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Cortical thickness and folding deficits in conduct-disordered adolescents

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Abstract

Background—Studies of pediatric conduct disorder (CD) have described frontal and temporal lobe structural abnormalities that parallel findings in antisocial adults. The purpose of this study was to examine previously unexplored cortical thickness and folding as markers for brain abnormalities in "pure CD"-diagnosed adolescents. Based on current fronto-temporal theories, we hypothesized that CD youth would have thinner cortex or less cortical folding in temporal and frontal lobes than control subjects.

Methods—We obtained T1-weighted brain structure images from n=24 control and n=19 CD participants aged 12–18 years, matched by overall gender and age. We measured group differences in cortical thickness and local gyrification index (regional cortical folding measure) using surface-based morphometry with clusterwise correction for multiple comparisons.

Results—CD participants, when compared with controls, showed both reduced cortical thickness and folding. Thinner cortex was located primarily in posterior brain regions, including left superior temporal and parietal lobes, temporoparietal junction and paracentral lobule, right superior temporal and parietal lobes, temporoparietal junction and precuneus. Folding deficits were located mainly in anterior brain regions and included left insula, ventro- and dorsomedial prefrontal, anterior cingulate and orbitofrontal cortices, temporal lobe, right superior frontal and parietal lobes and paracentral lobule.

Conclusions—Our findings generally agree with previous CD volumetric studies, but here show the unique contributions of cortical thickness and folding to gray matter reductions in pure CD in different brain regions.

Keywords

Conduct disorder; cortical thickness; local gyrification index; cortical folding; somatic marker hypothesis; empathy

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Introduction

Conduct disorder (CD) is characterized by aggression, property destruction, deceitfulness or theft, and serious rule violations occurring before age 18 (1) that occurs in as many as 16.0% of boys and 9.2% of girls (2). Neurodevelopmental theories suggest that early expression of brain abnormalities may increase the risk for lifelong antisocial behavior (3–5). According to these theories, pediatric structural brain abnormalities may persist into adulthood, thereby providing a substrate for adult antisocial personality (APD) or psychopathy. Studies of brain volume in CD found gray matter deficits in orbitofrontal cortex (OFC), hippocampus (6), amygdala (6–8), insula (7,8), cerebellum (6,9), dorsomedial prefrontal cortex, caudate nucleus, fusiform gyrus/occipital cortex (8) and bilateral temporal lobes (6,10). A recent study of boys with disruptive behavioral disorders found reduced cortical thickness in left anterior cingulate cortex (ACC) (11). In contrast, one study of youth with callous-unemotional traits found increases in gray matter concentration in frontal lobes and both volume and concentration in temporal lobes compared with controls (12). Despite emerging uniformity of abnormal brain volume findings across regions and ages, there is a need to determine with improved consistency which brain regions show structural abnormalities in antisocial disorders.

With one exception (11), all published structural brain studies of CD youth have focused exclusively on volume deficits (e.g., (13)). In recent years, surface-based measurements of cortical thickness (11,14) and folding (15) increasingly have been used to compare groups. Surface-based measurements are important because the two-dimensional folded laminar structure of the cerebral cortex is a function of both cortical thickness and surface area (where surface area is proportional to the degree of cortical folding for a fixed intracranial volume) (16–20). Cortical thickness and folding are increasingly viewed as important, separable endophenotypes for understanding the relationship of genetic influences on brain structure and function (16,19,21,22). Because volumetric techniques may obscure the degree to which each factor contributes to gray matter volume differences (19,20), focusing on these two more specific measures of brain structure abnormality might help clarify previously discrepant findings in CD.

Inconsistencies in CD structural findings might also be due to comorbid psychopathology, such as ADHD, depression, anxiety and substance use disorders. Notably, almost all CD published structural brain studies have examined samples with documented high ADHD comorbidity. While statistical control can mitigate the confounding effects of comorbid psychopathology, it is essential to examine CD individuals without comorbidity to ensure any brain structure abnormalities cannot be attributed to other disorders. However, CD without comorbidity is the norm, not the exception. The recent National Comorbidity Survey Replication study (23) found that less than 40% of adolescents met lifetime criteria for more than one disorder, with current comorbidity rates in community-recruited CD youth long known to be only between 7–28% for ADHD, depression or anxiety (24). Although childhood CD and ADHD have both been proposed to predict future adult antisocial behavior, Lahey and colleagues determined that only CD directly predisposes individuals to the development of antisocial personality disorder (APD) in adulthood (25). Because recent studies have provided evidence for gray matter volume deficits in adult APD (26–28) and psychopathy (29–31) in regions that overlap with structural brain abnormalities in CD, identification of such abnormalities in a more “pure” CD sample may elucidate specific neurobiological factors underlying the development of adult APD and psychopathy.

The primary purpose of this study was to identify cortical thickness and folding differences in a relatively pure CD adolescent sample. We hypothesized that CD adolescents without other significant psychopathology would show cortical thickness or folding deficits in

prefrontal cortex (e.g., ventromedial, OFC, insular cortex, rostral cingulate) and bilateral temporal lobes. This prediction was based not only on previous CD brain volume abnormality findings, but also on findings of structural abnormalities in similar regions in adult APD and psychopathy. Although we were uncertain whether lateral prefrontal regions would show cortical thickness or folding deficits in a sample of pure CD youth because of inconsistencies in previous findings and due to questions about disorder specificity (i.e., comorbid ADHD) these regions were previously linked to antisocial behavior in functional and structural neuroimaging (32) and in lesion-based studies (33). Therefore, we also predicted CD cortical thickness or folding deficits in dorso- and ventrolateral prefrontal cortex.

