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Neuroanatomy of Childhood Disruptive Behavior Disorders

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Our aims were to (1) examine possible neuroanatomical abnormalities associated with the Disruptive Behavior Disorders (DBDs) as a group and (2) assess neuroanatomical anomalies specific to each DBD (i.e., conduct disorder [CD] and oppositional defiant disorder). Cortical thickness analysis and voxel-based morphometry were analyzed in 47 8-year-old boys (22 DBDs with and without CD and/or ODD and 25 healthy controls) from Magnetic Resonance Imaging brain scans. DBD symptoms were assessed using the Dominic-R. In DBD subjects relative to controls, we found (1) a decreased overall mean cortical thickness; (2) thinning of the cingulate, prefrontal and insular cortices; and (3) decreased gray matter density (GMd) in the same brain regions. We also found that scores on the Dominic-R were negatively correlated with GMd in the prefrontal and precuneus/superior temporal regions. There was a subdiagnostic main effect for CD, related to thinning of the middle/medial frontal, and for ODD in the left rectal/orbitofrontal. Findings suggest that thinning and decreased GMd of the insula disorganizes prefrontal circuits, diminishing the inhibitory influence of the prefrontal cortex on anger, aggression, cruelty, and impulsivity, and increasing a person's likelihood of aggressive behavior. These findings have implications for pathophysiologic models of the DBDs, their diagnostic classification system, and for designing more effective intervention programs. Aggr. Behav. 37:326–337, 2011. © 2011 Wiley-Liss, Inc.

Keywords: disruptive behavior disorder; oppositional defiance disorder; conduct disorder; cortical thickness; voxel-based morphometry

INTRODUCTION

The psychiatric disorders of childhood and adolescence defining the general class of DSM-IV [APA, 1994] disruptive behavior disorders (DBDs) are as follows: (1) conduct disorder (CD), which comprises aggressive/cruel behaviors that result in or threaten physical harm to other people or animals, property loss or damage, deceitfulness or theft, and frequent lying and (2) oppositional defiant disorder (ODD), which is typified by anger, a pattern of negativistic and defiant behavior, i.e., increased levels of noncompliance with authority, tendency to disrupt others, and general irritability.

Behavioral and Genetic Studies in Disruptive Behavior Disorders

Although a heterogeneous group, the DBDs share common symptoms; for example, callous–unemotional traits (i.e., lack of empathy, remorselessness, and shallow affects in ODD and CD) [Barry et al., 2000] aggression [Turgay, 2004], and lack of self-regulation [Berger et al., 2007]. Of particular note, clinically in some cases, DBDs are characterized less by impulsivity and more by oppositionality or rule-breaking. Rather than a lack of thinking/planning/attribution, many individuals with ODD/CD have distorted thinking or attributions that lead to mistaken assumptions of hostile intent from others or threat from the

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environment. Children and adolescents affected with one or more DBDs are at risk for a several comorbid disorders, i.e., anxiety, depression, substance abuse, somatoform disorder, antisocial personality disorders, psychopathy, and ADHD [Loeber et al., 2000]. The externalization of these conditions toward parents, siblings, teachers, peers, and eventually strangers conspire to make DBDs one of the most serious public health problems in today's societies. Along these lines, disregard for rules, which is a key component of ODD and CD, was recently investigated in a genetic/envrironment study [Petitclerc et al., 2011]. The authors investigated the relative importance of genetic and environmental factors underlying this early developmental stability. They concluded that developmental stability in early symptoms of disregard for rules is best explained by the stable action of genetic factors, suggesting that preventive interventions should take an intergenerational approach, targeting at-risk families as early as possible.

Neuroimaging Studies in Disruptive Behavior Disorders

The major factor hindering the treatment of children/adolescents with DBDs is a lack of known neurobiological etiology. Therefore, a neurobiological investigation is important for improving our understanding of the anatomical underpinnings of the anger, negative, hostile and disobedient behavior (ODD), and aggression/cruelty (CD) complexes. In this context, the paucity of studies investigating these disorders, other than ADHD, is alarming. Of the few structural neuroimaging studies, Li et al. [2005] investigated white matter (WM) abnormalities using diffusion tensor imaging (DTI) in adolescents with DBDs (including ADHD, ODD, and CD). The authors found significantly reduced fractional anisotropy within the arcuate fasciculus, which has projections extending from the temporal lobe to the frontal lobe. They concluded that a lower extent of myelination and less coherent fiber track structures were present in the fasciculus, which in turn may indicate communication weakness among the associated cortical areas. Another article by Sterzer et al., using structural imaging [Sterzer et al., 2007] showed, using optimized voxel-based morphometry (VBM), decreased grey matter volumes in bilateral anterior insular cortex and the left amygdala in CD. Huebner et al. [2008] reported that CD symptoms correlated primarily with GM reductions in limbic brain structures. The authors suggested that boys with CD and comorbid ADHD show brain abnormalities in frontolimbic areas that resemble structural brain deficits, which are typically observed in adults with antisocial behavior. Another interesting study used VBM to investigate whole brain gray matter volumes in boys with elevated levels of callous–unemotional conduct problems. Boys with callous–unemotional conduct problems, as compared with typically developing boys, presented increased gray matter concentration in the medial orbitofrontal (OFC) and anterior cingulate cortices, as well as increased gray matter volume and concentration in the temporal lobes bilaterally. The authors concluded that these findings may indicate a delay in cortical maturation in several brain areas implicated in decision making, morality, and empathy in boys with callous–unemotional conduct problems [De Brito et al., 2009]. Functional neuroimaging findings reported abnormal function of the anterior cingulate cortex (ACC) in patients with CD [Sterzer et al., 2005]. In another study, Herpertz et al. [2008] found enhanced left-sided amygdala activation in response to negative pictures, as compared with neutral pictures in CD boys. In addition, subjects exhibited no reduced activation in the OFC, anterior cingulate, and insular cortices. Conversely, reduced amygdala response to fearful expressions has also been reported [Jones et al., 2009; Passamonti et al., 2010].

