and inconclusive results. This is likely due to an underrepresentation of female participants in these studies[22] and hence insufficient power to detect sex-by-diagnosis interactions. There is preliminary evidence that CD is associated with reductions in amygdala[23] and orbitofrontal cortex (OFC)/vmPFC GMV[24] in both males and females. In contrast, one study found reduced anterior insula volume in females with CD relative to female controls, but the reverse effect in males.[23] Furthermore, a negative association between CD severity and superior temporal cortex GMV was reported in females but not in males.[25]

The current study addressed the lack of reliable evidence regarding possible sex differences in CD-related structural abnormalities by including a large, balanced sample of male (n = 48) and female (n = 48) adolescents with CD and similar-sized typically developing control groups. We used surface-based morphometry (SBM), which, in contrast to voxel-based morphometry (VBM), distinguishes among different cortical properties with distinct etiologies and developmental trajectories,[26] namely, cortical thickness (CT), surface area (SA), and gyrification (i.e., the amount of cortex folded within a sulcus compared to outside the sulcus). Although CT and SA display inverted-U trajectories across childhood and adolescence (peaking at 8.5 and 9 years, respectively), gyrification peaks in infancy and decreases over childhood.[27] Despite the fact that males and females show different brain developmental trajectories using these metrics,[27] previous SBM studies of CD have combined data from both sexes.

These studies have reported lower CT in the prefrontal cortex (PFC),[28-31] superior temporal cortex,[28-32] supramarginal/angular gyrus,[29,32,33] precuneus,[28,29,31,32] and fusiform gyrus,[29,32] and lower SA in PFC[29,33] in participants with CD compared to controls. Furthermore, lower gyrification in the OFC/vmPFC,[32] and higher gyrification in the superior frontal gyrus (SFG), insula, fusiform gyrus,[30] and precentral gyrus[32] have been reported in individuals with CD versus controls. Despite considerable overlap between the regions that have been identified using SBM and VBM methods, SBM studies have highlighted additional regions that have not yet been incorporated in neurodevelopmental models of CD. For example, the most robust finding from these studies—lower superior temporal gyrus CT—has not been incorporated into theories of CD, despite various functional magnetic resonance imaging (fMRI) and VBM studies also reporting abnormalities in this region.[11,34]

Accordingly, we predicted that CD would be associated with the following: lower CT in the OFC/vmPFC and superior temporal cortex; gyrification abnormalities in the insula and PFC; and lower SA in the PFC. We further hypothesized that cortical abnormalities would be most evident in the most severely disordered individuals, namely, those with more CD symptoms,[35] and potentially those with elevated callous-unemotional (CU) traits.[36] We also studied subcortical volumes to test for potential sex differences in the relationship between CD and the volume of subcortical structures such as the amygdala and striatum. Given the small number of females included in previous studies, it is not possible to make strong predictions regarding sex differences. Nevertheless, based on the hypothesis that the etiology and pathophysiology of CD is similar in males and females, but that females might require a higher loading of risk to surpass the threshold required to manifest the disorder,[21] we expected to observe CD-related structural alterations in similar regions in males and females, but to detect more pronounced or widespread deficits in females.

METHOD

Study Participants

The sample was selected from the Neurobiology and Treatment of Female Conduct Disorder (FemNAT-CD) study. It included 96 adolescents (48 females) with CD and 104 healthy adolescents (52 females; see Table S1, available online, for distribution of participants across sites). All participants were 14 to 18 years of age and classified as late- or postpubertal using the Pubertal Development Scale.[37] The study was approved by ethics committees at each site (Supplement 1, available online), and written informed consent was obtained for all participants.

Diagnoses of CD and comorbid disorders were made using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL[38]), conducted separately with participants and parents by trained masters- and doctoral-level staff. The interrater reliability of CD was high (Cohen's $\kappa = 0.91$), and agreement across raters was 94.5%. Similarly high Cohen's κ values were obtained for attention-deficit/hyperactivity disorder (ADHD), major depressive disorder (MDD), and oppositional defiant disorder diagnoses (0.84–1.00). CD severity was defined as the number of CD symptoms endorsed across informants in the K-SADS-PL interviews. CU traits were assessed using the CU subscale of the self-report Youth Psychopathic traits Inventory (YPI).[39] Exclusion criteria included IQ < 70, neurological disorders, history of head trauma, autism spectrum disorders, and psychosis, as well as standard MRI exclusion criteria. Healthy

controls (HC) were free of current *DSM-IV* disorders as assessed using the K-SADS-PL. IQ was estimated using the vocabulary and matrix reasoning subtests of the Wechsler Abbreviated Scale of Intelligence[40] or the same subtests from the Wechsler Intelligence Scale for Children–IV.[41]

MRI Data Acquisition

Structural MRI data were acquired using Siemens 3T (Tim-Trio and Prisma) or Philips 3T (Achieva) scanners (see Table S2, available online, for scanning parameters across sites). Each site underwent a site qualification procedure prior to commencing data collection (Supplement 2, available online). T1-MPRAGE scans were acquired (TE[Philips] = 3.7 milliseconds, TE[Siemens] = 3.4 milliseconds, TR = 1900 milliseconds, flip angle = 9°, FHxAP field of view [FoV] = 256 mm, RL FoV = 192 mm, matrix = 256, voxel size = 1 × 1 × 1mm, sagittal slices = 192, bandwidth[Philips] = 174 Hz/pixels, bandwidth[Siemens] = 180 Hz/pixels, total scan time = 4 minutes 26 seconds [Siemens] or 6 minutes 5 seconds [Philips]). Image quality was assessed immediately after the scan by the MRI operator, and repeated until a high-quality image was acquired.