Methods

Study participants

We selected n=19 adolescents (ages 12–18) diagnosed with CD and n=24 adolescents without psychiatric disorders from an original sample of 310 datasets collected in an NIMH-funded study comparing CD, ADHD, and control group participants (K23 MH070036). Participants were recruited by community advertisements, direct referral from clinical treatment programs at The Institute of Living (http://www.instituteofliving.org), and letters sent to families of youth on probation following arrest in the Connecticut Court Support Services Division. The CD group had one left-handed and one mixed-dominant participant. All participants were healthy as determined from responses on a parent-report medical questionnaire. Informed assent for study participation and parental permission were obtained jointly from the participants and their parent or legal guardian. The Hartford Hospital Institutional Review Board approved all consent and study procedures.

Clinical diagnoses for research purposes were made using the K-SADS-PL (34) conducted by trained bachelor's- and master's-level staff working under the supervision of a licensed clinical psychologist. The K-SADS-PL, based on DSM-IV, is a validated, reliable and widely-used semi-structured clinical research interview. Interviews were performed separately for both adolescents and parents. Information was synthesized and diagnoses confirmed in weekly research group meetings. All participants tested negative on a urine screen for marijuana, cocaine and heroin on the MRI day. No participants met lifetime criteria for ADHD and all CD participants, except one, reported zero or one current ADHD symptoms. By design, none of the CD sample had current co-morbid psychiatric diagnoses or substance dependence. However, one CD adolescent was diagnosed with cannabis abuse, another with past cannabis dependence, while another had past Major Depressive Disorder. (Primary analyses were re-run omitting the these three subjects, and no significant differences were found.) Seven CD participants also would have qualified for an Oppositional Defiant Disorder diagnosis if their behavior had not been better accounted for by Conduct Disorder. Healthy control participants were free of any DSM-IV Axis I psychopathology. Sample demographic and clinical characteristics are listed in Table 1. Verbal ability was estimated using the Wide Range Achievement Test (3rd Edition) (WRAT-3) (35) because numerous CD participants did not exert adequate effort on more challenging WISC-III/WAIS-III Vocabulary subtests originally intended to estimate verbal-conceptual ability. WRAT-3 is strongly correlated with verbal IQ (36,37). Consistent with previous research (38,39), CD verbal ability was significantly lower compared to controls (t_{39}=5.09, p<.001). Nonverbal intelligence (estimated by available WASI Matrix Reasoning scores) also differed between groups. However, both groups were well within the average range on both measures.

MRI Data Collection

We obtained MRI images on a Siemens 3T Allegra MRI machine at the Olin Neuropsychiatry Research Center at The Institute of Living/Hartford Hospital. T_1-weighted brain structure images were collected using a 3D MPRAGE pulse sequence (TR/TE/TI=2300/2.74/900 ms, flip angle=8°, FOV=176×256 mm, matrix=176×256×176, voxel size=1×1×1 mm, pixel bandwidth=190 Hz; 7:09 minutes).

Image Processing

We prepared brain structure images for cortical reconstruction by correction of the estimated MRI bias-field using SPM5 software (http://www.fil.ion.ucl.ac.uk/), followed by noise reduction using FSL SUSAN filtering software (http://www.fmrib.ox.ac.uk/). We then performed anatomical reconstruction of the cortical surfaces using the FreeSurfer image analysis suite (v5.0; http://surfer.nmr.mgh.harvard.edu/). SPM5 and FSL preprocessing was used only to facilitate FreeSurfer analyses.

FreeSurfer surface-based cortical reconstruction and analysis has been described previously (17,40) and validated in a number of studies (41–44). The reconstruction estimated the white surface, comprised of the gray/white matter interface, and the pial surface, comprised of the gray matter/cerebrospinal fluid interface via two-dimensional mesh of triangular elements comprised of >100,000 vertices per hemisphere. The estimated white and pial surfaces were manually corrected for inconsistencies by visual inspection and addition of control points where necessary to aid gray and white matter differentiation. Typically, only the temporal poles required manual edits to improve reconstructed surface accuracy. Cortical thickness at each vertex was calculated by measuring the shortest distance between the white and pial surfaces at that vertex (41). Estimated total intracranial volume for each subject also was obtained.

Gyrification Index

Schaer and colleagues developed a measure of cortical folding called the local gyrification index (*I*GI) that is implemented in Freesurfer (45). The *I*GI is a surface-based, three-dimensional extension of the linear, two-dimensional coronal section gyrification measurement method of Zilles and colleagues (46). The *I*GI measures the ratio of a vertex-based, 25 mm radius circular region of interest (ROI) of folded pial surface area to the corresponding surface area of a tight-fitting contour enveloping the cortex's outer perimeter. The resulting cortical surface maps of *I*GI represent the amount of cortical folding, *i.e.*, extent of cortex buried within the sulcal folds, at each pial surface location.

Statistical Analyses

Surface-based group analyses were performed using FreeSurfer's general linear model (GLM) tools. Prior to group comparison, each participant's data were resampled into a common anatomical space. Surface-based measurements of cortical thickness and *I*GI for all subjects were smoothed using Gaussian kernels of 10 mm and 5 mm full-width/half-maximum, respectively.