This Study

In an attempt to add further evidence of structural brain changes in DBDs, we addressed the question whether the DBDs as a group (CD and ODD) are associated with neuroanatomical abnormalities. Then, we assessed the association between gray matter density (GMd) and symptoms profile. Finally, we investigated potential neuroanatomical abnormalities specific to each of the DBDs. À priori we predicted (1) thinning and decreased GM of the prefrontal cortex (PFC) in the DBDs in general, in accordance with the DBDs symptoms; (2) that each of the disorders would show specific regional thinning and decreased GMd correlating with its symptoms profile. Our à priori predictions were based on the relationship between DBDs clinical symptoms profile and prefrontal regional brain functions. Specifically, we anticipated decreased cortical thickness and GMd in the brain regions implicated in DBDs clinical symptomatology, i.e., prefrontal cortrex and the limbic system. To that end, we used structural magnetic resonance imaging (MRI) in conjunction with cerebral cortical thickness and VBM analysis to examine GM in 8-year-old

children. On one hand, the 3D-cerebral cortical thickness *t*-maps, i.e., the distance from the outer cortical surface to the inner cortical WM-GM boundary can reveal where in the brain differences are located and how significant they are [Lerch and Evans, 2005]. On the other hand, VBM is a voxel-wise comparison of the local concentration of GM between two groups of subjects on a voxel-by-voxel basis [Ashburner and Friston, 2000]. In essence, the aims were to (1) examine possible neuroanatomical abnormalities associated with the DBDs as a group and (2) assess neuroanatomical anomalies specific to each DBD (i.e., CD and ODD).

MATERIALS AND METHODS

Quebec Newborn Twin Study

The present sample was withdrawn from the Quebec Newborn Twin Study (QNTS) longitudinal study on developmental psychopathology [Forget-Dubois et al., 2007], where subjects were selected using the Québec Ministry of Health and Social Services registry of new births occurring in the Province of Quebec, between April 1, 1995 and December 31, 1998. Subjects were followed from birth at the Sainte-Justine hospital. Extensive psychophysiological, hormonal, and observational measures were taken in the laboratory from the participating twins and their mothers focusing on temperament, cognitive, physiological, and behavioral precursors of mental disorders. These assessments were followed within 2 weeks by a home visit to obtain social, demographic, health, and further behavioral data on the twins and their families. The home assessments were accomplished through three methods: interview of both parents, self-reported questionnaires filled out by both parents, and direct observation of the infant, home, and neighborhood by the interviewer. Interviews were done in French or English, according to the language of the respondent. The QNTS sample was followed from birth till the participants were scanned at 8 years of age. DBD symptomatology was first assessed in the QNTS at 19 months [Dionne et al., 2003], 3.5 years [Tremblay et al., 2004], 6 years [Brendgen et al., 2005; van Lier et al., 2007], and 8 years. Five-month-old twins were evaluated at home and in the laboratory. The total sample was $N = 672$ pairs. Zygosity was established for 667 twin pairs (254 monozygotic [MZ: 120 boys; 134 girls] and 413 dizygotic [DZ: 204 boys; 209 girls] pairs). This sample was then followed longitudinally at 18, 30, and 48 months using the similar protocol [Brendgen et al., 2005; Dionne et al., 2003; Tremblay et al., 2004]. A fifth wave was started in June 2001 as the twins reached 60 months and continued at 72 and 84, focusing on DBDs and school-readiness variables, such as verbal and nonverbal IQ, reading ability, numeracy, executive functioning, and peer interactions during kindergarten in the complete sample. One other wave (100 months) is currently underway, bearing on the same variables. Recent funding was obtained—Canadian Institute of Health Research New Emerging Team grant to collect functional, anatomical MRI, and DTI data at 100 months (8.33 years) in relation to mental disorders. During this wave, we scanned 223 twins using MRI.