Image Processing

CT, SA, and gyrification were estimated at each vertex using Freesurfer v5.3.0 (http://surfer.nmr.mgh.harvard.edu).[42-44] This involved segmentation of the white matter and identification of the white–gray matter interface, and the gray matter–cerebrospinal fluid interfaces to create the pial surface. All surfaces were visually inspected and segmentation errors or topological defects were manually corrected by two authors (A.S., H.C.) who were blinded to participant group status. The corrections included manual edits to the white and gray matter boundaries, and adding control points where needed. CT, SA, and gyrification (termed "local gyrification index" [lGI]) were calculated as detailed in previous publications.[42,45,46] CT and SA were smoothed using 10-mm full-width/half-maximum Gaussian kernels. lGI was not smoothed at the analysis level, in line with previous studies, as it is calculated with reference to a local neighborhood value at each vertex and it is therefore inherently smooth.[47] Total GMV was estimated for each participant and included to control for interindividual variability in global brain size. Finally, amygdala, hippocampus, caudate, pallidum, putamen, and thalamus volumes were computed using the automated subcortical segmentation pipeline in FreeSurfer.[48]

Statistical Analysis

First, for each hemisphere, a full-factorial general linear model (GLM) was fitted separately for CT, SA, lGI, and subcortical volumes, which tested for effects of diagnosis, sex, and sex-by-diagnosis interactions. Second, separate GLM correlational analyses were conducted within the CD group to test for correlations between CD severity (from K-SADS-PL) and CT, SA, lGI, and subcortical volumes. We also tested for sex-by-CD severity interactions. A similar approach was used to test for correlations between CU traits and cortical structure and subcortical volumes. Third, given previous evidence suggesting quantitative brain structural differences between childhood-onset (CO) and adolescence-onset (AO) CD,[23,30] we compared these subgroups to assess the validity of collapsing across them in our main analyses. All models included age, IQ, total GMV, and scan site (each site coded as a separate categorical variable) as covariates of no interest. In addition, each analysis was repeated including lifetime ADHD, MDD, and substance abuse symptoms (from K-SADS-PL) as covariates of no interest, as well as excluding left-handed individuals and those currently taking medication (see Supplement 3, available online, for detailed information about medication). Consistent with previous research,[29,30] we first used a cluster-forming threshold of $p < .05$ (two-tailed); results were then corrected for multiple comparisons at a whole-brain level using a Monte Carlo *z*-field simulation in the case of the cortical analyses, and false-discovery-rate (FDR) correction for the subcortical analyses. Clusters were reported if they met a whole-brain corrected threshold of $p < .05$ (two-tailed; see Hagler et al.[49] for more information about this approach).

RESULTS

Table 1 provides information about the sample's demographic characteristics. The four groups did not significantly differ in age, pubertal status, or handedness. Within the male and female samples, the CD groups had lower full-scale IQs and reported more CD and ADHD symptoms and higher levels of CU traits than HCs. Males with CD further displayed more ADHD symptoms and higher levels of CU traits than the other three groups. Furthermore, by design, our control groups were free of current psychiatric disorders; thus the CD group had significantly higher levels of comorbidity and medication use. However, apart from ADHD comorbidity, the male and female CD groups did not differ in terms of comorbidity or medication use. Total GMV was higher in males overall compared to females ($p < .001$), as expected,[50] but there were no significant differences in total GMV between males with CD and male controls ($p = .81$) or females with CD and female controls ($p = .92$).

Main Effects of Diagnosis

Relative to controls, participants with CD showed lower CT in the bilateral vmPFC, left rostral middle frontal gyrus, and left precentral gyrus (Figure 1A; Table S3, available online). Participants with CD also showed greater SA in the left precentral/postcentral gyrus, left middle temporal gyrus/fusiform gyrus, and right lateral occipital cortex compared with controls (Table S4, available online). The CD group showed higher lGI in the left superior temporal gyrus/posterior insula, vmPFC/lateral OFC, and postcentral/precentral gyrus (Figure 1B) and lower lGI in right inferior frontal gyrus (IFG) and supramarginal gyrus, relative to controls (Table S5, available online).

Main Effects of Sex

Relative to males, females showed higher CT in pre- and postcentral gyrus, and higher SA and lGI in several temporal and frontal regions (Tables S3–S5, available online), consistent with previous studies investigating sex differences.[51-53]