Statistical significance of between-group cortical thickness and *I*GI differences was evaluated using a clusterwise correction for multiple comparisons from Monte Carlo *z*-field simulation (47). For each iteration, a *z*-field was synthesized, smoothed with a Gaussian filter (using residual FWHM value from GLM), thresholded at a user-chosen vertexwise value, and finally clusters were extracted and sized. This was repeated 10,000 times to derive the distribution of cluster sizes expected under the null hypothesis. Clusters were initially obtained using a $p<0.05$ (two-tailed) vertexwise threshold, and then reported only if

they met additional clusterwise probability ($P_{cluster}$) of $p<0.05$ (two-tailed). The $P_{cluster}$ is the probability of forming a cluster that size by chance.

We performed several *post hoc* analyses of CD data. We defined regions-of-interest (ROIs) as 3 mm radius spheres in volume space, with each ROI center located at the cluster vertex coordinate having the peak statistical group difference (HC > CD) in cortical thickness or *I*GI. We then transformed each spherical volume ROI into an area (cluster) ROI in surface-space and measured the mean cortical thickness or *I*GI at each cluster ROI for each subject.

The linear association of ROI values with symptom count for CD participants was assessed using Pearson correlation to determine whether structural deficits were linked to disorder severity. To ensure that our findings were not due to intellectual differences between groups, we also examined cluster ROI value correlations with WRAT-3 Reading or WASI Matrix Reasoning scores. Unavailable scores on WRAT-3 (CD/HC, n=2/5) and WASI-MR (CD/HC, n=5/2) were replaced by group means. We then performed linear regression of cluster ROI values with subjects' WRAT-3 or WASI-MR scores, and statistically compared regression coefficients between CD and HC groups. To ensure our CD<HC findings were unrelated to gender, we examined ROI values into a two-way group-by-gender ANOVA. We also performed one "whole brain" *post hoc* analysis to explore potential CD differences between subgroups defined by age of disorder onset. Cortical thickness and *I*GI data differences between CD childhood-onset versus adolescent-onset classifications were compared using multiple regression, controlling for gender. Finally, we compared estimated total intracranial volume between groups. All *post hoc* findings were reported if they met $p<.05$ uncorrected threshold.

Results

Cortical thickness

Compared with HC, CD adolescents had reduced cortical thickness in four clusters in the left hemisphere, including the supramarginal/angular gyri and superior temporal lobe ($P_{cluster}=0.0003$), superior parietal lobe ($P_{cluster}=0.007$), lingual, fusiform and inferior temporal gyri ($P_{cluster}=0.007$) and paracentral lobule ($P_{cluster}=0.0018$) (Figure 1).

In the right hemisphere, cortical thickness was reduced in CD in three clusters, including the superior/inferior parietal lobe and postcentral gyrus ($P_{cluster}=0.0004$), supramarginal/angular gyri and superior temporal sulcus ($P_{cluster}=0.0003$) and precuneus ($P_{cluster}=0.0497$) (Figure 2). Tables 2 and 3, *top*, summarize left and right hemisphere cortical thickness cluster measurements, respectively. Cortical thickness was not found to be greater in CD than HC.

IGI

When compared with HC, we found reduced *I*GI in CD participants in two relatively large left hemisphere clusters. The first included insula, lateral orbitofrontal and inferior frontal cortices and anterior temporal lobe ($P_{cluster}=0.0001$). The second cluster comprised ventro- and dorsomedial prefrontal regions including ACC ($P_{cluster}=0.0001$) (Figure 1).

In the right hemisphere, there were two significant clusters with reduced *I*GI in CD versus HC. The first cluster consisted of the superior frontal lobe, including frontal eye fields, pre- and postcentral gyrus as well as dorsomedial prefrontal lobe ($P_{cluster}=0.0047$); and the second cluster, the superior parietal lobe and precuneus ($P_{cluster}=0.0141$) (Figure 2). Tables 2 and 3, *bottom*, summarize left and right hemisphere *I*GI cluster measurements. *I*GI was not greater in CD than HC in any significant cluster.

Post Hoc Analyses

CD Severity—There were no significant correlations in each cluster ROI between CD symptom count and cortical thickness or *I*GI.

Verbal and Nonverbal Abilities—One cluster in the superior temporal sulcus, supramarginal and angular gyri showed a relationship between WRAT-3 verbal ability and cortical thickness (p=.041 uncorrected; cluster 2T; Table 3). Another cluster in the superior parietal lobe and paracentral lobule showed a WRAT-3 relationship with *I*GI (p=.034 uncorrected; cluster 2G; Table 3). These did not survive corrections for multiple comparisons.

Gender—An ROI analysis of group-by-gender interaction found a significant effect in only one cortical thickness ROI (p=.011 uncorrected; cluster 1T; Table 3). This interaction effect also did not survive corrections for multiple comparisons.

Age-of-Onset—Cortical thickness differed between childhood-onset and adolescent-onset CD in several small clusters (p<.05 uncorrected), but none survived corrections for multiple comparisons. *I*GI values were greater for childhood-onset CD in two left and three right hemisphere clusters (Figure 3) that survived clusterwise correction for multiple comparisons (Table 4).

Total Intracranial Volume—There were no significant group differences in mean estimated total intracranial volume.