Participants

All 223 twins were scanned using the same scanner at 8 years old. Brain images and behavioral data were collected between April 2004 and August 2006. Only fraternal twins were included, no cotwin was included in the study. Eighty-four percent of the families were of European descent, 3% African descent, 2% Asian descent, and 2% Native North Americans. The remaining families (9%) did not provide ethnicity information. The average yearly household income (CAN$54,000) in the twin sample was slightly above the national average for couples with children. However, a comparison of family characteristics of this sample at 5 months of age with an epidemiological sample of singletons from the Montreal area indicated that the samples were very similar regarding parental education, yearly income, age of parents at the birth of the children, and marital status. Written informed consent was obtained from the parents, and the study protocol was approved by the ethics review board of Sainte-Justine Hospital, Montreal, Canada (Table I).

Psychiatric Assessment

Of the 223 twins, 22 met the diagnosis of DBDs as assessed by the Dominic-R Interactive [Valla et al., 2000], which is a computerized, self-answered, DSM-IV-based [APA, 1994] cartoon specially designed to assess mental health in children 6–11 years of age. The Dominic was further used to divide the subjects into DBDs children [CD $n = 11$ and ODD $n = 11$] and into normal controls group [NC, $n = 25$]. The first consecutive 25 subjects to score 1 point or less on the same scales were selected to be the normal controls. Instead of being organized in diagnostic modules, the pictures have been randomly mixed with strengths and competencies situations intermixed with

TABLE I. Characteristics of Subjects

Characteristics: Mean (Std)	Disruptive behavior disorder ($N = 22$)	Controls ($N = 25$)
Age in years	8.39 (0.10)	8.36 (0.07)
Gestational age	36.47 (2.25)	37.04 (1.57)
Birth weight	2.54 (0.43)	2.43 (0.51)
Gender	22 (12G; 10B)	25 (12G; 13B)
Block design score (WPPSI)	13.00 (4.85)	14.68 (4.50)
Vocabulary score (WPPSI)	20.28 (7.07)	20.66 (5.95)
Conduct disorder score	7.83 (3.06)	0.25 (0.49)**
Oppositional defiant disorder score	7.11 (0.33)	0.70 (0.88)**

G, girls; B, boys.
**Significant at $P = .001$.

DSM-IV abnormal behaviors. The Dominic has been through an extensive development and validation process since it was designed in the early 1980s, and has been used with children from various ethnic groups in clinical and research settings in Québec [Valla et al., 1994, 2000] and elsewhere [Murphy et al., 2000; Rousseau et al., 2005]. A validation study based on clinical judgment yielded values ranging from .64 to .88 between Dominic-based diagnoses and DSM-III-R diagnoses based on each judge's clinical judgment. Best values between diagnoses generated by the instrument and those of clinicians were achieved for ODD (.82, .79, .82) [Valla et al., 2000]. The cutoff points for the DBDs were as follows: CD: above 6 (minimum 3, maximum 14) and ODD: above 7 (minimum 5, maximum 9) on the corresponding disorder scale. These cutoff points are the minimum scores for a subject to receive a clinical diagnosis. Both DBD and NC subjects scored below the clinical cut-off score on all other psychiatric disorders assessed with the Dominic-R (separation anxiety, generalized anxiety, specific phobias, and depression). All subjects were right handed, medication free, unrelated, and had no history of epilepsy, febrile seizures, or other neurological condition. Subject characteristics are outlined in Table I.

Cognitive Assessment

Children's cognitive development was assessed using the block design subscale of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) [Wechsler, 1989]. The WPPSI-R is an individually administered clinical instrument for assessing the cognitive skills of young children. The WPPSI-R block design that we used measures nonverbal intelligence, which is highly correlated to verbal IQ. The block Design subtest was the best predictor of school achievement in grades one and two [Novak et al., 1991]. One of the features of the Dominic-R is that it does not rely on the vocabulary on the participants because it is based on visual cartoons. However, we also analyzed a verbal component "the vocabulary subtest," which was administered to the subjects at 84 months (Table I).

Imaging Protocol and Data Analysis

Images were acquired using a 1.5 Tesla system (Magnetom Vision, Siemens Electric, Erlangen, Germany). A T1 mprage sequence was acquired (scan time 8 min, 6 sec; pixel size 0.98×0.98 mm). TR=9.7 msec; TE=4 msec; TI=300 msec; TD=0 msec using a 12° flip angle. Number of slabs = 1 fixed; slab thickness = 160 mm; slice thickness = 0.98 mm; number of partitions = 164; 3D-OS = 0%; matrix size 266×256.

Magnetic Resonance Imaging Analysis

All MRIs were submitted to the fully automated CIVET pipeline for morphological image analyses (version 1.1.7, http://wiki.bic.mni.mcgill.ca/index.php/CIVET; [Evans, 2006; Giedd et al., 2007; Lerch and Evans, 2005; Shaw et al., 2006, 2007a,b; Zijdenbos et al., 2002]).

