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Right Anterior Cingulate: A Neuroanatomical Correlate of Aggression and Defiance in Boys

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Variation in emotional processes may contribute to aggressive and defiant behavior. This study assessed these problem behaviors in a large sample of children and adolescents in relation to the volume of two cortical regions with prominent roles in emotion processing, the anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (vmPFC). One hundred seventeen participants (61 boys, 56 girls), ages 7–17, were recruited from the community. Aggressive and defiant behavior was measured using the parent- and teacher-reported Pediatric Behavior Scale and volumetric measures were generated using structural MRI. Regression analyses indicated a significant sex X ACC volume interaction in predicting aggressive and defiant behavior, without significant results for the vmPFC. Follow-up analyses showed that aggressive and defiant behavior is associated with decreased right ACC volume in boys and a nonsignificant reduction in left ACC volume in girls. These results are consistent with the notion that the right ACC acts as a neuroanatomical correlate of aggression and defiance in boys. The authors discuss this finding in light of its implications for understanding the neural correlates of antisocial behavior.

Keywords: antisocial, children, FreeSurfer, sex differences, structural MRI

Humans are an exceptionally social species and, as such, much of our cognitive and behavioral repertoire is adapted to accommodate a social existence. Over the course of development new competencies emerge that facilitate pro-social behavior, such as the ability to modulate aggression and hostile behavior in accord with the contextual appropriateness of such behavior. The emergence of pro-social behavior likely relies on a combination of learning experiences and the maturation of specific neural systems in the brain, though the details of this process are not well understood. Also, variations in social behavior may reflect differences in the structural and functional organization of these neural systems. Better understanding of the neurobiological contribution to social behavior could offer important clues regarding the etiology of pathological antisocial behavior and violence.

Prominent theories suggest that neural systems that underlie emotional processes may play a critical role in the development of pro-social behavior, and deficits in emotion processing may contribute to antisocial behavior (Damasio, 2000; Davidson, Putnam, & Larson, 2000). Support for these theories is derived from converging evidence of three main types: 1) emotion deficits are often found in association with pathological antisocial behavior (Scarpa & Raine, 1997; Blair, Morris, Frith, Perrett, & Dolan, 1999; Blair, Colledge, & Mitchell, 2001a; Blair, Colledge, Murray, & Mitchell, 2001b; Cimbora & McIntosh, 2003; Frick & Morris, 2004; Blair, Budhani, Colledge, & Scott, 2005), 2) circumscribed damage to emotion processing regions of the brain sometimes leads to antisocial behavior (Damasio, Tranel, & Damasio, 1990; Tonkonogy, 1991; Tranel & Damasio, 1994; Grafman et al., 1996; Blair & Cipolotti, 2000), and 3) functional imaging studies have detected abnormal activity in emotion processing regions of the brain in association with pathological antisocial behavior (Veit et al., 2002; Sterzer, Stadler, Krebs, Kleinschmidt, & Poutska, 2005). Two emotion processing regions of the cerebral cortex that have been implicated in social behavior are the anterior cingulate cortex (ACC) (Devinsky, Morrell, & Vogt, 1995) and the ventromedial prefrontal cortex (vmPFC) (Damasio, 2000; also see discussion).

Also of interest to research on emotion and social behavior is the issue of sex differences. The prevalence of pathological antisocial behavior in males is much higher relative to females (American Psychiatric Association, 1994), perhaps due to differences in the brain. There are early reports of hemispheric asymmetry in emotion processing structures that differ by sex. For instance, more severe emotional and behavioral impairments follow unilateral damage to the *right* vmPFC in males and *left* vmPFC in females (Tranel, Bechara, & Denburg, 2002; Tranel, Damasio, Denburg, & Behcara, 2005). Preliminary reports of early onset vmPFC damage

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also follow this pattern (Anderson, Barrash, Bechara, & Tranel, 2006).

The current study was designed to investigate whether aggressive and defiant behavior corresponds to volumetric differences in the ACC and vmPFC. Specifically, we hypothesized that, in a large sample of children and adolescents without any psychiatric diagnosis, subjects with higher aggression-defiance would have lower ACC and vmPFC volume. Another aim of the study was to assess whether sex differences exist in the aforementioned relationship. Specifically, we hypothesized a stronger relationship of aggression-defiance and ACC/vmPFC volumes in the right hemisphere in boys and in the left hemisphere in girls.