Discussion

Cortical thickness

As hypothesized, we found reduced cortical thickness bilaterally in the posterior aspect of CD participants' superior temporal lobes, including the superior temporal sulcus (STS). We also discovered cortical thickness deficits in CD in superior and inferior parietal lobe regions, left fusiform and inferior temporal gyrus, left paracentral lobule and right precuneus. Our bilateral superior temporal lobe findings agree not only with prior volumetric brain research showing bilateral temporal lobe abnormalities in CD youth (6,10), but also with temporal lobe abnormalities in antisocial adults (27,31,48,49) and gray matter volume deficits in bilateral mid- and posterior STS of adult psychopaths (50). Temporo-parietal junction, parietal lobe or angular and supramarginal gyri volume deficits generally have not been found in either CD or antisocial adults, with exception of De Brito *et al.* (12) who examined boys aged 10–13 years high on callous-unemotional traits. That report described gray matter volume and concentration increases, rather than decreases, in widespread regions including the parietal lobe. Differences between the De Brito et al. study and our study, however, might be attributed to different age ranges (10–13 vs. 12–18 years of age) and diagnostic groupings (e.g., high levels of callous-unemotional traits as well as conduct problems vs. "pure" CD) used in the two studies.

Recent functional imaging studies have shown that superior temporal lobe and temporo-parietal regions play an important role in social abilities such as empathy (51–53), perspective taking (54), attention to emotions (55) and moral reasoning (48,56). Decety et al. reported aggressive CD youth had lower neural responses versus controls in right temporo-parietal junction to visual images of pain inflicted on people (57). In particular, the posterior superior temporal sulcus (STS) was found to be crucial for understanding social cues and correct interpretation of the actions and behaviors of others, concepts central to "Theory of Mind" (ToM) research (50,58,59). Dolan and Fullam (60) found that antisocial adults had

subtle impairments in brain regions that have been linked to ToM. They speculated such impairments may play a role in the antisocial individual's apparent indifference to the suffering of potential victims. Although some early behavioral studies found either no difference in perspective-taking between antisocial youth and controls (61), or even antisocial youth superiority in this regard (62–64), more recent studies found CD youth were impaired in empathy and perspective-taking (65,66). Because the ToM construct originated from autism research, it is unlikely that it will be a sufficient explanatory framework for CD. However, such neurobiological studies no doubt will inform efforts to accurately describe socialization deficits in CD. CD cortical thickness deficits bilaterally in the superior temporal lobe including the STS, temporoparietal junction and angular and supramarginal gyrus might form a possible structural substrate for socialization impairments often associated with CD, including compromised empathy, perspective-taking, social functioning and the ability to attend to emotions.

Until this study, there have been no structural MRI studies in CD youth samples without significant co-morbidity. Rubia and colleagues, however, found non-comorbid CD boys (aged 9–16 years) had activation deficits relative to controls in bilateral temporo-parietal regions, superior temporal lobes and right precuneus (67–69). Rubia has postulated (69) that CD might be distinguished from ADHD by abnormalities in the "hot" paralimbic system, which includes superior temporal lobes. The impaired regions found in these recent functional studies in non-comorbid CD youth overlap well with our own structural findings of cortical thinning in the bilateral temporal-parietal regions, superior temporal lobes and right precuneus. This convergence of functional and structural evidence suggests that posterior temporo-parietal regions should be the focus of future inquiry in CD.

IGI

We also discovered reduced prefrontal cortex *I*GI (cortical folding) in prefrontal regions. In summary, in the left hemisphere, we detected *I*GI deficits in CD in insular cortex, inferior frontal gyrus, lateral OFC and a large cluster on the medial surface including ventro- and dorsomedial prefrontal cortices (vmPFC and dmPFC) and ACC. In the right hemisphere, clusters of CD *I*GI deficits were found in superior parietal lobe, precuneus, primary motor and somatosensory cortex, and superior prefrontal cortex including supplementary motor area (SMA) and premotor regions. Several recent fMRI studies of CD found abnormal activation in OFC (57,68–73) and insula (57,70,72,73), regions in which we found *I*GI deficits. Herpertz and colleagues, however, found no abnormalities in OFC or insula activation in CD youth (74). The medial regions in the left hemisphere exhibiting *I*GI deficits in CD include regions known to be critical for emotional regulation (ACC, vmPFC) (75,76), error detection and resolution (ACC, dmPFC) (77,78), attentional processes (ACC) (79) and risk evaluation (dmPFC) (80).

In the left hemisphere, a large cluster of reduced *I*GI in CD versus controls included nearly all insular cortex. Medford and Critchley have highlighted the joint role of the anterior cingulate and anterior insular cortices in both the experience of emotions and coordination of appropriate responses to events (79). According to the somatic marker hypothesis, insular cortex is essential to formation of subjective feeling states (79,81). In particular, joint action of these regions is postulated to be responsible for the awareness of self, in contrast to third-person awareness and empathy previously discussed as the function of the temporo-parietal regions. Dysfunction in CD in both these prefrontal regions, along with vmPFC dysfunction, might arise from a diminished capacity to learn from, as well as avoid, risky situations and negative consequences when prompted by internal emotional states. Recent behavioral studies in disruptive behavioral disorders (82–84) provide additional evidence supporting this hypothesis.