Cortical Thickness Generation

T_1 images were registered to the (International Consortium in Brain Imaging) ICBM152 nonlinear sixth generation template with a 12-parameter linear transformation, RF inhomogeneity corrected, and tissue classified. Deformable models were then used to create white and GM surfaces for each hemisphere separately, resulting in four surfaces of 41,962 vertices each. From these surfaces, the *t*-laplace metric was derived by using the Laplacian method for determining the distance between the white and gray surfaces. The thickness data were subsequently blurred using a 25 mm surface-based diffusion-blurring kernel in preparation for statistical analyses. Unnormalized, native space thickness values were used in all analyses, owing to the poor correlation between cortical thickness and brain volume [Ad-Dab'bagh et al., 2005; Sowell et al., 2007]. Normalizing global brain size when it has little pertinence to cortical thickness risks introducing noise and reducing power.

Voxel-Based Morphometry

T_1 images were linearly registered to the ICBM152 nonlinear sixth generation template with

a 12-parameter linear transformation, RF inhomogeneity corrected, and tissue classified. Each of the GM and WM tissue classes was then averaged across subjects to create study-specific GM and WM templates that served as targets for a subsequent nonlinear registration, with a 16-mm node spacing between vectors in the deformation grid. This degree of nonlinear normalization further reduces global variance without distorting local features of anatomy. Resulting GM images were convolved with a three-dimensional Gaussian blurring kernel with a 10-mm full-width half-maximum.

Analyses

A series of whole brain analyses were performed according to the general linear model: (1) cortical thickness and VBM contrasts of DBDs and NC; (2) cortical thickness contrast of the subdiagnostic categories of the DBDs (ODD and CD) of the 22 DBDs subjects; (3) a regression analysis of the DBDs symptomatology scores of the Dominic-R onto VBM images of the 22 DBDs subjects. All statistical thresholds were determined by application of the false discovery rate technique [Genovese et al., 2002].

RESULTS

The two groups did not differ with respect to birth weight, gestational age, age at MRI scanning, sex, educational level, or IQ.

Cerebral Cortical Thickness

(a) Significant decreased overall mean cortical thickness was found in the DBD subjects compared with controls.
(b) A significant main effect of elevated DBDs symptomatology was found, with DBD subjects having thinner cortex in the left cingulate, ACC, medial prefrontal (MdPFC), rectal/OFC, uncus, parietal (precuneus), insula and the right middle frontal, superior temporal, posterior cingulate relative to controls (Table II) (Fig. 1).
(c) A subdiagnostic main effect was found, which survived adjustment for multiple comparisons [Mean $\pm$ SD Group 1; Mean $\pm$ SD Group 2; Mean difference] (Fig. 2):
   - CD subjects showed thinning of the middle/MdPFC compared with controls [4.42 ± 0.28; 4.74 ± 0.23; –0.32].
   - ODD subjects specifically had thinner cortex in the left rectal/OFC relative to controls [4.28 ± 0.39; 4.86 ± 0.38].

TABLE II. Cortical Thickness (in mm) in the Regions That Differed Significantly Between Groups (Disruptive Behavior Disorders vs. Normal Controls)

	DBD group, Mean (SD)	Controls, Mean (SD)
Mean cortical thickness	4.06 (0.05)	4.48 (0.03)
Left cingulate	4.36 (0.27)	4.65 (0.36)
Left anterior cingulate	4.36 (0.27)	4.67 (0.36)
Left medial frontal	4.66 (0.36)	4.98 (0.36)
Left rectal/orbitofrontal	4.49 (0.34)	4.81 (0.39)
Left superior temporal, uncus	4.17 (0.71)	4.64 (0.50)
Left parietal, precuneus	3.93 (0.23)	4.19 (0.25)
Right middle frontal	4.57 (0.28)	4.79 (0.32)
Right superior temporal	4.35 (0.37)	4.79 (0.32)
Right posterior cingulate	3.34 (0.38)	3.63 (0.42)
Left insula	3.40 (0.96)	4.1 (0.78)

$t > 3.73$; Cohen's $d = 1.099$; effect size $r = .482$; $P < .05$; $n = 47$.

Voxel-Based Morphometry

(a) Differences in GM whole brain volume (volumes in cm^3, mean $\pm$ SD) between the two groups were not significant ($n = 47$: DBD vs. NC, $P = .76$).
(b) A group effect was found for GMd between DBD and NC subjects. There was a significant decrease in the local concentration of GMd in DBD subjects in the left MdPFC Brodmann area (BA) 11, medial frontal BA8, claustrum, insula; and the right inferior frontal BA47, inferior parietal BA40 compared with controls (Table III) (Fig. 3).
(c) Increasing score on the Dominic-R (DBDs) was associated with decreases in GMd in the left medial middle and superior frontal, precuneus, the right superior temporal, and occipital/cuneus (Table IV) (Fig. 4).

DISCUSSION

This study yielded two major findings: (1) DBDs are associated with significant cingulate–fronto–insular cortices thinning and decreased GMd and (2) each of the DBDs subsymptomatology (CD and ODD) showed a specific neuroanatomical anomaly. As discussed below, these neuroanatomical findings are consistent with the DBDs' symptomatology profiles.