Sex-by-Diagnosis Interactions

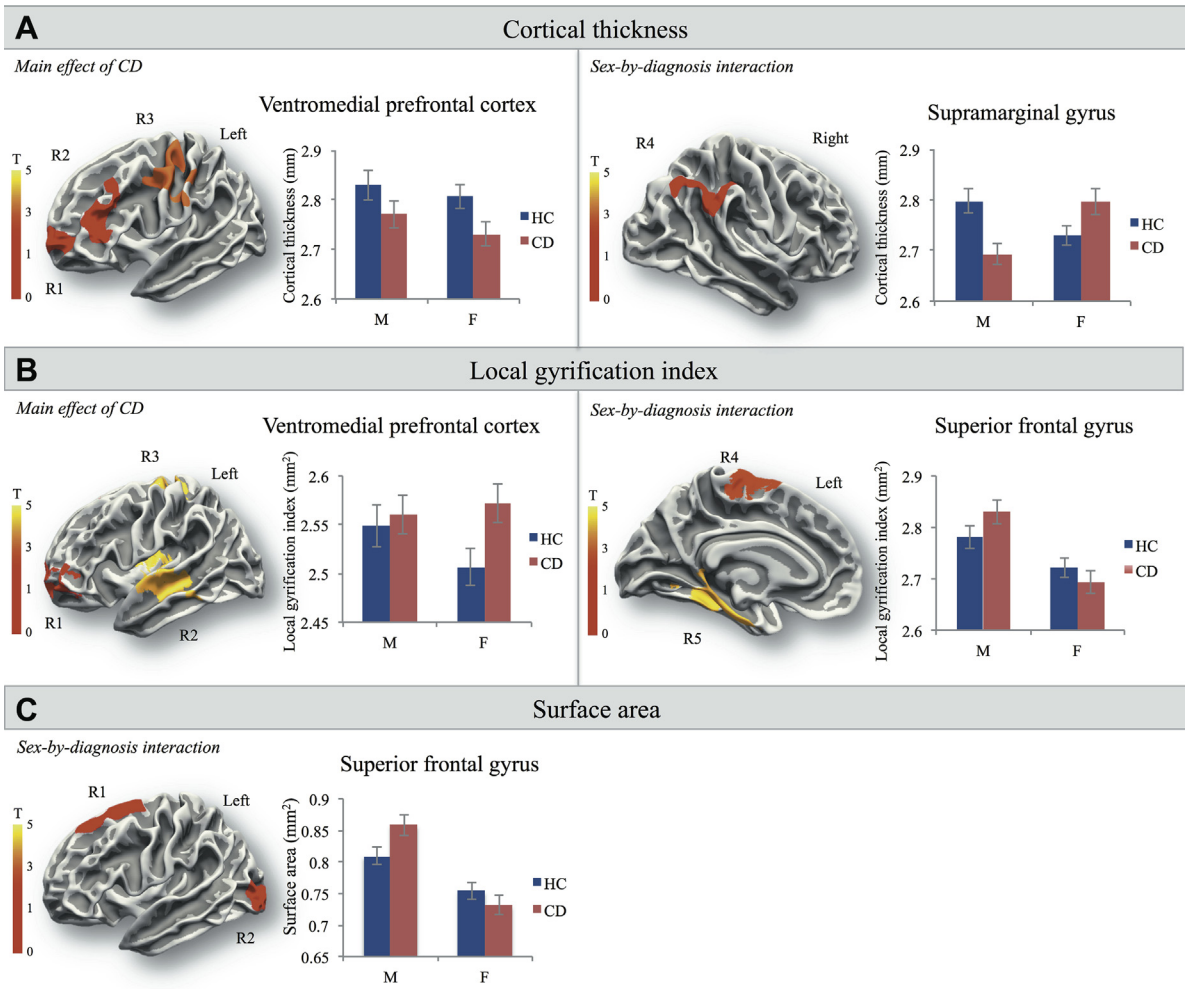
Significant sex-by-diagnosis interactions were observed for all SBM measures. Males with CD showed lower, and females with CD showed higher, CT relative to their respective control groups in the left superior parietal lobule and right supramarginal gyrus (Figure 1A). In left SFG, males with CD displayed higher, while females with CD displayed lower, lGI and SA relative to their respective control groups (Figure 1B and 1C, respectively). In the left parahippocampal cortex, males with CD displayed higher,

TABLE 1 Sample Demographics and Clinical Characteristics

Characteristic/Variable	Female CD	Female HC	Male CD	Male HC	*T*group (*p*)	*T*sex (*p*)	*F*group × sex (*p*)
Age (y), mean (SD)	15.83 (1.29)	16.13 (1.07)	15.92 (1.32)	16.21 (1.14)	T = 1.75 (.08)	T = 0.46 (.64)	F = 1.09 (.35)
Estimated IQ, mean (SD)	92.51 (12.26)	99.67 (12.01)	93.01 (11.95)	101.33 (11.42)	T = 4.58 (<.001)	T = 0.66 (.51)	F = 7.14 (<.001)
Lifetime CD symptoms, mean (SD)	6.06 (2.78)	0.37 (1.12)	7.50 (2.84)	0.42 (0.67)	T = 21.42 (<.001)	T = 1.33 (.18)	F = 164.30 (<.001)
ADHD symptoms, mean (SD)	4.98 (6.53)	0.13 (0.60)	8.75 (6.62)	0.06 (0.42)	T = 10.11 (<.001)	T = 2.17 (.03)	F = 41.98 (<.001)
CU subscale of YPI, mean (SD)	21.57 (4.61)	18.67 (4.84)	26.44 (11.25)	22.42 (3.75)	T = 3.43 (.001)	T = 4.34 (.001)	F = 11.18 (<.001)
Number with lifetime *DSM-IV* diagnoses (%)							
ODD	31 (66)	1 (2)	32 (70)	0 (0)	χ^2 = 99.83 (<.001)	χ^2 = 0.002 (1.00)	χ^2 = 100.01 (<.001)
ADHD	10 (21)	0 (0)	24 (52)	0 (0)	χ^2 = 42.95 (<.001)	χ^2 = 7.14 (.008)	χ^2 = 61.49 (<.001)
MDD	20 (43)	0 (0)	10 (22)	0 (0)	χ^2 = 39.58 (<.001)	χ^2 = 3.81 (.073)	χ^2 = 47.38 (<.001)
Alcohol abuse, n (%)	3 (6)	1 (2)	4 (9)	0 (0)	χ^2 = 5.43 (.022)	χ^2 = 0.00 (1.00)	χ^2 = 6.00 (.11)
Drug abuse (cannabis), n (%)	7 (15)	0 (0)	10 (22)	2 (4)	χ^2 = 15.07 (<.001)	χ^2 = 1.51 (.24)	χ^2 = 47.38 (<.001)
Medication, n (%)	4 (8)	1 (2)	8 (17)	0 (0)	χ^2 = 10.94 (.001)	χ^2 = 0.74 (.57)	χ^2 = 13.84 (.003)
Puberty (PDS), n (%)							
Late	34 (71)	34 (65)	34 (71)	40 (77)	χ^2 = 0.02 (.96)	χ^2 = 0.87 (.35)	χ^2 = 1.68 (.64)
Post	14 (29)	18 (35)	14 (29)	12 (23)			
Age of onset, n (%)							
Childhood	19 (40)		26 (54)				
Adolescent	27 (56)		22 (46)			χ^2 = 1.58 (.45)	
Missing	2 (4)		0 (0)				
Handedness, n (%)							
Right	41 (86)	48 (92)	38 (79)	48 (92)	χ^2 = 4.92 (.09)	χ^2 = 2.37 (.31)	χ^2 = 15.93 (.14)
Left	3 (6)	4 (8)	10 (21)	2 (4)			
Ambidextrous	3 (6)	0 (0)	0 (0)	1 (2)			
Missing	1 (2)	0 (0)	0 (0)	1 (2)			