Topographical differences: Frontal versus posterior

In our CD subjects, cortical thickness deficits occurred chiefly in posterior brain regions, whereas in contrast, *I*GI deficits occurred primarily in the frontal lobe. Overlap of deficit types were surprisingly limited (Figures 1–2). Current theories propose that cortical folding (*I*GI) is determined largely prenatally, whereas in contrast, cortical thickness is determined postnatally and undergoes significant changes throughout the human life span (85,86). Therefore, in CD individuals, reduced *I*GI in the prefrontal cortex may be congenital, resulting in lifelong impairment in social and cognitive behavior. These observations are interesting in light of our *post hoc* comparison of CD age-of-onset subgroups (87). We found greater *I*GI deficits in CD youth whose symptoms appeared *after* age 10, suggesting that possibly congenital abnormalities did not result in demonstrable behavioral effects until puberty. These data agree with Fairchild *et al.* (8), who found greater insular cortex volume deficits in adolescent- versus childhood-onset CD. These findings raise intriguing possibilities for future gene-by-environment and developmental studies, particularly those that focus on pubertal influences on brain structure and function.

Additional topics

Comparing our CD results with published adult APD studies, we note that Yang et al. (30,88) found cortical thickness deficits in OFC, whereas we found *I*GI deficits in this same region. They also found thickness deficits in superior temporal lobe, in agreement with our findings. In violent APD subjects, Narayan *et al.* (28) discovered cortical thickness deficits in medial prefrontal cortex, whereas we found *I*GI deficits in similar regions. However, they also measured thickness deficits in sensorimotor regions that partially overlap with superior parietal regions found in our study. Our *post hoc* analysis of possible CD gender effects found only one significant interaction in the right hemisphere superior parietal cluster (1T) at $p<.05$ uncorrected. We therefore conclude that gender did not significantly impact study findings.

Study limitations

One study limitation is that structural measurements are confined to cortical regions only using surface-based methods. Other limitations include somewhat broad clusters that prevented fine-grained abnormality localization needed to most effectively advance neurobiological theories of antisocial behavior disorder, and a comparatively small sample size for a structural MRI study. Indeed, our failure to find any relationship *post hoc* between CD severity and structural deficits might simply be due to querying the wrong regions (*i.e.*, our small sample size may have precluded an effective whole brain correlational analysis). Also, CD and non-CD verbal and nonverbal abilities differed significantly as in previous studies of verbal ability (38,39). Although *post hoc* analyses found no consistent relationships between verbal or nonverbal intellectual estimates and CD brain structure in the regions of CD deficits, we noted at significance levels uncorrected for multiple comparisons that verbal ability was linked to cortical thickness in one right-hemisphere superior temporal sulcus/supramarginal/angular gyri cluster and cortical folding in a left-hemisphere superior parietal lobe/paracentral lobule cluster. Although these clusters did not simply represent classic language-related areas, the implicated cortex does include regions where cortical thickness has been found to covary with Full Scale IQ (89–92) and verbal IQ (92). This suggests that factors related to reading achievement or verbal intelligence might contribute to these particular CD deficits. However, the majority of CD brain structure deficits were empirically unrelated to intelligence estimates. Finally, we did not collect measures of behavioral traits of high interest in CD research, including callous-unemotional traits, psychopathy and aggression. In particular, both aggression and psychopathy have been linked to structural abnormalities in the temporal lobe and associated limbic structures, the hippocampus and amygdala (27,93). Future studies should focus on examining the link

between aggression and CD-related temporal lobe cortical thickness or gray matter abnormalities.