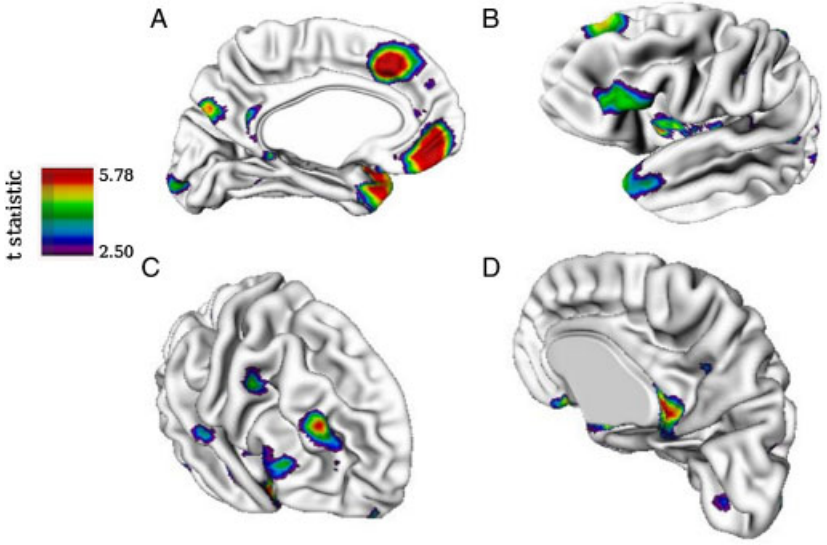

Fig. 1. *t*-maps of cortical thickness thinning in disruptive behavior disorders (DBDs) $N = 22$ compared with controls $N = 25$. Significantly thinner regions in the DBDs group are shown in (A) left (L) medial view of the anterior cingulate, medial prefrontal, rectal/orbitofrontal, superior temporal, uncus and parietal, precuneus; (B) L lateral view of the left anterior cingulate, medial prefrontal, insula; (C) right (R) lateral view of the right middle prefrontal, superior temporal; (D) R medial view of the posterior cingulate. Note the accordance between the neuroanatomical abnormalities and the functional behavioral deficits of the DBDs subjects.

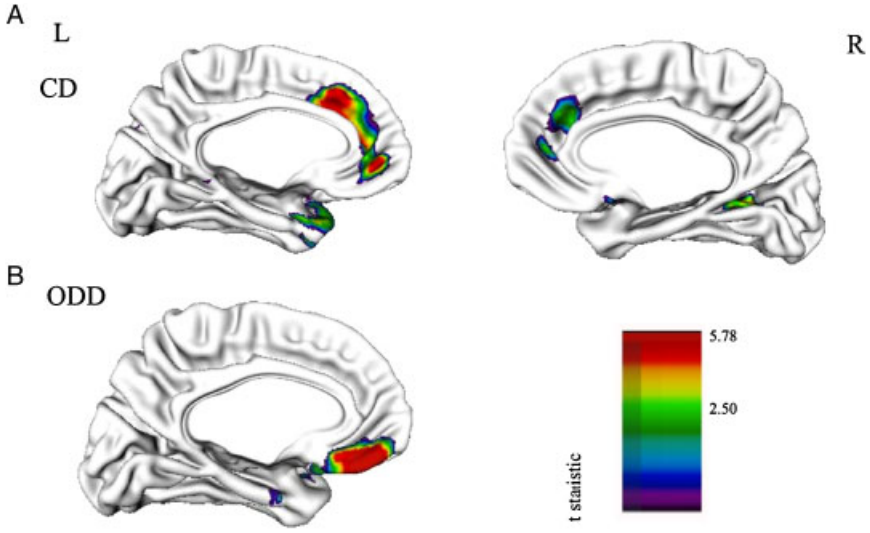

Fig. 2. Contrasts between patients with DBDs subdisorders separately and controls. (A) The *t*-statistical maps of contrasts between conduct disorder (CD) and controls in the L and R medial, middle, and superior prefrontal cortex. (B) the *t*-statistical map of contrasts between oppositional defiant disorder (ODD) and controls on the L orbitofrontal cortex. Note the specificity, which accords with the symptoms of each of the disorders neuroanatomical deficit.

