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The Relationship Between Large Cavum Septum Pellucidum and Antisocial Behavior, Callous-Unemotional Traits and Psychopathy in Adolescents

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Abstract

Background—The presence of a large cavum septum pellucidum (CSP) has been previously associated with antisocial behavior/psychopathic traits in an adult community sample.

Aims—The current study investigated the relationship between a large CSP and symptom severity in disruptive behavior disorders (DBD; Conduct Disorder and Oppositional Defiant Disorder).

Method—Structural MRI scans of youth with DBDs (N=32) and healthy comparison youth (N=27) were examined for the presence of a large CSP and if this was related to symptom severity.

Results—Replicating previous results, a large CSP was associated with DBD diagnosis, proactive aggression and level of psychopathic traits in youth. However, the presence of a large CSP was unrelated to aggression or psychopathic traits *within* the DBD sample.

Conclusions—Early brain mal-development may increase the risk of a DBD diagnosis but does not mark a particularly severe form of DBD within patients receiving these diagnoses.

There is a growing literature indicating that many patients with disruptive behavior disorders (DBD), including Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD), show neurobiological abnormalities (Blair, 2010). This may be particularly the case for those youth showing psychopathic traits (PT); i.e., callous-unemotionality (e.g., lack of guilt and empathy), narcissism (e.g., brags excessively about abilities) and impulsivity (e.g., acts without thinking; Barry et al., 2000). Functional MRI studies support the suggestion of amygdala, caudate and ventromedial prefrontal cortex dysfunction in this population (Finger et al., 2011; Finger et al., 2008; Jones, Laurens, Herba, Barker, & Viding, 2009; Marsh et al., 2008; Passamonti et al., 2010; White et al., in press). However, no previous work has assessed whether this population might show a structural brain abnormality reflective of early neural mal-development.

Interestingly, recent work by Raine and colleagues examined whether adults with a large cavum septum pellucidum (CSP) would show higher levels of psychopathy and antisocial personality disorder (Raine, Lee, Yang, & Colletti, 2010). A large CSP is a marker of abnormal brain development, particularly in regards to midline structures (Bodensteiner & Schaefer, 1990; Sarwar, 1989). The septum pellucidum is one component of the septum. It

consists of a deep, midline, limbic structure made up of two translucent leaves of glia separating the lateral ventricles and forms part of the septohippocampal system. A second component of the septum, the septum verum, contains the septal nuclei. At approximately the twelfth week of gestation, a space forms between the two laminae: the CSP. This space begins to close at approximately the twentieth week of gestation and finishes closing shortly after birth (3–6 months postnatally (Sarwar, 1989). The rapid development of the alveoli of the amygdala, hippocampus, septal nuclei, fornix, corpus callosum and other midline structures is attributed to fusion of the CSP (Kim et al., 2007; Nopoulos, Krie, & Andreasen, 2000). Disruption in the development of these limbic structures interrupts this posterior-to-anterior fusion and leads to the preservation of the CSP (see Figure 1). The presence of a large CSP is associated with an increased risk of several disorders including post traumatic stress disorder (PTSD; May et al., 2004), schizophrenia (Nopoulos, Krie, et al., 2000) and bipolar disorder (Kim et al., 2007). Additionally, Raine and colleagues reported that adults with a large CSP had significantly higher levels of antisocial personality, psychopathy, arrests and convictions relative to those without a large CSP (Raine et al., 2010).

The goal of the current study was to examine the relationship between the presence of a large CSP and psychopathic traits/antisocial behavior in youth and to address a limitation of Raine and colleagues study. Namely, it was unclear whether a large CSP was specifically related to psychopathic traits or if a large CSP was simply associated with elevated levels of antisocial behavior, but not specifically psychopathic traits. We therefore made three predictions for the current study. First, we expected to replicate the Raine et al findings indicating a greater likelihood of CSP in youth diagnosed with DBD. Second, we hypothesized that given the greater severity of youth with CD relative to ODD (Burke, Waldman, & Lahey, 2010), youth with a large CSP would be more likely to be diagnosed with CD relative to ODD. Third, we predicted that DBD youth *with* a large CSP would show significantly higher levels of psychopathic traits and aggression than all other youth.