Note: IQ was measured using the Wechsler Abbreviated Scale of Intelligence or the Wechsler Intelligence Scale for Children—4th Edition; diagnoses of conduct disorder (CD) and comorbid disorders were made using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime version. Group and sex differences were computed using independent-sample t *tests or* χ^2 *tests, and sex-by-diagnosis interactions were computed using univariate analyses of variance and* χ^2 *tests. ADHD = attention-deficit/hyperactivity disorder; CU = callous-unemotional traits; HC = healthy control; MDD = major depressive disorder; ODD = oppositional defiant disorder; PDS = Pubertal Development Scale; SD = standard deviation; YPI = Youth Psychopathic traits Inventory.*

FIGURE 1 Main effects of conduct disorder (CD) diagnosis and sex-by-diagnosis interactions in cortical thickness, gyrification, and surface area. Note: Panel A shows the main effects of CD on cortical thickness in left ventromedial prefrontal cortex (R1), rostral middle frontal gyrus (R2), precentral gyrus (R3), and a sex-by-diagnosis interaction in right supramarginal gyrus (R4). Panel B presents the main effects of CD on local gyrification index in left ventromedial prefrontal cortex (R1), insula/superior temporal gyrus (R2), pre/postcentral gyrus (R3), and sex-by-diagnosis interactions in gyrification in left superior frontal gyrus (R4), and parahippocampal cortex (R5). Panel C displays the sex-by-diagnosis interactions in left superior frontal gyrus (R1) and lateral occipital cortex (R2) surface area. The color bars show T values from red to yellow/white, whereas the error bars show ± 1 standard error. HC = healthy control.



whereas females with CD displayed lower, lGI compared with their sex-matched control groups.

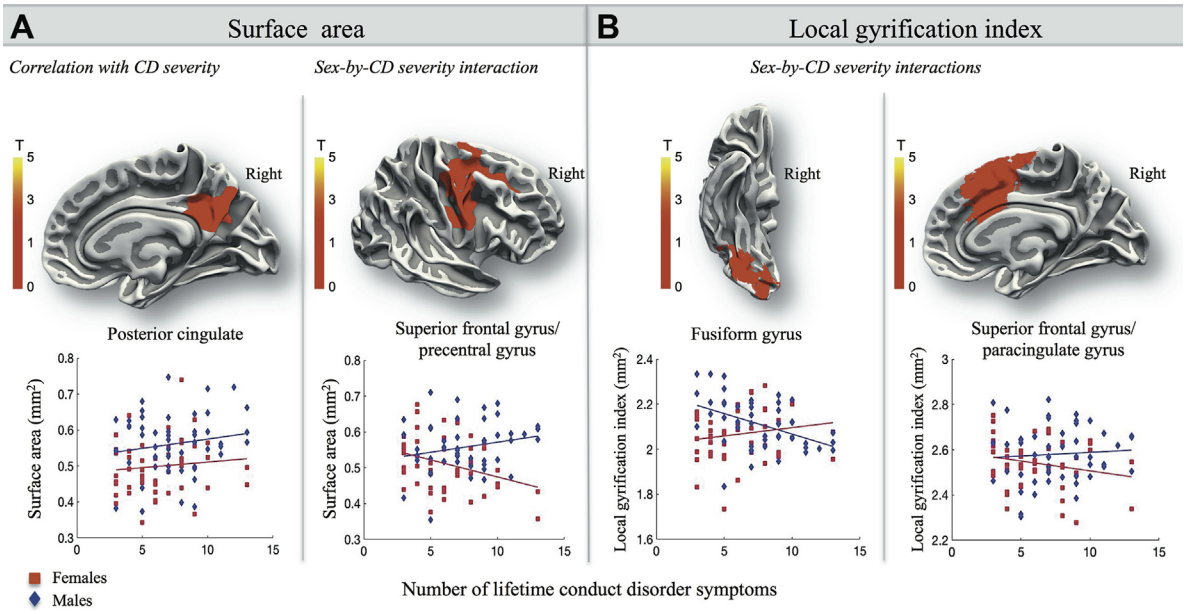
Subcortical Structures

There were no main effects of diagnosis or sex-by-diagnosis interactions on amygdala, hippocampal, or striatal volumes. However, females overall showed higher bilateral pallidum volumes than males (left: $p < .001$ and right: $p = .004$, FDR-corrected; Table S6, available online).

CD Severity Effects

There were no significant correlations between CD severity and CT or subcortical volumes, and no sex-by-CD severity interactions for these measures. However, CD severity was positively correlated with right posterior cingulate cortex/precuneus SA in males and females. A sex-by-CD severity interaction was observed for SA: males showed a positive, whereas females showed a negative, correlation between CD severity and right superior frontal/precentral gyrus SA (Figure 2A, Table S7, available online). Finally, two sex-by-CD severity interactions were observed for lGI: females showed a positive and males showed a negative correlation between CD severity and left fusiform gyrus lGI. Conversely, CD severity was negatively correlated with left SFG/paracingulate cortex lGI in females, but not in males (Figure 2B, Table S7, available online).

FIGURE 2 Correlations between conduct disorder (CD) severity and surface area, and sex-by-CD severity interactions in surface area and gyrification within the CD group. Note: The brain maps illustrate the clusters identified by these correlational analyses, whereas the scatter plots show the relationships detected between CD severity and surface area (Panel A) and local gyrification index (Panel B). The color bars show T values from red to yellow/white. Blue lines show the correlations with CD severity observed in males with CD, whereas red lines show those observed in females with CD.



Effects of CU Traits

There were no significant correlations between CU traits and SA or subcortical volumes. CU traits were negatively correlated with occipital pole CT, and bilateral fusiform gyrus and left superior parietal cortex lGI. In addition, we observed several sex-by-CU traits interactions, whereby males showed a positive and females showed a negative correlation between CU traits and lGI, including in the left vmPFC and right SFG (Table S8, available online).

Childhood-Onset Versus Adolescent-Onset CD

There were no differences between the CO-CD and AO-CD subtypes in CT, SA, or subcortical volumes. There were differences between these subgroups in lGI in several regions including the anterior insula (Table S9, available online); however, these regions were not altered as a function of CD, sex, or their interaction, thus we did not distinguish between these subgroups in the main lGI analyses.