Cortical Thickness

In conjunction with the reported decreased GMd in the fronto–insular regions, we demonstrated thinning of the cingulate, frontal and insular cortices. Functional neuroimaging has shown that abnormal function of the ACC is observed in patients with CD [Sterzer et al., 2005], antisocial personality disorder [Veit et al., 2002a,b], and in criminal psychopaths [Kiehl et al., 2001]. Adolphs [2003] and Davidson et al. [2000] argued that aggressive and antisocial behavior may arise from functional deficits in ACC and OFC, which are involved in the regulation of emotional behavior. In this vein, the ACC, through its connections with the PFC, plays an important role in the regulation

of cognitive and emotional processes [Bush et al., 2002]. For example, the ACC is implicated in error detection, monitoring, response inhibition, set shifting, attentional selection, and strategy formation [Gehring and Fencsik, 2001]. Of special relevance to the DBDs, the cingulate and MdPFCs act to constrain the expression of affect. Deficits in this circuit are hypothesized to increase a person's affinity toward aggressive behavior [Davidson et al., 2000]. In addition, the ACC has strong connections to the dorso–lateral PFC, which is also considered to play a critical role in the impaired functions characteristic of DBDs, i.e., target detection, response selection, error detection, and reward-based decision making [Bush et al., 2002]. Similarly, the OFC is thought to constrain affective impulses through its connections with other prefrontal regions, as suggested by evidence from the study of patients with OFC lesions [Anderson et al., 1999], as well as structural [Raine et al., 2000] and functional neuroimaging [Kiehl et al., 2001; Raine et al., 2000] in antisocial and psychopathic individuals.

TABLE III. Gray Matter Density Comparison Between Disruptive Behavior Disorder Subjects and Normal Controls

Region	*x*	*y*	*z*
L medial frontal	−7	37	−16
L medial frontal	−9	31	40
R Inferior frontal gyrus	37	31	−3
R inferior parietal	35	−53	45
L claustrum	−25	23	3
Right insula	36	17	4
Left insula	−39	11	4
Right inferior frontal	60	20	4

x, *y*, *z* are the coordinates in Talairach space. These coordinates represent the location of the voxel with the highest significance (*t*-value). L, left; R, right. $t > 3.73$; Cohen's $d = 1.099$; effect-size $r = .482$; $P < .05$; $n = 47$.

Voxel-Based Morphometry

DBD subjects demonstrated decreased bilateral insular GMd. This decreased volume may account for some of the DBD symptoms, i.e., heightened emotional arousal resulting in impulsive anger, aggression, cruelty, and hostility. Indeed, the insula contributes to emotional-feeling states originating in representations of visceral arousal [Critchley et al., 2004]. It is involved in the initial/rapid orienting and not sustained processing of socioemotional situations [Williams et al., 2004] and the rapid somatic/visceral responses [Damasio, 1999]. In accordance with our findings, Sterzer et al. [2007] demonstrated,

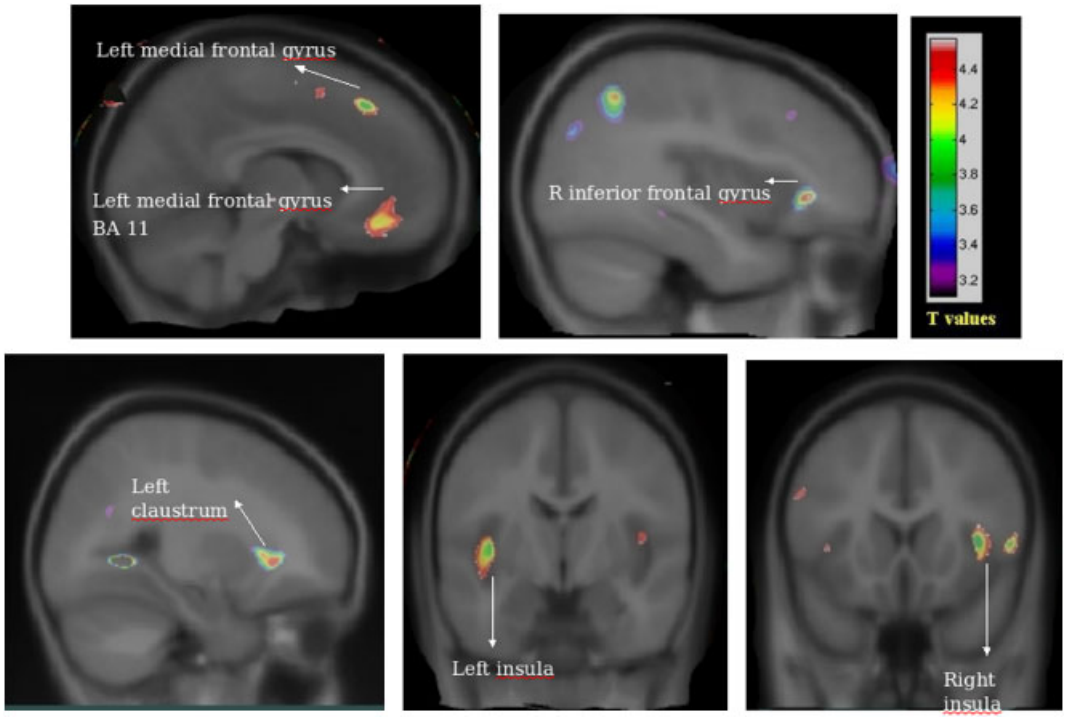

Fig. 3. General linear model *t*-maps of the regions where a significant reduction was found in gray matter density in the disruptive behavior disorders ($n = 22$) vs. normal controls ($n = 25$). Note that the decreased gray matter density is evidenced in the frontal and insular regions, which functionally accord with the disruptive behavior disorders symptoms profile and with the cerebral cortical thickness findings.

using VBM, decreased GM volume in the insula bilaterally in CD subjects. Functional neuroimaging studies report that physiological changes in bodily states (modulated by the insula) give rise to conscious feelings, and consequently emotional modulation, regulation, and expression, through the PFC [i.e., Cameron and Minoshima, 2002; Craig, 2002; Harper et al., 2000]. Although in normal individuals these brain regions act to regulate the expression of affect, deficits in the insular–frontal circuit is hypothesized to increase a person's inclination toward vulnerability to aggressive behavior [Davidson et al., 2002].

