Association of regional gray matter volumes in the brain with disruptive behavior disorders in male and female children

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1. Introduction

Because the disruptive behavior disorders are highly impairing conditions, it is important to determine if structural variations in brain are associated early in life with these problems among children. Structural MRI data were acquired from 111 9–11 year olds (58 girls and 53 boys), 43 who met diagnostic criteria for oppositional defiant disorder and/or conduct disorder and 68 healthy controls. Voxel-based morphometry was used to examine associations of behavioral measures with gray matter volumes in whole-brain analyses. Unlike previous studies, variation in gray matter volume was not found to be associated with a disruptive behavior disorder diagnosis in any brain region at p < .05 with FWE correction. Nonetheless, an inverse nonlinear association of the number of conduct disorder (CD) symptoms with gray matter volume along the left superior temporal sulcus was significant in the full sample (p < .05 with FWE correction), with a trend in the right hemisphere (p < 0.001 uncorrected). There also was a trend toward a stronger association of the number of CD symptoms with gray matter volume along the left superior temporal sulcus in girls than boys. The present findings did not replicate previous findings of reduced gray matter volumes in the anterior insula, amygdala, and frontal cortex in youth with CD, but are consistent with previous findings of reduced gray matter volumes in temporal regions, particularly in girls.

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empathic concern for others are common in youth with CD (Frick and White, 2008; Lahey et al., 1999). Four studies have reported smaller insula volume in adolescents with disruptive behavior disorders than in healthy controls (Fairchild et al., 2011b; Huebner et al., 2008; Sterzer et al., 2007a), but one study of preadolescent boys with both conduct problems and psychopathic-like traits did not find differences in the anterior insula compared to healthy controls (De Brito et al., 2009).

The medial OFC plays a role in emotion regulation and reward and punishment processing (O’Doherty et al., 2001). Several studies have linked deficits in these processes to disruptive behavior disorders in adolescents (Fairchild et al., 2013a; Huebner et al., 2008) and antisocial personality disorder (Raine et al., 2011) and psychopathy in adults (de Oliveira-Souza et al., 2008; Decety et al., 2013; Decety et al., 2013; Yang et al., 2010).

In addition, studies of children and adolescents with disruptive behavior disorders found evidence of reduced gray matter volume (GMV) in temporal regions (Huebner et al., 2008; Kruesi et al., 2004), although a third study found larger volumes in a community sample of boys with CD problems (De Brito et al., 2009). Similar findings of smaller temporal lobe volumes have been reported in both incarcerated adults with personality disorders (Dolan et al., 2002) and incarcerated adult psychopaths (Barkataki et al., 2006). One functional magnetic resonance imaging (fMRI) study observed less activation in the temporal cortex in violent adult offenders compared to non-aggressive offenders (Raine et al., 2001) and another documented activation deficits in antisocial and psychopathic individuals in the right posterior superior temporal gyrus during a semantic processing task (Kiehl et al., 2004).

Because ODD and CD are considerably less prevalent in females during childhood (Lahey et al., 2000; Loeber et al., 2000; Maughan et al., 2004), it is important to test for differences in the neural correlates of the disruptive behavior disorders in females and males. To date, however, only one structural MRI study of adolescents and young adults with CD has included both males and females (Fairchild et al., 2011b; Fairchild et al., 2013b) and no studies have included preadolescent girls with disruptive behavior disorders.

Therefore, we test the general hypothesis based on previous studies that individual differences in regional GMV will be found to be associated with the disruptive behavior disorders in a sample of 9–11 year old girls and boys. It is important to note that our study tests these associations at younger ages than in most previous studies, which means that we are not conducting strict attempts to replicate.