Method

Participants. One hundred and seventeen healthy children and adolescents (61 boys, 56 girls), ages 7–17, were recruited from the community using local advertisements. These subjects served as a comparison group for another study on brain structure and function in children with cleft lip and palate (Nopoulos, Langbehn, Canady, Magnotta, & Richman, 2007). A phone screening interview was performed to exclude subjects with any medical or neurological disease that required significant medical intervention. Additional exclusion criteria included any reported current or past diagnosis of a psychiatric disorder or learning disorder. The protocol was approved by the University of Iowa Human Subjects Institutional Review Board and written informed consent was obtained for all subjects prior to participation.

Demographics. Demographic data included age, parental socioeconomic status (SES), IQ, birth history, and handedness. SES was determined using a modified Hollingshead scale of 1 to 5, with a lower number corresponding to higher social class (Hollingshead, 1975). IQ was estimated using the full scale Wechsler Intelligence Scale for Children, 4th ed. (Wechsler, 2003). Prenatal, obstetrical, and developmental history was obtained using a 40 item Birth and Developmental History (DeLisi, Dauphinais, & Gershon., 1988). Handedness was determined using the Physical and Neurologic Evaluation of Subtle Signs (Denckla, 1985).

Behavioral measure. The Pediatric Behavior Scale, short version (PBS) is a screening tool for emotional and behavioral problems derived from the Child Behavior Checklist (CBCL) (Achenbach & Edelbrock, 1983) and Pediatric Behavior Scale (Lindgren & Koeppl, 1987). For each subject a parent and a teacher were asked to rate problems on a 4 point Likert scale (0–3), with a lower score indicating fewer problems. For the current study the conduct scale provided the behaviors of interest, which assessed symptoms of aggression and defiance. Individual items included: 1) mean or cruel to others, 2) threatens, bullies, or picks on other children, 3) starts fights, 4) hits, bites, or throws things at people, 5) disobedient; won't mind or follow rules, 6) argues or quarrels, 7) irritable; gets angry or annoyed easily, 8) loses temper; has temper tantrums, and 9) shouts or screams a lot. Due to a high cooccurrence of conduct problems with symptoms of impulsivity and hyperactivity a second PBS scale, the impulse control scale, was included. This scale assessed the following behaviors: 1) impulsive; acts without stopping to think, 2) can't stand waiting; wants things right away, 3) interrupts, talks out of turn, or blurts things out, 4) fails to finish things he or she starts, 5) hyperactive; always "on the go," 6) squirms or fidgets, 7) restless, can't sit still. This scale was used as a covariate in statistical analyses to ensure that individual differences in impulsiveness and hyperactivity did not confound structure-function findings with regards to aggression-defiance.

The parent and teacher response rate for the PBS was 99% and 90% respectively. As a means of data reduction the PBS scores from the parent and teacher were summed. If only one rating was present (e.g. parent only), it was doubled. Other methods of data reduction were attempted (average, higher of two ratings) and produced the same results. The sum rating was selected because both parent and teacher ratings were preserved and the behavioral variance was maximized in the sample. The summed conduct ratings correlated significantly with individual parent- and teacher-reported ratings using Pearson correlation [$r = .82$, $p = .000$; $r = .79$, $p = .000$; respectively]. The reliability of the PBS conduct scale was established using a longer version of the PBS, which estimated the internal consistency coefficient of the conduct scale at .92 (Lindgren & Koeppl, 1987). The PBS scales were derived from factor analysis with varimax rotation from a sample of 600 children ages 6–12. The scales were obtained from a 4-factor solution with all eigenvalues greater than one. All questions in this analysis correspond to similar items on the CBCL. Also, all of the items on this scale do not cross-load to any significant degree (less than .30) with other PBS scales.

MRI acquisition. MRI scans were obtained using a 1.5 Tesla General Electric SIGNA System (GE Medical Systems, Milwaukee, WI). Three-dimensional (3D) T1 weighted images were acquired in the coronal plane using a spoiled grass sequence with the following parameters: 1.5 mm coronal slices, 40° flip angle, 24 msec repetition time (TR), 5 ms echo time (TE), 2 number of excitations (NEX), 26 cm field of view (FOV) and a 256 × 192 matrix. The proton density (PD) and T2 weighted images were acquired with the following parameters: 3.0 mm coronal slices, 36 msec TE (for PD) or 96 msec TE (for T2), 3000 msec TR, 1 NEX, 26 cm FOV, 256 × 192 matrix and an echo train length = 1.