Potential Confounds

The main effects of diagnosis on vmPFC CT and lGI and the sex-by-diagnosis interactions for supramarginal CT and SFG lGI and SA remained significant after controlling for ADHD symptoms. In addition, all main effects of sex, CD severity correlations, and sex-by-CD severity interactions reported above remained significant. We also tested the impact of including depression and substance abuse as additional covariates, excluding site and IQ as covariates, and excluding left-handed participants, and participants who were currently taking medication. Finally, we ran an additional analysis with IQ-matched subgroups. The overlap in brain areas identified in the main analyses and these additional analyses is shown in Tables S10 to S12, available online. Although the majority of the findings remained significant at a whole-brain–corrected level, controlling for depressive symptoms attenuated the significance of some of the findings, although all were present at an uncorrected level, and the effect of diagnosis on vmPFC CT remained significant at a whole-brain–corrected level.

DISCUSSION

To our knowledge, this is the first SBM study specifically designed and with a large-enough sample to test for sex differences in the relationship between CD and cortical structure. Our results support previous studies showing associations between CD and alterations in cortical thickness (CT), surface area (SA), and local gyrification index (lGI). As hypothesized, and as previously found in predominantly male samples,[28-32] CD was associated with lower ventromedial prefrontal cortex (vmPFC) CT. This was accompanied by higher gyrification in overlapping regions of vmPFC, as well as the posterior insula, in the CD group. As noted above, the vmPFC is implicated in stimulus valuation and reward processing,[54] although it is also involved in emotion regulation[55] and empathic processing.[56] Neuropsychological studies have consistently provided evidence for deficits in these processes in CD.[8,57,58] Although CD-related alterations were observed in a more posterior

location in the present study, higher insula gyrification has been reported previously in CD.[30] The insula plays a key role in empathy and processing aversive stimuli,[59,60] both of which are reported to be abnormal in CD.[56] Against expectation and previous findings,[30,33] we found greater SA in participants with CD relative to controls, although the affected regions differed from those reported previously. These observations of higher SA and lGI in males with CD may reflect delayed brain development in CD in general, superimposed on sex differences in brain maturation (i.e., earlier maturation in females). These combined effects of sex and diagnosis mean that males with CD show the most protracted brain development of the four groups studied here. Of interest, a recent longitudinal imaging study suggests that individuals with conduct problems show delayed brain development relative to that in healthy peers,[61] similar to earlier findings in children with ADHD.[62]

Significant sex-by-diagnosis interactions were detected in several brain regions across the three SBM measures—e.g., males with CD showed lower, and females with CD showed higher, supramarginal gyrus CT relative to their sex-matched control groups. Lower supramarginal gyrus CT has been reported in two SBM studies of CD,[29,32] both of which used mixed-sex (but predominantly male) samples. Lower supramarginal CT therefore appears to be specific to males with CD. Interestingly, this area is implicated in decision making[63] and emotion processing.[64] Therefore, supramarginal gyrus structural alterations may be related to the deficits reported in decision-making and emotion-recognition tasks in males with CD.[56,65]

Sex-by-diagnosis interactions were also observed in the superior frontal gyrus (SFG), an area involved in higher cognitive functions such as working memory.[66] In this region, males with CD showed higher, and females with CD showed lower, lGI and SA relative to their control groups. Higher SFG lGI and SA in males with CD is consistent with findings obtained using a predominantly male sample.[32] However, this is the first study to show that males and females with CD show changes in SFG lGI and SA in opposite directions relative to their respective control groups. Furthermore, males and females showed different relationships between CD severity and lGI and SA in several regions, including the fusiform gyrus. Again, this suggests that the relationship between CD and cortical structure partly differs by sex. The fusiform gyrus is functionally connected to the amygdala,[67] and CD-related changes in fusiform activity have been reported in fMRI studies of emotion processing.[67,68] However, given the novelty of these findings, they need to be interpreted with caution, and replication is required.

It was surprising that we did not find lower amygdala or striatal volumes in the CD compared to the control group, considering results from previous work using similar subcortical volume measures[31] and VBM studies of CD.[23,35,69,70] However, the current study included participants within a narrower age range than other studies, and used an integrated measure of volume rather than assessing gray matter volume specifically; these factors may have influenced the results.

We note that some of our findings were influenced by comorbidity. This was most apparent for the main effects of diagnosis on SA and lGI, whereas the sex-by-diagnosis interactions and CD severity correlations largely remained unaffected. Due to the strong overlap between ADHD and CD, and the idea that CD-related findings should be interpreted both with and without considering ADHD comorbidity,[71] we have focused on the findings that remained significant across the two analyses. However, controlling for depression attenuated some of the results, and future studies need to account for the effects of depression—ideally by comparing individuals with CD with, versus without, depression.

The present findings did not support the hypothesis that females who reach the diagnostic threshold for CD would show similar, but simply more pronounced, brain abnormalities than their male counterparts. Instead, we observed opposite CD-related effects in males and females for all three cortical structure measures and in multiple brain regions. This study is one of the first to provide evidence that the neurobiological basis of CD may be qualitatively, rather than quantitatively, different in males and females. However, we acknowledge that further research is required to investigate the possibility that there may be sex differences in the pathophysiology, and possibly the pathogenesis, of CD. Conversely, complex effects of sex and diagnosis on brain development may partly explain these findings that, in general, CD is associated with delayed brain maturation, but this effect is most pronounced in males in late adolescence.

On the basis of the findings presented here, we recommend that researchers avoid collapsing across the sexes in neuroimaging studies of CD, because combining males and females runs the risk of canceling out diagnosis effects that are either present only in one sex or altered in opposite directions in males and females. Accordingly, future cross-sectional studies of CD might opt to recruit single-sex samples if they can test only relatively small samples, or deliberately recruit large numbers of males and females to contrast these groups with sex-matched control groups.