Summary

To our knowledge, this is the first examination of both cortical thickness and cortical folding (*I*GI) deficits in CD adolescents. Our study examined "pure" CD subjects to assess two dissociable facets of brain volume at the whole brain level with statistical correction for multiple comparisons. Our findings suggest that previously-reported gray matter volume abnormalities in CD youth reflect both cortical thickness and folding deficits each localized to generally different brain structures. We also found novel evidence for CD cortical thickness abnormalities in parietal lobe regions, left paracentral lobule and right precuneus. Psychiatric comorbidity in previous antisocial brain volume studies might have obscured this finding. Parietal lobe structural abnormalities in antisocial disorders require replication before being integrated into neurocognitive theories, but existing research suggests mechanisms through which these abnormalities could contribute to antisocial behavior. The anterior-posterior distinction of cortical folding versus thickness CD deficits implies that specific localized volumetric abnormalities in antisocial samples might result from different neurobiological factors, possibly with distinct genetic correlates. Future studies should attempt structural and functional measurements in the same samples, using integrative "fusion" methods to jointly examine relationships among the measures, particularly social neuroscience fMRI paradigms. Finally, longitudinal studies would help address the question whether structural brain abnormalities found in CD youth persist into adulthood in cases where antisocial behavior also endures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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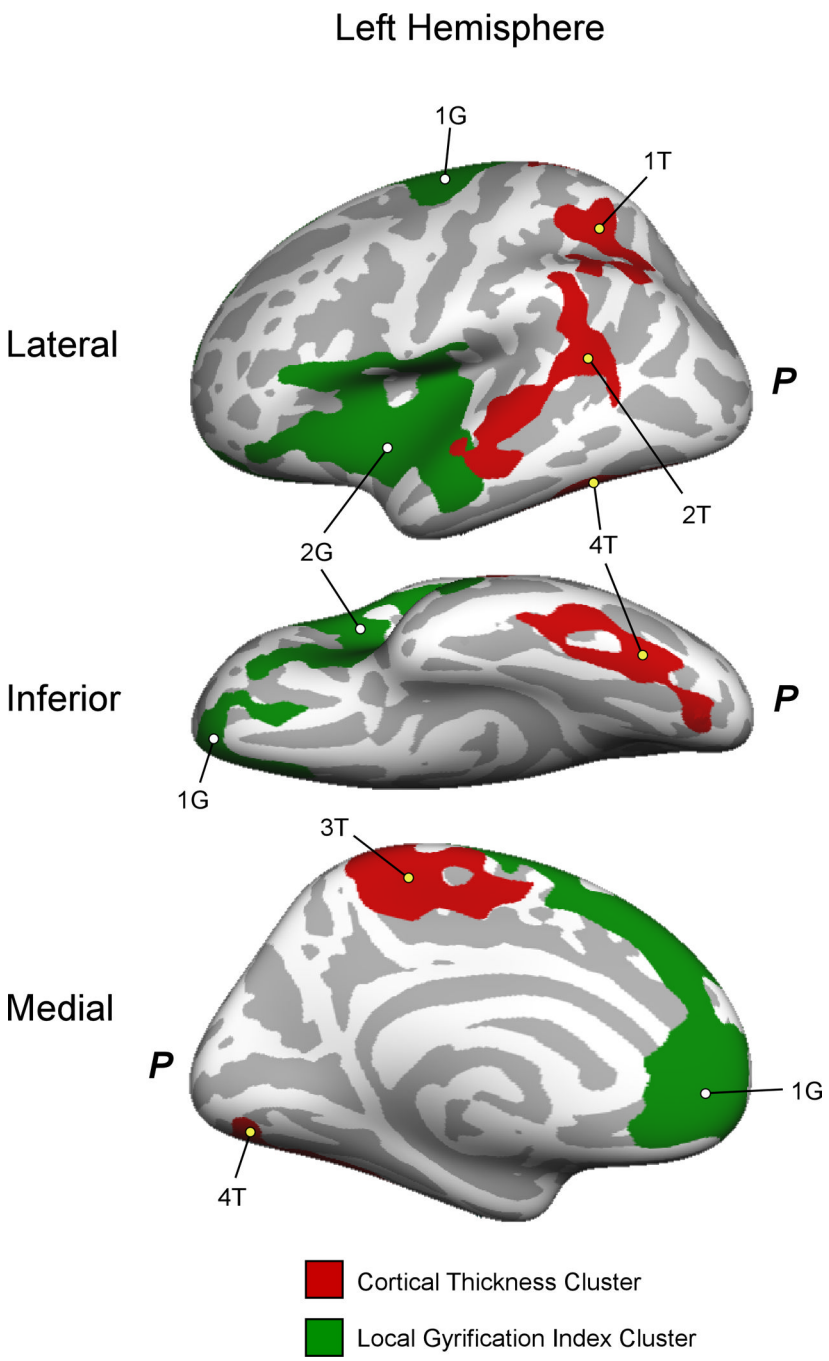

Figure 1.
Left hemisphere clusters with significant cortical thickness (*red*) and *l*GI (*green*) differences (CD < HC). The lateral (*top*), inferior (*middle*) and medial (*bottom*) views of the left hemisphere are shown. Cluster labels (numbers) correspond to those provided in Table 2. ***P***, Location of the posterior of the left hemisphere.