2. Methods

2.1. Participants and measures.

A stratified sample of boys and girls and their caretakers was selected based on the child’s sex, race-ethnicity, and risk for high numbers of CD symptoms. A cost-efficient extreme group sampling strategy was used (Preacher et al., 2005). Based on a screening interview, children were recruited into either a “high-risk” stratum of children likely to meet DSM-IV diagnostic criteria for ODD and/or CD and “low-risk” stratum of children who are unlikely to meet criteria for these diagnoses. Recruitment of children into the high-risk stratum was done with flyers calling for children with behavior problems posted in child mental health clinics and private practices. Children in the low-risk stratum were recruited from pediatric well-visit waiting rooms using a flyer calling for well-behaved children. Parents and children who consented to be screened were sequentially administered the DISC Predictive Scale (DPS) for CD, which predicts the full diagnosis of CD with high sensitivity and specificity (Lucas et al., 2001). The DPS consists of 8 “stem questions” from the reliable and valid Diagnostic Interview Schedule for Children (DISC-IV) CD module (Shaffer et al., 2000). Eight DPS questions refer to symptoms of CD and one to school expulsion. Children were selected for the high-CD stratum if the parent alone endorsed 2 or more DPS items, the child alone endorsed 3 or more items, or the parent and child collectively endorsed 3 or more items. Because ODD and CD are very highly correlated during childhood (Lahey et al., 2008), participants were screened only on CD.

Children were selected for the low-risk stratum if neither informant endorsed any DPS CD items. To spread the distribution, children with intermediate scores of 1 on the DPS were not included in the study. Selection continued until equal numbers of high- and low-risk children of each sex and race-ethnicity agreed to participate. Exclusion criteria included the presence of a pervasive developmental disorder, history of head trauma with loss of consciousness exceeding 15 min, and safety contraindications for neuroimaging. Participants who assented and whose parents gave written maternal consent were enrolled in the study, which was approved by the University of Chicago Institutional Review Board.

On the day of scanning, the full DISC-IV (Shaffer et al., 2000) was administered in separate rooms to the primary caregiver and to the child by trained interviewers querying symptoms during the last 12 months. A total of 169 children were screened for participation and 126 attended the MRI session and gave written informed parental consent and child assent. Three of these children aborted the scan prior to completion and were excluded. After scanning, an additional 2 children were excluded due to abnormal structural scans and 12 children were excluded due to excessive movement or failure in the segmentation step of the processing.

Demographic and behavioral characteristics of the 111 children included in the present analyses are shown in Table 1. Among the scanned children, 43 met criteria for a disruptive behavior disorder (i.e., they met DSM-IV criteria for ODD and/or CD) in the full DISC-IV interviews. Of that number, 21 met criteria for CD. The remaining 68 scanned children did not meet diagnostic criteria for either ODD or CD. There were no significant differences between the three groups on sex, race-ethnicity, or maternal education. As shown in Table 1, consistent with the high levels of correlations among dimensions of psychopathology in children in the population (Lahey et al., 2008), there were differences in the numbers of all dimensions of symptoms.

2.2. Neuroimaging procedures

2.2.1. Data acquisition

Structural MRI was acquired using a Philips Achieva 3T MRI scanner with a Quasar dual gradient system and a 16-channel head coil at the University of Chicago Medical Center. Images were acquired using a gradient echo, 3D T1-weighted pulse sequence (voxel size = 1 × 1 × 1 mm, TR/TE = 8.1/3.7 ms, matrix size = 224 × 224 × 169, inversion time = 940 ms, and flip angle = 8°).

2.2.2. Image processing

Images were first inspected by a neurologist (TZ) for structural abnormalities, as well as for image artifacts and excessive motion or failure of tissue segmentation. Voxel-based morphometry (VBM) analysis was performed on the final sample of 111 children using SPMB (Wellcome Trust Department of Imaging Neuroscience, London). VBM is a voxel-wise method for comparing regional GM concentrations (Ashburner and Friston, 2000, 2001). Preprocessing of the T1-weighted images was done using the VBM8 anatomy toolbox (http://dbm.neuro.uni-jena.de). All T1-weighted images were corrected for intensity inhomogeneity, then spatially normalized into MNI space and segmented into GM, WM, and cerebrospinal fluid (CSF) probability maps using the same generative model (Ashburner and Friston, 2005). The spatially normalized GM probability maps were then modulated by the amount of non-linear deformation, resulting in regional GMV maps. Quality assurance review of the GM tissue probability maps was done using the VBM8 tools. Total brain volume was estimated with the Easy Volume toolbox (Pernet et al., 2009).
2.3. Analyses