The current study had several strengths. We included a large, sex-balanced sample, matched at the group level for age and pubertal status, and examined three separate SBM measures and subcortical volumes. We also accounted statistically for group differences in IQ, site, and several comorbid disorders. However, several limitations should be noted. First, although data acquisition protocols were matched across sites, it is possible, as with any multisite study, that scanner hardware and software differences between sites could introduce error/noise into the data. In addition, there were differences between the results obtained at the four sites, potentially due to the different sample sizes (see Figure S1, available online, for uncorrected effect size maps from the four sites). Thus, combining data across several relatively small samples poses a potential threat to the validity of the overall results. Second, we did not correct across the three SBM measures simultaneously, potentially increasing the risk of type I errors. However, this is not commonly performed, and given that our results were

already whole-brain corrected, this could have introduced type II errors instead. In addition, although performing multiple supplementary analyses provided important information about the impact of comorbidity and IQ on our findings, it was not possible to control for the number of analyses performed, stressing the provisional nature of the findings and the importance of further investigation.

Third, we were unable to match the CD and control groups on IQ in the main analysis. However, because both CD groups in this study had lower IQs compared to controls, IQ differences cannot explain the observed sex-by-diagnosis interactions. Fourth, controlling for comorbid disorders reduced the significance of some of the results. It may be informative for future studies to explicitly investigate the impact of these variables, ideally by comparing CD individuals with versus without comorbidity, or by including a psychiatric control group. Fifth, by design, we matched our groups on pubertal development to reduce the possibility of group or sex differences in brain developmental stages.[72] However, we note that the relationship between pubertal stage and brain development may differ by sex. Future analyses of data from younger children, as well as longitudinal imaging data, are needed to investigate whether the results reported here are stable across development. Finally, using the number of CD symptoms as a measure of severity is suboptimal, as these symptoms are not equivalent to each other, for example, weapon use versus lying.

We observed similarities and differences between males and females in the relationship between CD and cortical structure, providing initial evidence that there may be important sex differences in the neurobiological basis of CD. Because this is the first study of its kind, it will be important to examine whether the findings can be replicated in future studies. These results were largely unrelated to ADHD and substance abuse comorbidity, differences in IQ, or CD age-of-onset effects, although controlling for comorbid depression reduced the strength of some of the findings. The findings demonstrate the importance of studying males and females with CD separately and potentially treating them differently in clinical settings. &

Accepted May 25, 2017.

Drs. Smaragdi, Riccelli, Martin-Key, Sidlauskaite, Professor Sonuga-Barke, and Mss. Cornwell, Gonzalez-Madruga, Batchelor, and Wells are with the University of Southampton, Southampton, UK. Dr. Fairchild is with the University of Southampton and the University of Bath, Bath, UK. Dr. Toschi is with the University of Rome "Tor Vergata," Rome, Italy. Dr. Puzzo is with the West London Mental Health Trust, Broadmoor High Secure Hospital, London, UK. Drs. Baker, Rogers, and De Brito and Ms. Clanton are with the University of Birmingham, Birmingham, UK. Professor Freitag and Mss. Bernhard and Martinelli are with the University Hospital Frankfurt, Frankfurt, Germany. Dr. Kohls, Professor Konrad, and Ms. Baumann are with the University Hospital RWTH Aachen, Aachen, Germany. Dr. Raschle and Professor Stadler are with the Psychiatric University Clinics and University of Basel, Basel, Switzerland.

This study was funded by the European Commission's Seventh Framework Programme for research, technological development, and demonstration (FP7/2007-2013) under Grant Agreement no. 602407 (FemNAT-CD). The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Preliminary data from this study were presented at the Society for the Scientific Study of Psychopathy, Chicago, USA, June 25–26, 2015, and the European Association for Forensic Child and Adolescent Psychiatry, Porto, Portugal, May 11–13, 2016.

Dr. Toschi served as the statistical expert for this research.

The authors thank the participants and their families for taking part in this study.

Disclosure: Dr. Konrad has received speaker fees from Shire Pharmaceuticals and Medice. Professor Sonuga-Barke has received speaker fees, research funding, and conference support from Shire Pharmaceuticals, speaker fees from Janssen Cilag and Medice, book royalties from Oxford University Press and Jessica Kingsley, and consultancy from Neurotech solutions, Aarhus University, Copenhagen University, and KU Leuven. He is editor-in-chief of the Journal of Child Psychology and Psychiatry, for which he receives an honorarium. Dr. De Brito has received speaker fees from the Child Mental Health Centre and the Centre for Integrated Molecular Brain Imaging. Drs. Smaragdi, Toschi, Riccelli, Rogers, Martin-Key, Puzzo, Sidlauskaite, Kohls, Raschle, Stadler, Freitag, Fairchild, and Mss. Cornwell, Gonzalez-Madruga, Wells, Clanton, Baker, Batchelor, Bernhard, Martinelli, and Baumann report no biomedical financial interests or potential conflicts of interest.

Correspondence to Areti Smaragdi, PhD, Academic Unit of Psychology, Building 44, University of Southampton, SO17 1BJ, Southampton, UK; e-mail: A.smaragdi@soton.ac.uk

0890-8567/$36.00/©2017 American Academy of Child and Adolescent Psychiatry. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