Image processing. MRI data were processed using BRAINS2 (Brain Research: Analysis of Images, Networks, and Systems), our locally developed software, described elsewhere (Magnotta et al., 2002). T1 weighted images were spatially normalized and resampled to 1.015625 mm^3 voxels and the anterior-posterior axis of the brain was realigned parallel to the anterior commissure—posterior commissure line. The interhemispheric fissure was aligned by selecting points along the fissure in the coronal and axial views. T2 and PD weighted images were aligned to the spatially normalized T1 weighted image (Woods, Cherry, & Mazziotta, 1992) to allow the use of a multimodal discriminant classifier. The resulting classified image was used for the application of an artificial neural network that creates an automated brain mask (Harris et al., 1999). This mask was visually inspected and manually edited by trained, reliable technicians. The resulting intracranial volume (ICV) mask includes all brain tissue and both internal and surface cerebrospinal fluid.

The T1 acquisition was processed using FreeSurfer (http://www.martinos.org/freesurfer), an automated parcellation software program (Desikan et al., 2006). The output of interest was volumetric measures of the total cerebral cortex gray matter volume and volume of the predefined regions of interest (ROIs), the ACC and vmPFC. The anatomical accuracy of FreeSurfer parcellation in the ROIs was visually inspected (by A.D.B. and P.N.) and those with unacceptable parcellation were excluded from all analyses (2 right ACC and 5 left ACC). Common reasons for exclusion included problems with the corpus callosum bleeding into the rostral ACC or only the outer portion of a double cingulate being labeled.

ACC and vmPFC definition. Figure 1 displays the anatomical ROIs for the current study, which were defined using standard FreeSurfer parcellation. The ACC includes a rostral and caudal division, (rACC and cACC, respectively). The vmPFC is composed of two regions defined by FreeSurfer, the medial orbitofrontal cortex (mOFC) and lateral orbitofrontal cortex (lOFC). The mOFC is composed of the ventral surface of the medial prefrontal cortex and the straight gyrus. The lOFC contains the rest of the OFC, excluding the lateral-most sector. The anatomical boundaries of these regions and the intraclass correlation coefficient describing the correlation of automated and manual parcellation methods for each region are reported elsewhere (Desikan et al., 2006).

Statistical analysis. All analyses were performed using SPSS 13.0 for Windows (SPSS Inc. Chicago). Independent samples t tests analyzed sex differences in quantitative descriptive data, including demographic, behavioral, and volumetric measures. The relationship of conduct ratings to multivariate predictors was assessed with hierarchical multiple regression. Significant structural findings in the regression model were followed up with Spearman partial correlation coefficients to investigate the nature of the relationship of the conduct ratings and volumetric measures. We performed two additional analyses aimed at assessing the specificity of our correlation test and ruling out alternative explanations. First, we chose a specific region of the cortex, the occipital lobe, that we hypothesized would have no relationship to our behavioral measure, and correlated its gray matter volume with conduct ratings. Next, we performed the same statistical analysis as described for conduct ratings with the physical health PBS measure, predicting a nonsignificant correlation.

ROI volumes that significantly correlated with conduct ratings were compared in subjects with high versus low conduct scores using general linear models analysis of variance (ANCOVA). High and low conduct ratings were defined by separating subjects into terciles according to their scores. The purpose of this analysis was to determine whether volumetric differences driving significant correlations reached statistical significance in comparing subjects at each end of the behavioral distribution. Also, demographic variables were compared among these "high" and "low" groups using independent t tests.