Following preprocessing, statistical analyses were performed in SPM8 using general linear models. In the primary analyses, whole-brain analyses were conducted to test for differences in peak-level regional GMVs between (a) children who did and did not meet criteria for a disruptive behavior disorder diagnosis (ODD and/or CD), and (b) children who met criteria for CD compared to children who met criteria for neither ODD nor CD. Owing to the considerable range of CD symptoms within the group of children with a disruptive behavior disorder, follow-up analyses tested linear and quadratic terms for the number of CD symptoms in the scanned sample. In all models, total brain volume, age, child’s sex, two dummy variables for race-ethnicity (African American and Hispanic versus non-Hispanic white), and maternal education were included as covariates of no interest. Maternal education was included because it is robustly associated with the child’s tested intelligence (Bornstein et al., 2013; Edwards and Roff, 2010; Ghassabian et al., 2014). In follow-up analyses, the number of ADHD symptoms also was included as a covariate of no interest to control this common correlate of CD. The critical threshold for whole-brain analyses was set at \( p < 0.05 \), using family-wise error (FWE) correction for multiple testing (Nichols and Hayasaka, 2003).

3. Results

3.1. Demographic and behavioral characteristics

Demographic and behavioral characteristics of the sample described are in Table 1.

3.2. Group comparisons and tests based on CD symptom counts

3.2.1. Group comparisons

In whole-brain analyses, there were no significant regional differences in GMV between the children with and without a disruptive behavior disorder diagnosis. Similarly, there were no significant regional differences in GMV between the 21 children who met criteria for CD and the 68 children who met criteria for neither ODD nor CD. The group-by-sex interaction was not significant in any region at \( p < 0.05 \), with FWE correction in either comparison.

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**Table 1**

Demographic characteristics of the 111 scanned children included in the analyses.

| Groups       | N  | Girls (%) | Child’s age (M, SD) | Afr-Am (%) | Hispanic (%) | Number of symptoms (M, SD) | HS (%) | ODD* | CD* | ADHD* | GAD* | MDD* |
|--------------|----|-----------|---------------------|------------|--------------|----------------------------|--------|------|-----|-------|------|------|
| Not DBD      | 68 | 48.5      | 10.0 (0.8)          | 57.4       | 4.4          | 82.4                       | 0.5 (1.0) | 0.4 (0.7) | 2.7 (3.9) | 2.6 (1.9) | 0.3 (1.1) |
| ODD-only     | 22 | 50.0      | 10.1 (0.8)          | 50.0       | 13.6         | 77.3                       | 5.5 (1.3) | 1.0 (0.9) | 10.5 (5.2) | 3.9 (2.0) | 0.8 (1.6) |
| CD           | 21 | 42.9      | 10.1 (0.9)          | 52.4       | 14.3         | 90.5                       | 6.1 (1.9) | 4.6 (1.5) | 13.3 (4.9) | 6.0 (2.6) | 2.8 (3.1) |

Note: DBD = disruptive behavior disorder; ODD = oppositional defiant disorder; CD = conduct disorder; Afr-Am = African American; HS = mother completed high school; ADHD = attention-deficit/hyperactivity disorder; GAD = generalized anxiety disorder; MDD = major depressive disorder.

* 2 df test \( p < .05 \); CD > ODD > controls.