http://dx.doi.org/10.1016/j.jaac.2017.05.015

REFERENCES

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Arlington, VA: American Psychiatric Publishing; 2013.
2. Scott S, Knapp M, Henderson J, Maughan B. Financial cost of social exclusion: follow up study of antisocial children into adulthood. BMJ. 2001;323:191.
3. Blair RJR, Leibenluft E, Pine DS. Conduct disorder and callous-unemotional traits in youth. N Engl J Med. 2014;371:2207-2216.
4. Blair RJR. The neurobiology of psychopathic traits in youths. Nature Rev Neurosci. 2013;14:786-799.
5. Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. Empathy for pain involves the affective but not sensory components of pain. Science. 2004;303:1157-1162.
6. Craig AD. How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci. 2009;1:59-70.
7. Martin-Key N, Brown T, Fairchild G. Empathic accuracy in male adolescents with conduct disorder and higher versus lower levels of callous-unemotional traits. J Abnorm Child Psychol. 2016 Dec 29. http://dx.doi.org/10.1007/s10802-016-0243-8. [Epub ahead of print].
8. Sonuga-Barke EJS, Cortese S, Fairchild G, Stringaris A. Annual Research Review: Transdiagnostic neuroscience of child and adolescent mental disorders—differentiating decision making in attention-deficit/hyperactivity disorder, conduct disorder, depression, and anxiety. J Child Psychol Psychiatry. 2016;57:321-349.
9. Broulidakis MJ, Fairchild G, Sully K, Blumensath T, Darekar A, Sonuga-Barke EJ. Reduced default mode connectivity in adolescents with conduct disorder. J Am Acad Child Adolesc Psychiatry. 2016;55:800-808.
10. Van Overwalle F. Social cognition and the brain: a meta-analysis. Hum Brain Mapp. 2009;30:829-858.
11. Rogers JC, De Brito SA. Cortical and subcortical gray matter volume in youths with conduct problems: a meta-analysis. JAMA Psychiatry. 2016;73:64-72.
12. Fontaine N, Carbonneau R, Vitaro F, Barker ED, Tremblay RE. Research review: a critical review of studies on the developmental trajectories of antisocial behavior in females. J Child Psychol Psychiatry. 2009;50:363-385.
13. Moffitt TE, Caspi A, Rutter M, Silva PA. Sex Differences in Antisocial Behaviour: Conduct Disorder, Delinquency, and Violence in the Dunedin Longitudinal Study. New York, NY: Cambridge University Press; 2001.

14. Nock MK, Kazdin AE, Hiripi E, Kessler RC. Prevalence, subtypes, and correlates of DSM-IV conduct disorder in the National Comorbidity Survey Replication. Psychol Med. 2006;36:699-710.
15. Merikangas KR, He J, Burstein M, *et al*. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A). J Am Acad Child Adolesc Psychiatry. 2010;49:980-989.
16. Pajer KA. What happens to "bad" girls? A review of the adult outcomes of antisocial adolescent girls. Am J Psychiatry. 1998;155:862-870.
17. Baker K. Conduct disorders in children and adolescents. Paediatr Child Health. 2013;23:24-29.
18. Gorman-Smith D, Loeber R. Are developmental pathways in disruptive behaviors the same for girls and boys? J Child Fam Stud. 2005; 14:15-27.
19. Rosenfield S, Mouzon D. Gender and mental health. In: Aneshensel CS, Phelan JC, Bierman A, eds. Handbook of the Sociology of Mental Health. Haarlem, Netherlands: Springer Netherlands; 2013:277-296.
20. Meier MH, Slutske WS, Heath AC, Martin NG. Sex differences in the genetic and environmental influences on childhood conduct disorder and adult antisocial behavior. J Abnorm Psychol. 2011;120:377-388.
21. Cloninger CR, Christiansen KO, Reich T, Gottesman II. Implications of sex differences in the prevalences of antisocial personality, alcoholism, and criminality for familial transmission. Arch Gen Psychiatry. 1978;35: 941-951.
22. Rutter M, Pickles A. Annual research review: threats to the validity of child psychiatry and psychology. J Child Psychol Psychiatry. 2016;57: 398-416.
23. Fairchild G, Hagan CC, Walsh ND, Passamonti L, Calder AJ, Goodyer IM. Brain structure abnormalities in adolescent girls with conduct disorder. J Child Psychol Psychiatry. 2013;54:86-95.
24. Dalwani MS, McMahon MA, Mikulich-Gilbertson SK, *et al*. Female adolescents with severe substance and conduct problems have substantially less brain gray matter volume. PLoS One. 2015;10:e0126368.
25. Michalska KJ, Decety J, Zeffiro TA, Lahey BB. Association of regional gray matter volumes in the brain with disruptive behavior disorders in male and female children. NeuroImage Clin. 2015;7:252-257.
26. Panizzon MS, Fennema-Notestine C, Eyler LT, *et al*. Distinct genetic influences on cortical surface area and cortical thickness. Cereb Cortex. 2009;19:2728-2735.
27. Raznahan A, Shaw P, Lalonde F, *et al*. How does your cortex grow? J Neurosci. 2011;31:7174-7177.
28. Fahim C, He Y, Yoon U, Chen J, Evans A, Pérusse D. Neuroanatomy of childhood disruptive behavior disorders. Aggress Behav. 2011;37: 326-337.
29. Hyatt CJ, Haney-Caron E, Stevens MC. Cortical thickness and folding deficits in conduct-disordered adolescents. Biol Psychiatry. 2012;72: 207-214.
30. Fairchild G, Toschi N, Hagan CC, Goodyer IM, Calder AJ, Passamonti L. Cortical thickness, surface area, and folding alterations in male youths with conduct disorder and varying levels of callous–unemotional traits. NeuroImage Clin. 2015;8:253-260.
31. Wallace GL, White SF, Robustelli B, *et al*. Cortical and subcortical abnormalities in youths with conduct disorder and elevated callous-unemotional traits. J Am Acad Child Adolesc Psychiatry. 2014;53: 456-465.
32. Jiang Y, Guo X, Zhang J, *et al*. Abnormalities of cortical structures in adolescent-onset conduct disorder. Psychol Med. 2015;45:3467-3479.
33. Sarkar S, Daly E, Feng Y, *et al*. Reduced cortical surface area in adolescents with conduct disorder. Eur Child Adolesc Psychiatry. 2015;24: 909-917.
34. Passamonti L, Fairchild G, Goodyer IM, *et al*. Neural abnormalities in early-onset and adolescence-onset conduct disorder. Arch Gen Psychiatry. 2010;67:729-738.
35. Fairchild G, Passamonti L, Hurford G, *et al*. Brain structure abnormalities in early-onset and adolescent-onset conduct disorder. Am J Psychiatry. 2011;168:624-633.
36. Frick PJ, Cornell AH, Bodin SD, Dane HE, Barry CT, Loney BR. Callous-unemotional traits and developmental pathways to severe conduct problems. Dev Psychol. 2003;39:246-260.
37. Petersen AC, Crockett L, Richards M, Boxer A. A self-report measure of pubertal status: reliability, validity, and initial norms. J Youth Adolesc. 1988;17:117-133.
38. Kaufman J, Birmaher B, Brent D, *et al*. Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry. 1997;36:980-988.
39. Andershed HA, Kerr M, Stattin H, Levander S. Psychopathic traits in non-referred youths: a new assessment tool. In: Blaauw E, Sheridan L, eds. Psychopaths: Current International Perspectives. Hague, Netherlands: Elsevier; 2002:131-158.
40. Wechsler D. Wechsler Abbreviated Scale of Intelligence. San Antonio, TX: Psychological Corporation; 1999.
41. Wechsler D. Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV). San Antonio, TX: Psychological Corporation; 2003.
42. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis: I. Segmentation and surface reconstruction. NeuroImage. 1999;9:179-194.
43. Fischl B, Sereno MI, Tootell RBH, Dale AM. High-resolution intersubject averaging and a coordinate system for the cortical surface. Hum Brain Mapp. 1999;8:272-284.
44. Winkler AM, Sabuncu MR, Yeo BTT, *et al*. Measuring and comparing brain cortical surface area and other areal quantities. NeuroImage. 2012; 61:1428-1443.
45. Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci. 2000;97:11050-11055.
46. Schaer M, Cuadra MB, Tamarit L, Lazeyras F, Eliez S, Thiran J. A surface-based approach to quantify local cortical gyrification. IEEE Trans Med Imaging. 2008;27:161-170.
47. Schaer M, Ottet M, Scariati E, *et al*. Decreased frontal gyrification correlates with altered connectivity in children with autism. Front Hum Neurosci. 2013;7:750.
48. Fischl B, Salat DH, Busa E, *et al*. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron. 2002; 33:341-355.
49. Hagler DJ, Saygin AP, Sereno MI. Smoothing and cluster thresholding for cortical surface-based group analysis of fMRI data. Neuroimage. 2006;33: 1093-1103.
50. Giedd JN, Blumenthal J, Jeffries NO, *et al*. Brain development during childhood and adolescence: a longitudinal MRI study. Nat Neurosci. 1999;2:861-863.
51. Im K, Lee J-M, Lee J, *et al*. Gender difference analysis of cortical thickness in healthy young adults with surface-based methods. NeuroImage. 2006; 31:31-38.
52. Sowell ER, Peterson BS, Kan E, *et al*. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. Cereb Cortex. 2007;17:1550-1560.
53. Luders E, Narr KL, Thompson PM, *et al*. Gender differences in cortical complexity. Nat Neurosci. 2004;7:799-800.
54. Knutson B, Fong GW, Adams CM, Varner JL, Hommer D. Dissociation of reward anticipation and outcome with event-related fMRI. Neuroreport. 2001;12:3683-3687.
55. Goldin PR, McRae K, Ramel W, Gross JJ. The neural bases of emotion regulation: reappraisal and suppression of negative emotion. Biol Psychiatry. 2008;63:577-586.
56. Shamay-Tsoory SG, Tomer R, Berger BD, Aharon-Peretz J. Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. J Cogn Neurosci. 2003;15: 324-337.
57. Fairchild G, Van Goozen SHM, Calder AJ, Stollery SJ, Goodyer IM. Deficits in facial expression recognition in male adolescents with early-onset or adolescence-onset conduct disorder. J Child Psychol Psychiatry. 2009;50:627-636.
58. Puzzo I, Smaragdi A, Gonzalez K, Martin-Key N, Fairchild G. Neurobiological, neuroimaging, and neuropsychological studies of children and adolescents with disruptive behavior disorders. Fam Relat. 2016;65: 134-150.
59. Craig MC, Catani M, Deeley Q, *et al*. Altered connections on the road to psychopathy. Mol Psychiatry. 2009;14:946-953.
60. Singer T, Critchley HD, Preuschoff K. A common role of insula in feelings, empathy and uncertainty. Trends Cogn Sci. 2009;13:334-340.
61. Oostermeijer S, Whittle S, Suo C, *et al*. Trajectories of adolescent conduct problems in relation to cortical thickness development: a longitudinal MRI study. Transl Psychiatry. 2016;6:e899.
62. Shaw P, Eckstrand K, Sharp W, *et al*. Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. Proc Natl Acad Sci. 2007;104:19649-19654.
63. Silani G, Lamm C, Ruff CC, Singer T. Right supramarginal gyrus is crucial to overcome emotional egocentricity bias in social judgments. J Neurosci. 2013;33:15466-15476.
64. Herpertz SC, Huebner T, Marx I, *et al*. Emotional processing in male adolescents with childhood-onset conduct disorder. J Child Psychol Psychiatry. 2008;49:781-791.