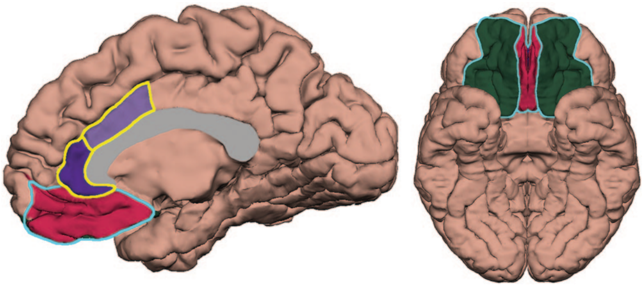

Figure 1. This figure shows a medial (left) and ventral (right) view of the cerebral cortex demonstrating the regions of interest for the current study. The anterior cingulate cortex is outlined in yellow and is composed of a rostral (dark purple) and caudal (light purple) division. The ventromedial prefrontal cortex is outlined in light blue and contains the medial orbitofrontal cortex (mOFC) in red and lateral orbitofrontal cortex (lOFC) in dark green, according to the FreeSurfer terminology (also see description in methods section). The corpus callosum (in gray) was generated manually and included to illustrate a relevant landmark.

Results

Descriptive. The boys and girls in the sample had similar outcomes on demographic measures (see Table 1). IQ scores were somewhat above the population mean of 100 for both genders (consistent with the demographics of Iowa City and the surrounding area). The behavioral data revealed fairly low mean levels of conduct problems and impulsiveness or hyperactivity in the sample, with a positive skew in the distribution. Boys had higher levels of behavioral problems relative to girls. Boys had larger total cortical gray matter volume than girls, though volume of the ROIs did not differ between sexes when expressed as a percentage of the cortical volume. Review of the Birth and Developmental History questionnaire revealed 1 subject with significant alcohol exposure prenatally.

Multiple regression. Results of the hierarchical multiple regression analysis are summarized in Table 2. Step 1 included demographic data (sex, IQ, SES, age), total gray matter volume of the cerebral cortex, and ratings of impulse control. Age and IQ were found to have a negligible effect on the model and were subsequently dropped. Step 2 included volumetric measures of the right and left ACC and vmPFC. Step 3 of the model included interaction terms for ROI volumes X sex. Nonsignificant interaction terms were dropped from the model. The volumetric data were centered by mean subtraction to avoid problems with multicollinearity. Behavioral data were rank-ordered to correct a positive skew. Change in R^2 was statistically significant for steps 1 and 3, with an effect size estimated at .29 and .10 using Cohen's f^2, which is considered moderate and small, respectively. Individual variables within step 1 that reached significance include SES and ratings of impulse control. In step 3 there was a significant interaction effect for sex X right ACC volume and sex X left ACC volume. As a result of the interaction effects, subsequent analyses were performed separately for boys and girls.

Correlation findings. Spearman partial correlation analyses of conduct ratings and ACC volume are illustrated in Table 3. Covariates included SES, total cortex volume, and impulse control. There was a statistically significant inverse (negative) correlation of conduct ratings and volume of the right ACC in boys ($r = -.42$, $p = .002$), whereas in girls there was a nonsignificant negative correlation with left ACC ($r = -.22$, $p = .12$).

Demonstration of specificity. The Spearman partial correlations of occipital lobe volume and conduct ratings were not significant in the right or left hemisphere for either sex. There were no significant correlations of the PBS physical health ratings with ACC volume. These results are displayed in Table 4.

Follow-up analyses of high and low conduct problem groups. Table 5 reports demographic, behavioral, and volumetric data for boys separated into upper and lower terciles according to their

Table 1
Descriptive Data: Demographic, Behavioral, and Structural

Variable	Measure	Boys ($n = 61$)	Girls ($n = 56$)	Sig. (p)
Age	Range	7.75–17.92	7.08–17.58	
	Mean (s.d.)	12.08 (2.71)	12.49 (2.87)	.42
IQ	Mean (s.d.)	112 (16)	108 (13)	.11
SES	Mean (s.d.)	2.29 (.57)	2.28 (.52)	.94
Handedness		53 RH, 7 LH, 1 A	50 RH, 6 LH	
Impulsivity Rating	Range	0–27	0–23	
	Mean (s.d.)	6.32 (5.39)	3.94 (4.76)	.01
Conduct Rating	Range	0–24	0–16	
	Mean (s.d.)	5.85 (5.28)	3.69 (3.36)	.01
Total Cortex Volume (cc)	Mean (s.d.)	504 (35)	468 (29)	.000
R ACC[*]	Mean (s.d.)	.78 (.11)	.81 (.14)	.23
L ACC[*]	Mean (s.d.)	.78 (.13)	.81 (.14)	.23
R vmPFC[*]	Mean (s.d.)	2.95 (.21)	2.96 (.29)	.74
L vmPFC[*]	Mean (s.d.)	3.03 (.24)	3.05 (.25)	.68