**Fig. 1.** Panels A and B show regions in and around the superior temporal sulcus (A = right hemisphere; B = left hemisphere) in which there was an inverse quadratic association between the number of conduct disorder (CD) symptoms and gray matter volumes in the full sample of boys and girls (left side \( p < .05 \), FWE-corrected; right side \( p < .0001 \) uncorrected). Panels C and D show regions in and around the superior temporal sulcus (C = right hemisphere; D = left hemisphere) in which there was a bilateral inverse quadratic association between the number of CD symptoms and gray matter volumes in girls only (both sides \( p < .05 \), FWE-corrected). Panels E and F show no areas of significant association in boys only (E = right hemisphere; F = left hemisphere). Coordinates and statistics for these associations are provided in the Results section. Panel G is a scatter plot illustrating the nonlinear association between the square of the number of CD symptoms in girls and gray matter volume in and around the superior temporal sulcus.
3.2.2. Associations with CD symptoms

Whole-brain tests of the linear term for the association of regional GMVs with the number of CD symptoms were not significant at $p < .05$, with FWE correction. As illustrated in Fig. 1, however, the quadratic term for the association of the number of CD symptoms with GMV along the left superior temporal sulcus (STS; $-63, -14, -9$) was significant, $F(2, 104) = 13.23, p = 0.05, k = 5$, with FWE correction in whole-brain analyses, with a trend in the right STS ($55, -45, 9$), $F(2, 104) = 10.91, p < .001$ uncorrected, $k = 1515$. Furthermore, trends toward interactions of the child’s sex with CD symptoms were observed bilaterally: left hemisphere, $f(1, 104) = 12.65, p < 0.001, k = 930$, uncorrected; right hemisphere, $F(1, 104) = 11.85, p < 0.001$, uncorrected, $k = 2197$. Because such interactions with sex are theoretically important, post hoc tests were conducted in an exploratory spirit. These revealed robust significant inverse quadratic associations for CD symptoms with regions in and around the STS (left hemisphere: $t = 4.95, p < 0.001$, FWE-corrected; right hemisphere: $t = 4.67, p < 0.001$, FWE-corrected) in females, but no significant associations or trends at even $p < .001$ uncorrected in males.

3.3.3. Association of CD symptoms when controlling ADHD symptoms

We repeated the analyses of associations between GMV and CD symptoms including the number of 12-month ADHD symptoms as a covariate of no interest. The results were qualitatively the same as without this covariate: The quadratic term for the association of the number of CD symptoms with GMV along the left STS ($-63, -12, -9$) remained significant, $F(2, 103) = 13.61, p = 0.05, k = 5$, with FWE whole-brain correction, as did the trend in the right STS ($56, -45, 9$), $F(2,103) = 10.74, p < .001$ uncorrected, $k = 1453$. The association with the linear term for CD remained non-significant.

4. Discussion

Unlike previous studies, we did not find significant regional differences in GMV between children with and without a disruptive behavior disorder diagnosis and in the comparison of groups who met criteria for CD versus children who met criteria for neither ODD nor CD. Although there are many reasons why differences between groups that are present in the population might be detected in one study and not in another, the failure to confirm previous findings at least indicates that there is still much to learn about variations in regional GMV and disruptive behavior disorder in children.

It is interesting that we found a nonlinear association in whole-brain analyses between the number of CD symptoms and GMV in and around the left STS ($p < .05$, FWE-corrected), with a trend toward an inverse quadratic association in the right STS. As illustrated in Fig. 1, the observed quadratic association with the left STS indicates that the decline in GMV is progressively steeper at higher numbers of CD symptoms. That is, it may be that smaller GMV in the left STS region is primarily found among children with particularly high numbers of CD symptoms.

It is quite plausible that variations in STS gray matter could be associated with CD symptoms in children. The STS is a component of the extended network that processes emotional information (Pessoa, 2008) and is part of the human ventral attention system that detects salient and biologically important stimuli in the environment (Corbetta et al., 2008). Of potential importance to CD, the STS is involved in the perception of faces and voices (Ethofer et al., 2013) and the interpretation of the goals and intentions of others (Vander Wyk et al., 2012). Furthermore, functional imaging studies of mentalizing and the attribution of intentionality have revealed involvement of the posterior temporal-parietal junction (TPJ)/STS region (Decety and Lamm, 2007; Pellegrino and Carter, 2008). Because the STS receives information from both dorsal and ventral visual streams, it serves as an attentional hub as well as playing a pivotal role in interpreting the mental states of others (Blakemore and Decety, 2001; Decety and Cacioppo, 2012; Decety et al., 2012). This combination of recognizing the actions and intentions of other people and categorizing them as threatening and making appropriate responses are relevant to antisocial behavior. Variation in STS activation during facial emotion processing has been associated with antisocial behavior (Marsh et al., 2008; Passamonti et al., 2010). Furthermore, the STS/TPJ has been implicated in generating P3 electrophysiological responses that promote attention and information processing and a large literature suggests that antisocial adolescents and adults exhibit deficits in P3 responding (Gao and Raine, 2009; Gao et al., 2013).