Defiance, Anger, Aggression, Cruelty, and Impulsivity: The Eruption of a Geyser

Overall, our findings related to cortical thickness in conjunction with VBM demonstrate similar cingulate–fronto–insular abnormalities in DDBs, which are consistent with the subjects' symptoms profile. Violent behavior has been correlated with prefrontal deficits in humans, suggesting that this brain area plays an important role in the inhibitory control of aggressiveness [Bassarath, 2001; Best et al., 2002]. DBD subjects react impulsively and aggressively, based on first order emotional representations without taking into account second order emotional modulation and regulation. It is like the "eruption of a geyser," allowing emotions to overwhelm thinking and behavior. For example, ODD children, whose tendency is to overreact to affectively charged situations in anger and defiance, find the physiological and emotional arousal associated with such situations difficult to regulate, become cognitively debilitated in the midst of such arousal, and consequently respond to such situations with more affect (e.g., screaming, swearing) than reason (rational problem solving) and a reduced capacity to inhibit aggression. *No single region in the brain works alone*, *and no behavior results from a single region in the brain*. Hence, we advance that the eruption of the geyser by the insula, when it is not assuaged by the ACC/MdPFC/OFC cortices, DBDs behaviors may arise. Indeed, the intrinsic cortico–cortical connections within the ACC/MdPFC/OFC and insular region are well demonstrated [Carmichael and Price, 1996]. Noteworthy, most of these connections are reciprocal. Interestingly, Halász et al. [2006] explored prefrontal neuronal activation patterns in resident rats exposed to psychosocial (sensory contact with the intruder) and aggressive encounters, and found that both psychosocial and aggressive interactions increased c-Fos activation in the ACC, insular, and OFC cortices. When insular inhibition is decreased, a specific configuration of pyramidal cell activation predicted the occurrence of violent attacks with high probability. As GABAergic

TABLE IV. Negative Associations ($t < -3.5$; $P < .001$) Between Gray Matter Density and the Clinical Score of the Dominic-R ($n = 22$)

Region	*x*	*y*	*z*
L medial frontal	−11	48	12
L inferior/middle frontal	−11	41	−18
L middle frontal	−20	34	39
L superior frontal	−20	48	27
R superior temporal	59	−41	21
R occipital	38	−73	23
Parietal, L precuneus	35	−71	35

x, *y*, *z* are the coordinates in Talairach space. These coordinates represent the location of the voxel with the highest significance (*t*-value). L, left; R, right.

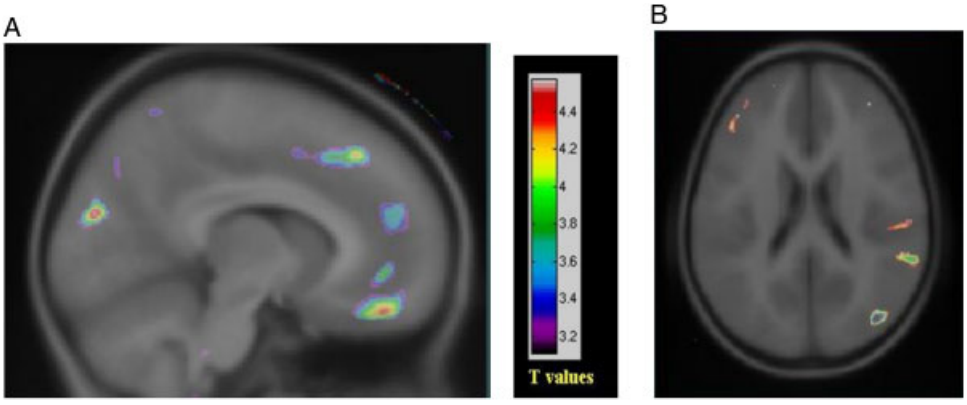

Fig. 4. Regions where a significant relation was found between increasing symptomatology and a decrease in gray matter density ($n = 22$). Note that higher the score (on DBDs), lower the gray matter density in the middle, medial, and superior frontal regions.

interneurons play an important role in the synchronization of pyramidal cell activity, Halász et al. concluded that the decreased activation lead to desynchronized pyramidal discharges, which reduced the "power" of the output of the PFC. According to the authors, abnormal aggression occurred as a consequence of a disorganized prefrontal/insular circuitry.