Method

Participants

The study sample was comprised of 59 adolescents: 32 youths with DBD and 27 healthy comparison youths (Table 1). Youths were recruited through newspaper ads, fliers, and referrals from area mental health practitioners. Informed assent and consent was obtained from participating children and parents. This study was approved by the NIMH IRB.

All youths and parents completed Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS; Kaufman, Birmaher, Brent, Rao, & et al., 1997) assessments conducted by a doctoral-level clinician as part of a comprehensive psychiatric and psychological assessment. The K-SADS has demonstrated good validity and inter-rater reliability ($\kappa > 0.75$ for all diagnoses; Kaufman et al., 1997). IQ was assessed with the Wechsler Abbreviated Scale of Intelligence (two-subtest form). Stringent exclusion were implemented to minimize the influence of potential confounds. Exclusion criteria were the presence of pervasive developmental disorder, Tourette's syndrome, lifetime history of psychosis, depression, bipolar disorder, generalized anxiety disorder, social or separation anxiety disorder, PTSD, neurological disorder, history of head trauma, history of substance dependence, and $IQ < 70$. Two youth with DBD met criteria for substance abuse (both with CD diagnoses). In addition, parents and children completed an assessment battery, which included the Inventory of Callous Unemotional Traits (Frick, 2004) and parents completed the Antisocial Process Screening Device (Frick & Hare, 2001) and a Proactive/Reactive Aggression scale (Dodge & Coie, 1987). Parent and child ratings on the ICU were combined in a manner suggested by the author (Frick, 2004), which has shown improved predictive validity relative to single reporter ratings in adolescents (White, Cruise, & Frick, 2009). The

groups did not differ significantly on IQ, age, race/ethnicity or gender (see Table 1). As would be expected, the DBD group had significantly higher APSD, ICU, Reactive Aggression, and Proactive Aggression scores than the healthy control group (Table 1).

Clinical Measures

Inventory of Callous-Unemotional Traits (ICU; Frick, 2004)—The ICU is a 24-item self-report scale designed to assess callous and unemotional traits in youth. The ICU was derived from the callous-unemotional (CU) scale of the Antisocial Process Screening Device (Frick & Hare, 2001) that has been widely used in various samples of youth. The construct validity of the ICU has been supported in community and juvenile justice samples (Essau, Sasagawa, & Frick, 2006; Kimonis et al., 2008; Lawing, Frick, & Cruise, 2010). The ICU has adequate internal consistency (Cronach's $\alpha = .77$; Essau et al., 2006).

Antisocial Process Screening Device (APSD; Frick & Hare, 2001)—The APSD is a 20-item parent-completed rating of callous-unemotional traits and conduct and impulsivity problems (Frick & Hare, 2001), designed to detect psychopathic traits in youth. A three-factor structure has been characterized and comprises the following dimensions: callous-unemotional, narcissism, and impulsivity (Frick & Hare, 2001). There is no established cutoff score for classification of a high level of psychopathic traits (Frick & Hare, 2001). Adequate Cronbach's alphas for the APSD have been established (α 's $> .7$; Frick & Hare, 2001).

Reactive/Proactive Rating Scale—These six items were taken from a rating scale developed by Dodge and Coie (Dodge & Coie, 1987). Dodge and Coie found a 3 item reactive aggression scale and a 3 item that proactive aggression scale yielded the best fitting model (Dodge & Coie, 1987) and were found to be useful in distinguishing aggression subtypes in children (Dodge & Coie, 1987) and adolescents (Pellegrini & Bartini, 2001). Coefficient alphas scale have been reported at .91 and .90 for the proactive and reactive aggression scales respectively (Dodge & Coie, 1987).