In previous studies, the direction of the association of temporal lobe gray matter with antisocial behavior in children has been reported to be both positive (De Brito et al., 2009) and negative (Huebner et al., 2008; Krueusi et al., 2004). There are more consistent findings of reduced temporal lobe gray matter in antisocial male adults, but it is not clear that if reduced volume is (Barkataki et al., 2006) or is not associated with psychopathy (Dolan et al., 2002).

4.1. Sex differences

The present findings are interesting in raising the possibility of sex differences in the association of STS GMV and CD symptoms. It should be emphasized that the sex-by-CD symptom interaction was not significant after FWE correction, but we tentatively discuss this issue because the post hoc tests revealed robust inverse nonlinear associations between the number of CD symptoms and STS gray matter bilaterally in girls ($p < 0.001$, FWE-corrected) that were not evident in boys. If this sex-by-CD symptom interaction is replicated in future studies, it may help understand the large sex differences in the prevalence and possibly the etiology of CD behavior (Moffitt et al., 2001; Van Hulle et al., 2007). Taylor and Ounsted (1972) and Eme (1992) refer to a “gender paradox” in many disorders with such unequal sex ratios: The gender with the lower prevalence also tends to be more seriously affected. The present findings raise the important possibility that more pronounced structural abnormalities in the STS may be needed to overcome other factors that protect girls from developing CD symptoms during childhood. If boys are less protected from social influences to engage in childhood antisocial behavior, they may be more likely than girls to develop CD symptoms in the absence of reduced GMV in the STS.

A related possibility is that a sex difference in the development of temporal lobe structures from childhood through adolescence and into adulthood (Hu et al., 2013; McClure et al., 2004) could result in temporal lobe structures being related to antisocial behavior in different ways at different ages in female and male children. For example, it is possible that the reductions of GMVs that have been documented in previous studies of antisocial male adolescents and adults only emerge after childhood. If the sex-by-CD symptom interaction is substantiated in future studies, longitudinal imaging studies beginning in childhood will be needed to determine if this sexual dimorphism is observed across age within the same sample and accounts for some of the sex differences in adolescent antisocial behavior. Such findings would not necessarily rule out other explanations, of course, such as sex differences in socialization (Keenan and Shaw, 1997).

4.2. Limitations

Although maternal education is robustly predictive of her child’s intelligence (Bornstein et al., 2013; Edwards and Roff, 2010; Ghassabian et al., 2014), our findings may have differed had child intelligence been directly measured in the present study (Wallace et al., 2014). In addition, our focus on gray matter volume is an important limitation of the present study. Gray matter volume is a function of both cortical surface area and thickness and there is emerging evidence that cortical surface area and thickness have different influences and correlates (Winkler et al., 2010). For example, one study failed to find differences
in GMV between children with a disruptive behavior disorder diagnosis and healthy controls, but found reduced cortical thickness in the disruptive behavior disorder group (Fahim et al., 2011). Similarly, two studies found reduced cortical thickness, but not surface area, in the superior temporal cortex in youth with CD (Hyatt et al., 2012; Wallace et al., 2014). Thus, the present study may have been more revealing had these components of GMV been distinguished.

5. Conclusions
The present findings were consistent with previous findings of an association between high levels of CD symptoms and reduced gray matter volumes in temporal regions, although this association may have been stronger in girls. The present findings did not support previous findings of reduced gray matter volumes in the anterior insula, amygdala, and frontal cortex in mostly older children and adolescents who met diagnostic criteria for ODD and/or CD relative to healthy comparison children.

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