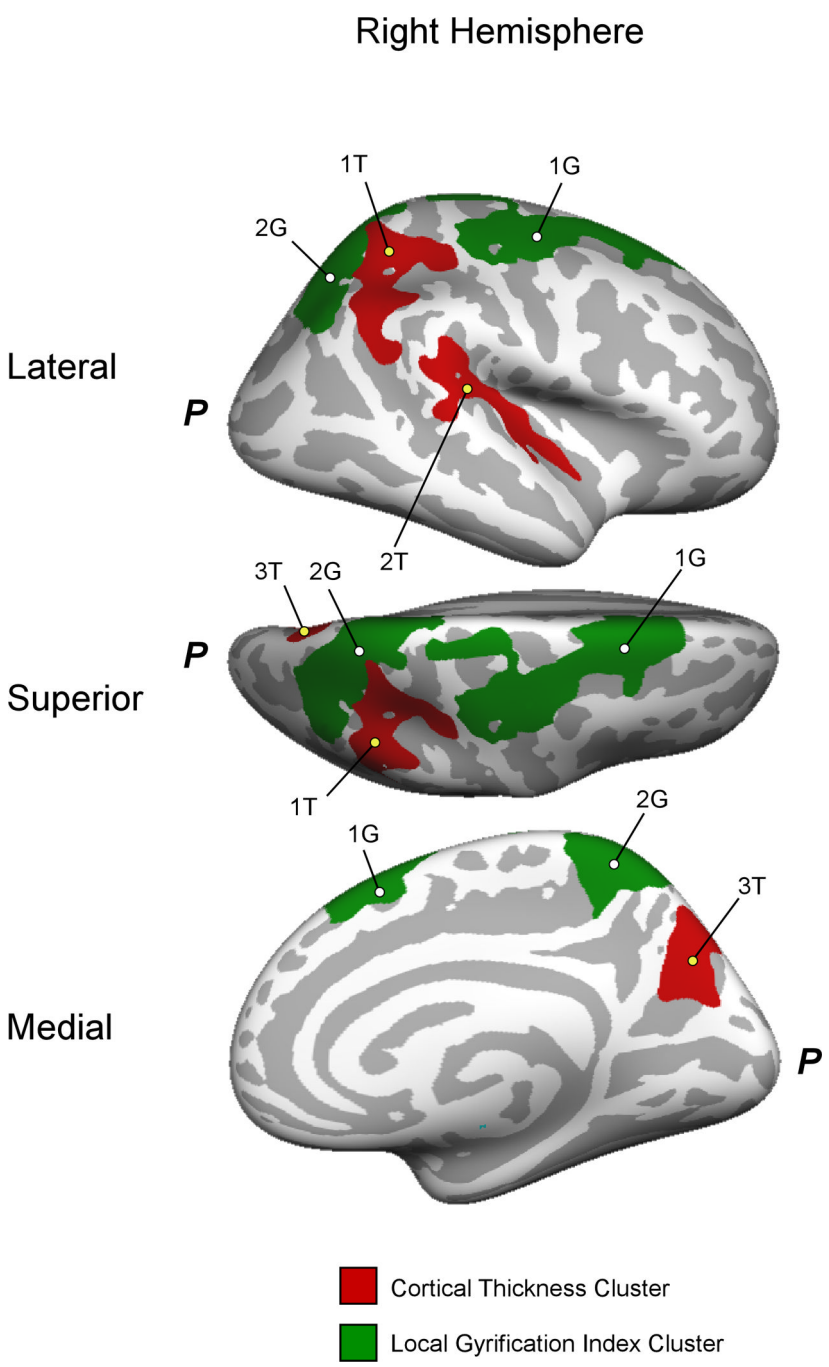

Figure 2.
Right hemisphere clusters with significant cortical thickness (*red*) and *l*GI (*green*) differences (CD < HC). The lateral (*top*), superior (*middle*) and medial (*bottom*) views of the right hemisphere are shown. Cluster labels (numbers) correspond to those provided in Table 3. ***P***, Location of the posterior of the right hemisphere.

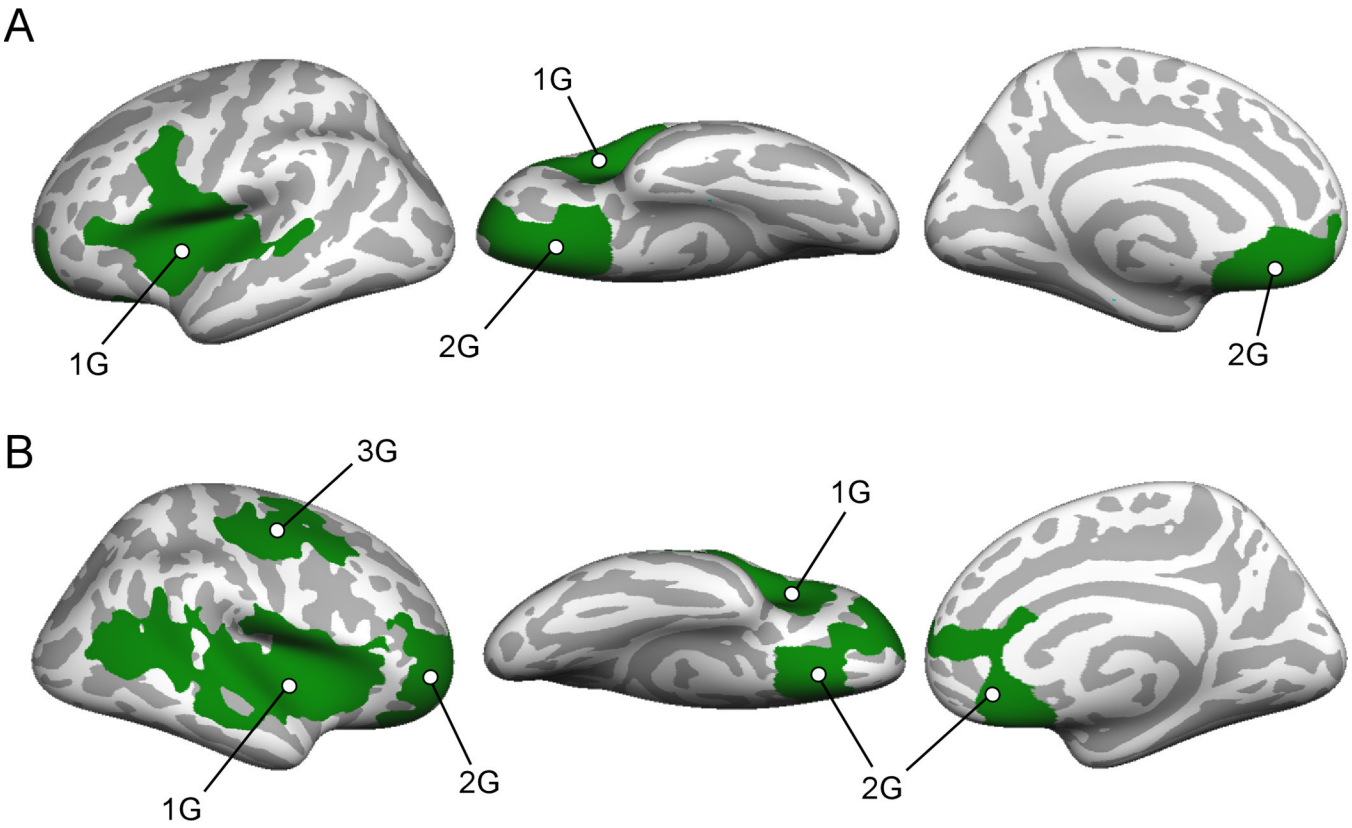

Figure 3.
Significant clusters where *I*GI is less in adolescent-onset than childhood-onset CD subjects. *A*, Left hemisphere, lateral, ventral and medial views. *B*. Right hemisphere, lateral, ventral and medial views.