Note. Sig. = Significance, independent samples t-test.
ACC = anterior cingulate cortex, A = ambidextrious, L = left, LH = left handed, R = right, RH = right handed. SES = parent socioeconomic status, vmPFC = ventromedial prefrontal cortex, Vol = volume.
[*] Regional structural measures are expressed as a percentage of total cortex volume.

conduct rating (extreme group comparison). Quantitative demographic variables were compared among the two groups using independent *t* tests, which revealed nonsignificant differences for all demographic variables. Significant differences in ratings of conduct and impulse control ratings were noted (as expected based on the classification approach). The Table also shows results from an ANCOVA (controlling for SES, total cortical volume, and impulse control rating) used to test whether significant differences in the right ACC exist in comparing boys with High versus Low conduct score. Boys with higher scores had significantly less volume of the right ACC, $F = 14.21$, $p = .001$. The effect size was large, estimated at .289 using partial Eta squared.

The analyses were repeated after excluding the subject with prenatal alcohol exposure. The results were identical, and thus the subject's data were included.

Table 2
Predictors of Conduct Behavioral Ratings

Variable	β	Sig
Step 1[a]		
SES	.20	.01
Sex	.02	.78
Total Cortex Volume	.14	.15
Impulse Control	.42	<.0005
Step 2[b]		
R ACC	−.12	.16
L ACC	.02	.76
R vmPFC	.04	.72
L vmPFC	−.09	.47
Step 3[c]		
R ACC × Sex	.72	.01
L ACC × Sex	−.53	.04

[a] R^2 Change = .23, *F* Change = 8.15, Sig. = .000; [b] R^2 Change = .02, *F* Change = .66, Sig. = .61; [c] R^2 Change = .07, *F* Change = 5.40, Sig. = .006.

Discussion

Our findings provide preliminary support for the right ACC as a neuroanatomical correlate of aggressive and defiant behavior in boys. Overall, the significant results were as follows: 1) there was a significant interaction of sex and ACC volume bilaterally in a regression model predicting aggressive and defiant behavior, 2) Spearman's partial correlation revealed a significant negative correlation of aggression-defiance ratings and volume of the right ACC in boys ($r = -.42$), and 3) In comparing subjects with high versus low levels of aggression-defiance, boys with high levels had significantly less volume of the right ACC.

In girls, the left ACC correlated negatively with aggression-defiance, but the result was not statistically significant. We did not find a significant relationship between aggression-defiance and vmPFC volumes in either boys or girls.

The finding of a neuroanatomical correlate of aggression-defiance in the ACC presents the possibility that anatomical variation in this cortical region may reflect functional variations manifest as behavioral differences. This idea is supported by

Table 3
Correlation[†] of Conduct Ratings and Anterior Cingulate Cortex Volume

	Conduct Behavioral Measure	
ROI	Boys ($n = 61$)	Girls ($n = 56$)
L ACC	.15 (.28)	−.22 (.12)
R ACC	−.42 (.002)	.15 (.27)

Note. ACC = anterior cingulate cortex, L = left, ROI = region of interest, R = right.
[†] Spearman partial correlations control for impulse control rating, total cortex volume, and parent socioeconomic status (SES).

Table 4
Correlations† *Demonstrating Specificity*

ROI	Conduct		Physical Health	
	Boys	Girls	Boys	Girls
L Occipital Volume	.02 (.83)	−.06 (.67)	—	—
R Occipital Volume	−.03 (.80)	.06 (.63)	—	—
L ACC	—	—	−.08 (.57)	.24 (.09)
R ACC	—	—	.07 (.61)	−.03 (.78)

† Controlling for impulse control, socioeconomic status, and total cortex volume. $N = 61$ boys, 56 girls.

convergent methods demonstrating a role of the ACC in social behavior and aggression.