65. Fairchild G, van Goozen SHM, Stollery SJ, *et al*. Decision making and executive function in male adolescents with early-onset or adolescence-onset conduct disorder and control subjects. Biol Psychiatry. 2009;66:162-168.
66. Boisgueheneuc F du, Levy R, Volle E, *et al*. Functions of the left superior frontal gyrus in humans: a lesion study. Brain. 2006;129:3315-3328.
67. Pujol J, Harrison BJ, Ortiz H, *et al*. Influence of the fusiform gyrus on amygdala response to emotional faces in the non-clinical range of social anxiety. Psychol Med. 2009;39:1177-1187.
68. Geday J, Gjedde A, Boldsen A-S, Kupers R. Emotional valence modulates activity in the posterior fusiform gyrus and inferior medial prefrontal cortex in social perception. NeuroImage. 2003;18:675-684.
69. Huebner T, Vloet TD, Marx I, *et al*. Morphometric brain abnormalities in boys with conduct disorder. J Am Acad Child Adolesc Psychiatry. 2008;47:540-547.
70. Sterzer P, Stadler C, Poustka F, Kleinschmidt A. A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy. NeuroImage. 2007;37:335-342.
71. De Brito SA, Hodgins S, McCrory EJ, *et al*. Structural neuroimaging and the antisocial brain: main findings and methodological challenges. Crim Justice Behav. 2009;36:1173-1186.
72. Marshall WA, Tanner JM. Puberty. In: Falkner F, Tanner JM, eds. Human Growth. New York: Plenum; 1986:171-209.