Table 1

Sample demographic and clinical characteristics

	Conduct Disorder Mean ± SD	Healthy Controls Mean ± SD	*p*
Age	16.3 ± 1.3	16.1 ± 1.4	*ns*
Gender (M/F)	10/9	14/10	*ns*
WASI Matrix Reasoning subtest[a]	46.9 ± 7.6 (33–59)	51.4 ± 5.8 (39–62)	0.049
WRAT-3 Reading subtest Scaled Score	89.3 ± 12.4	98.4 ± 9.2	0.010
K-SADS-PL			
CD symptoms	5.7 ± 2.0	0.0 ± 0.0	< 0.001
ADHD Hyperactivity/Impulsivity symptoms	0.3 ± 0.8	0.0 ± 0.2	*ns*
ADHD Inattentive symptoms	0.7 ± 1.4	0.1 ± 0.5	*ns*

[a] WASI information was not collected for 2 non-CD and 5 CD participants. Subtest score range in parentheses.

WASI, Wechsler Abbreviated Scale of Intelligence; WRAT, Wide Range Achievement Test; *ns*, not significant

Table 2

Left hemisphere cluster regions showing cortical thickness (*top*) and *l*GI (*bottom*) deficits in CD adolescents relative to HC in a whole brain analysis, clusterwise-corrected for multiple comparisons.

Cortical Thickness: CD < HC

Cluster #	Anatomical Regions	Max $-\log_{10}(p\text{-}val)$	Area (mm^2)	Talairach (x, y, z) maxima			$P_{cluster}$
1T	superior parietal lobe	3.51	1488	−27.4	−46.3	39.8	0.007
2T	superior temporal, supramarginal, & angular gyri	3.50	2289	−53.1	−46.2	14.7	0.0003
3T	paracentral lobule	2.83	1834	−7.4	−31.1	50.8	0.0018
4T	fusiform/inferior temporal gyri	2.10	1488	−13.8	−82	−6.7	0.007

Local Gyrification Index (*l*GI): CD < HC

Cluster #	Anatomical Regions	Max $-\log_{10}(p\text{-}val)$	Area (mm^2)	Talairach (x, y, z) maxima			$P_{cluster}$
1G	vm/dmPFC & ACC, OFC, precentral gyrus	3.97	5895	−18.7	−9.5	54.1	0.0001
2G	Insula, lateral OFC, anterior temporal lobe	2.32	5650	−55.7	−11.2	−18.0	0.0001

$P_{cluster}$, clusterwise probability; OFC, orbitofrontal cortex; vm/dmPFC, ventromedial and dorsomedial prefrontal cortex; ACC, anterior cingulate cortex

Biol Psychiatry. Author manuscript; available in PMC 2013 August 01.

Table 3

Right hemisphere cluster regions showing cortical thickness (*top*) and *l*GI (*bottom*) deficits in CD adolescents relative to HC in a whole brain analysis, clusterwise-corrected for multiple comparisons.

Cortical Thickness: CD < HC

Cluster #	**Anatomical Regions**	**Max $-\log_{10}(p\text{-}val)$**	**Area (mm^2)**	**Talairach (*x, y, z*) maxima**			**$P_{cluster}$**
1T	superior & inferior parietal lobe	4.82	2269	33.5	−30.7	45.4	0.0004
2T	STS, supramarginal & angular gyri	4.13	1546	39.2	−19.3	−4.6	0.0073
3T	precuneus	2.93	1143	19.5	−61.7	31.2	0.0497

Local Gyrification Index (*l*GI): CD < HC

Cluster #	Anatomical Regions	Max $-\log_{10}(p\text{-}val)$	Area (mm^2)	Talairach (*x, y, z*) maxima			$P_{cluster}$
1G	Superior frontal lobe	2.61	3929	20.8	18.1	51.4	0.0047
2G	Superior parietal lobe, paracentral lobule	2.51	3303	9.9	−44.7	66.0	0.0141

$P_{cluster}$, clusterwise probability; STS, superior temporal sulcus

Table 4

Clusters in the left and right hemispheres where *l*GI is greater for CD-CO than CD-AO subjects (clusterwise-corrected for multiple comparisons).

Left Hemisphere: Local Gyrification Index (*l*GI): Childhood-onset > Adolescent-onset

Cluster #	Anatomical Regions	Max $-\log_{10}(p\text{-}val)$	Area (mm^2)	Talairach (*x*, *y*, *z*) maxima			$P_{cluster}$
1G	insula, IFG, superior temporal	4.03	7281	−51	30	2	0.0001
2G	vmPFC, medial OFC, frontal pole	3.36	4128	−22	8	−14	0.0001

Right Hemisphere: Local Gyrification Index (*l*GI): Childhood-onset > Adolescent-onset

Cluster #	Anatomical Regions	Max $-\log_{10}(p\text{-}val)$	Area (mm^2)	Talairach (*x*, *y*, *z*) maxima			$P_{cluster}$
1G	insula, IFG, superior temporal, inferior parietal	3.53	9752	31	21	−3	0.0001
2G	vmPFC, rACC, medial OFC	3.21	5324	6	20	−16	0.0001
3G	precentral, postcentral	2.91	3432	38	−5	51	0.0003

$P_{cluster}$, clusterwise probability; OFC, orbitofrontal cortex; vmPFC, ventromedial prefrontal cortex; rACC, rostral anterior cingulate cortex; IFG, inferior frontal gyrus