The ACC, social behavior, and aggression. Several methodologies have implicated the ACC as a critical neural substrate of social behavior (Devinsky et al., 1995). Boys with conduct disorder have decreased activity in the right caudal ACC when viewing stimuli with negative emotional salience relative to a comparison group (Sterzer et al., 2005; Stadler et al., 2007). Studies of impulsive aggression have shown abnormally high levels of ACC activity (Eisenberger, Way, Tayor, Welch, & Leiberman, 2006) and decreased serotonin transporter levels in the ACC (Frankle et al., 2005). Also, a known genetic risk factor for impulsive aggression is associated with decreased overall cingulate cortex volume (Meyer-Lindenberg et al., 2006).

Consensus regarding the functional contribution of the ACC to social behavior is lacking. In the field of developmental psychology there has been extensive work describing the temperamental correlates of antisocial behavior. Temperament may provide a phenotype that is more proximal to the structure and function of specific neural systems than behavioral conduct problems. With this in mind, we turn to a discussion of the possible role of the ACC in the two temperamental traits most commonly implicated in conduct problems and antisocial behavior: 1) negative emotionality and 2) low effortful regulation of behavior (Casey & Schlosser, 1994; Rothbart, Ahadi, & Hershey, 1994; Davidson et al., 2000; Melnick & Hinshaw, 2000; Blair et al., 2001a, 2001b; Izard, Fine, Mostow, Trentacosta, & Campbell, 2002; Eisenberg et al., 2005; Garnefski, Kraaij, & van Etten, 2005; Hill, Degnan, Calkins, & Keane., 2006).

ACC and negative emotionality. Increased levels of negative emotions, such as anger, are commonly associated with temper tantrums, aggressive outbursts, and more generally, antisocial behavior. This may stem from hyperresponsive triggering of negative emotions, an inability to modulate negative emotions, or an inability to implement socially appropriate behavior under the influence of negative emotion. The ACC is believed to have a prominent role in modulating arousal, which is a central feature of negative emotions. ACC activity correlates with overall cortical arousal (Paus, 2000) and peripheral arousal (e.g., cardiovascular tone, skin conductance; Critchley, 2005), which is blunted following ACC damage (Tranel & Damasio, 1994). The connectivity of the ACC and amygdala may provide a means by which emotional arousal is modulated (Ghashghaei, Hilgetag, & Barbas, 2007). A recent study has shown that activity of the caudal ACC closely precedes inhibition of the amygdala, and decreased volume of the ACC corresponds to increased amygdala activity (Pezawas et al., 2005).

In contrast to overactive negative emotions, a severely restricted emotional repertoire may also be a vulnerability factor for antisocial behavior. Externalizing/antisocial behavior has been associated with fearlessness and guiltlessness (Rothbart et al., 1994; Keltner, Moffitt, & Stouthamer-Loebner, 1995; Kochanska, Gross, Lin, & Nichols, 2002; Frick & Morris, 2004) as well as physiologic underarousal (Blair, Jones, Clark, & Smith, 1997; Blair, 1999; Raine, Lencz, Bihrle, LeCasse & Colletti, 2000; Lorber, 2004; Ortiz & Raine, 2004; Herpertz et al., 2005). These individuals may be insensitive to punishment and other social cues that guide pro-social behavior, and more prone to take risks or engage in sensation-seeking behavior. Hypo-emotionality may also be reflected in ACC morphometry, as decreased surface area of the right ACC was reported in association with fearlessness in a healthy sample of children (Pujol et al., 2002).

Low effortful control. Effortful control is typically conceptualized as the voluntary capacity to regulate behavior; a mechanism that may interact with the influence of more basic drives and emotions in goal directed behavior (Posner & Rothbart, 1998).

Table 5
Extreme Group Comparison (Boys)

	Measure	Low ($n = 20$)	High ($n = 20$)	Sig
Age	Range	9.00–17.92	7.92–16.92	
	Mean (*SD*)	12.65 (2.77)	11.80 (2.63)	.29
IQ	Mean (*SD*)	114 (14)	112 (17)	.50
SES	Mean (*SD*)	2.16 (.48)	2.38 (.73)	.28
Handedness		16 RH, 4 LH	18 RH, 2 LH	
Impulsivity Rating	Range	0–9	0−27	
	Mean (*SD*)	3.85 (2.08)	9.25 (6.06)	.01
Conduct Rating	Range	0−3	5−24	
	Mean (*SD*)	1.65 (1.18)	11.40 (5.64)	.000
Total Cortex Volume (cc)	Mean volume (*SD*)	502.76 (3.54)	515.17 (8.66)	.29
R ACC Volume (cc)	Adjusted Mean volume (*SE*)	4.37 (.12)	3.64 (.12)	$F = 14.21$ (.001)

Note. ACC = anterior cingulate cortex, cc = cubic centimeters, L = left, LH, left handed, R = right, RH = right handed.