One DBD or Two Parallel Tracks?

The cortical thickness findings separately related to CD and ODD raise the question of whether our clinical concept should go beyond the DSM DBD entity and consider two tracks that may cross each other at some point, but at others may remain parallel. In this view, considerable dialogue has been taking place regarding the degree to which ODD and CD relate to and should be distinguished from one another [for example, Burke et al., 2002]. The majority of empirical clinical evidence supports a distinction between ODD and CD [Fergusson et al., 1994], as well as between ADHD and both ODD [Waldman and Lilienfeld, 1991] and CD [Hinshaw, 1994]. Therefore, the clinical subtyping of CD and ODD has been a matter of great concern and proved to be difficult because of the need to differentiate among youths who are likely to persist in disruptive behaviors, those who will escalate to serious levels of such behavior (i.e., antisocial personality disorder), and those who are likely to outgrow or to desist from the behavior. Hence, we made an attempt to assess each of the DBDs separately using cortical thickness analysis. Indeed, the two disorders were associated with specific neuroanatomical deficits. First, CD demonstrated thinning in the MdPFC, middle, and superior frontal cortices. Abnormalities in these regions accord with CD symptomatology (i.e., aggression, cruelty). Dysfunction of the MdPFC, middle, and superior frontal cortices reflect an inadequacy of socioemotional self-control [Harris, 2003]. An association between the frontal lobes and emotion regulation, aggressive and violent behavior has been reported in many studies [see reviews in Anderson and Bushman, 2002; Wood, 2003], specifically demonstrating the role of the PFC in regulating social behavior with respect to impulsivity, insensitivity to future consequences, inability to modify so-called risky behaviors even when more advantageous options are presented, and defective autonomic responses to punishment contingencies. Second, ODD showed specific thinning of the rectal/OFC. Functionally, the OFC is implicated in internal inhibitory control of emotions [Davidson, 2003; Moll et al., 2002; Phillips et al., 2003]. Interestingly, Coccaro et al. [2007] found that relative to controls, individuals with recurrent acts of impulsive anger, affectively-driven aggression that are disproportionate to any actual provocation, exhibited diminished OFC activation to faces expressing anger. Based on these results and on data supplied by behavioral and epidemiological findings [Egger and Angold, 2006; Greene et al., 2003] stating that abnormalities in emotional regulation/modulation and affiliated behaviors may play a role in ODD, we propose that ODD subjects may lack internal inhibitory control over their actions, a deficit embodied in the observed thinning of the OFC. Further to our neuroimaging findings, clinical evidence supports the distinction within the DBDs. For example, Connor et al. [2007] report clinically meaningful distinctions between ODD and CD in children. In the latter, significant differences emerged between ODD and CD in the domains of delinquency and overt aggression. In addition, Enebrink et al. [2005] investigated levels of callous–unemotional traits in CD and found that higher levels of conduct problems in subjects with callous–unemotional traits were not explained by the confounding presence of ADHD and/or ODD. Moreover, another study using self-ratings, electrodermal responses to pleasant, neutral, and unpleasant slides demonstrated that compared with healthy subjects and subjects with ADHD only, boys with CD and with ADHD+CD reported lower levels of emotional response to aversive stimuli and lower autonomic responses to all slides independent of valence [Herpertz et al., 2005].

We need to be very cautious in interpreting the present report, which needs to be followed with larger studies that replicate and expand the findings. First, although the results of this study are important and intriguing, they are essentially correlational. It has the limitations of any correlational study (e.g., a third variable other than symptomatology may be responsible for results; direction of causality may be reversed). Second, it is exploratory considering the relative scarcity of quantitative MRI analyses of DBDs in the literature, other than ADHD. Third, the DBD sample used is not large enough to stratify children with ODD and CD. However, our cortical thickness and VBM correlations with the clinical scores survived random-effects analysis and corrections for multiple comparisons. In addition, our findings fit well with each of the disorders' symptoms profile. Another limitation is that the Dominic-R does not measure the chronicity of symptoms and may overweigh more recent events, although a

test–retest reliability yielded intraclass correlations ranging from .69 to .88 according to diagnosis. Of note, sample used in this study are children aged 8 year old; hence, interpretation and generalizability of our findings to older samples should be with caution.

CONCLUSION

We found that 8-year-old children with DBDs show significant thinning of the cerebral cortex and decreased GMd relative to control subjects, and that these brain abnormalities are consistent with their behavioral and cognitive differences. This article thus provides a first report of cerebral cortical thickness and VBM differences in DBDs using unbiased standardized techniques. These findings, if replicated in larger samples, may serve as a marker of prefrontal/insular dysfunction in DBDs, and thus allow for the study of prefrontal/insular pathophysiology in the symptomatology and throughout the course and treatment of DBDs. Most important, clinical practice with the heterogeneous group of children affected with DBDs may benefit from improved formats for symptomatology subtyping. Determination of the clinical significance of potential DBD subtyping could yield better diagnostic decision making, treatment planning, and treatment outcomes.

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