Impairments in effortful control are associated with disruptive and antisocial behavior (Rothbart et al., 1994), particularly when coupled with increased negative emotionality (Eisenberg et al., 1996). Moreover, effortful control has a prominent role in the development of moral conduct (Kochanska & Aksan, 2006).

The ACC is believed to have a critical role in the development and implementation of effortful control (Rothbart et al., 2000). The ACC may facilitate bringing cognitive neural resources to bear on situations of conflict, supported by a positive correlative relationship of task performance requiring behavioral control and reciprocal activity of the caudal ACC-prefrontal cortex (Kerns et al., 2004). The ACC may also act as an interface between neural systems of emotion and cognition (Bush, Luu, & Posner, 2000), in line with ACC activity being linked to the conscious awareness of emotion (Lane et al., 1998). The volume of the ACC may also reflect its role in effortful control, as children with lower ACC volume demonstrate decreased attention when effortful control is needed (Casey et al., 1997).

The picture that emerges from this evidence is that the ACC may be involved in several processes that have known associations with antisocial behavior and aggression. In the current study we did not address emotion or effortful regulation explicitly. Future work must tease apart the neurobiology of each of these more proximal temperaments associated with antisocial behavior. This will be challenging, though. Despite the seemingly opposite ends of the emotion spectrum, the neural systems that mediate excessive negative emotionality and hypo-emotionality may lie in close proximity or overlap. Damage to the vmPFC, for instance, often leads to a paucity of emotion and lack of empathy with the exception of outbursts of negative emotion (Anderson et al., 2006; Koenigs & Tranel, 2007). Similarly, traits that are highly comorbid with antisocial behavior (e.g., impulsiveness) may rely on adjacent or overlapping neural systems and this will complicate the study of traits such as aggression in isolation. Moreover, the environment has an influence on these behaviors (evidenced here by SES being a significant predictor of aggressive and defiant behavior) and the degree to which environmental factors alter brain development is poorly understood.

Hemispheric asymmetry and sex differences. A second aim of the current study was to address whether sex differences exist in the relationship of aggression-defiance and structural measures, such that volume of ROIs would negatively correlate with conduct problems on the right side in boys and the left side in girls. The regression analysis did reveal a significant interaction of sex and ACC volume. Follow-up correlation tests fit the hypothesized pattern, with a negative correlation for the right ACC in boys and for the left ACC in girls. However, this structure-function relationship was not statistically significant for girls. The lack of significance may be attributable to much lower variance in conduct ratings in girls.

Neurobiology of normal behavior. It is important to emphasize that the participants in this study were children who were not demonstrating pathological conduct problems. There are some advantages to studying normal variance in behavior. It is possible to recruit large samples without comorbid substance abuse or medication use that may confound structure-function relationships in pathological groups. A limitation, though, is much lower behavioral variance relative to a between-groups comparison of subjects with pathological conduct problems versus a normal comparison group. Moreover, we cannot directly address whether the findings generalize to more severe antisocial problems. There is evidence that symptoms of antisocial behavior exist along a continuum with nonpathological symptoms, as a dimensional rather than categorical construct (Edens, Marcus, Lilienfeld, & Poythress, 2006). It is reasonable, then, to postulate that a similar continuum may exist in the neural correlates to these symptoms, though future work will be needed to address this issue empirically.

A limitation of the analysis is the absence of a formal assessment for substance use or psychopathology. A screening interview was performed to exclude any participants with reported psychopathology, so it is unlikely that the conclusions of the study were significantly influenced by this omission. We feel that even with such limitations, the data provide a convincing preliminary demonstration of a brain-behavior relationship.

The current study contributes to the ongoing effort to elucidate the biological underpinnings of antisocial behavior, which may complement alternate approaches such as functional neuroimaging and identifying the genes involved. Advances in this endeavor may ultimately inform the diagnostic approach and efforts at intervention for antisocial disorders. Ultimately, preventative efforts may target specific genetic, neural, and environmental risk factors.

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