MRI parameters

Anatomical MRI data was acquired for 51 participants (19 healthy comparison; 32 DBD youth) using a 1.5-T GE Signa and for 8 (8 healthy comparison youth) using a 3.0 MRI scanner. A high-resolution T1-weighted anatomical image was acquired covering the whole brain (3-dimensional spoiled gradient recalled acquisition in a steady state; 1.5-T: repetition time=9 milliseconds; echo time=2.872 milliseconds; 24 cm field of view; 20° flip angle; 128 axial slices; thickness, 1.5 mm; 256×192 matrix; 3.0-T: repetition time=7 milliseconds; echo time=2.984 milliseconds; 24 cm field of view; 12° flip angle; 128 axial slices; thickness, 1.2 mm; 256×192 matrix).

CSP assessment

Following previous work (Raine et al., 2010), anatomical boundaries for CSP were as follows: the genu of the corpus callosum defined the anterior boundary, the body of the corpus callosum defined the superior boundary, the rostrum of the corpus callosum and fornix defined the inferior boundary, and the junction of the splenium of the corpus callosum with the crus of the fornix defined the posterior boundary. The number of coronal 1 mm slices on which the CSP was present was recorded. Following previous work (Rajarethinam, Sohi, Arfken, & Keshavan, 2008), presence of a large CSP was defined as a CSP of 4 mm or greater length. Assessment was performed in the anterior-to-posterior direction in the coronal view, using a simultaneous sagittal view to ensure that consistent anatomical boundaries were maintained. Assessment was conducted by 2 independent raters masked to

all other participant data. Inter-rater reliability was high [ICC = 1.000, $r = .96$]. A coronal illustration of CSP is provided in Figure 1.

Statistical analyses

To test our first prediction, that DBD youth would be more likely to have a large CSP, we conducted a Chi-square analysis comparing the proportion of youth with a large CSP in the DBD group and the healthy comparison group. This prediction would be supported if a significantly greater proportion of the DBD youth were found to have a large CSP relative to the healthy comparison group. To test our second prediction, that a large CSP would increase the likelihood of CD relative to ODD diagnoses, we conducted a Chi-square analysis comparing the proportion of DBD youth with CD diagnoses relative to ODD diagnoses in the groups with and without a large CSP. This prediction would be supported if a significantly greater proportion of the DBD youth with a large CSP had diagnoses of CD relative to ODD. To test our third prediction, that DBD youth with a large CSP would show significantly higher rates of psychopathic traits and aggression than DBD youth *without* a large CSP, we conducted a series of Analysis of Variance (ANOVA). Our third prediction would be supported if DBD youth with a large CSP were found to have significantly higher levels of psychopathic traits and aggression relative both to healthy individuals *and* to DBD youth without a large CSP. All analyses, including post-hoc t-tests, were conducted using SPSS 19.

Results

Group differences in incidence of large CSP

To test our first prediction, that DBD would be more likely to have a large CSP, we conducted a Chi-square analysis comparing the proportion of youth with a large CSP in the DBD group and the healthy comparison group. This revealed a significant group difference in incidence of a large CSP [$\chi^2(1, N = 59) = 6.70, p = 0.01$]. Indeed, a large CSP was only observed in the patients with DBD (7/32, 22%) and was not seen in the healthy comparison youth. Our second hypothesis, however, was not supported, as the incidence of large CSP was not related to the probability that the participant received a diagnosis of ODD relative to CD (3/11 patients with ODD showed a large CSP, 4/21 patients with CD) [$\chi^2(1, N = 32) = .286, p = .59$].

Relationship of CSP with psychopathic traits and aggression

A series of ANOVAs comparing healthy comparison youth, DBD youth without a large CSP and DBD youth with a large CSP were conducted to test our third prediction. Significant main effects for group were observed for the APSD and its subscales, the ICU and both proactive and reactive aggression (see Table 2). A series of post-hoc t-tests revealed for all the ANOVAs that while the youth with DBD and a large CSP did have significantly greater levels of psychopathic traits and aggression relative to healthy youth [t 's ranging from 5.87 to 12.98, p 's $< .001$], they did *not* show significantly higher levels of psychopathic traits and aggression relative to DBD youth without a large CSP [t 's ranging from .10–1.28, p 's $> .2$]. There is a lack of statistical power in these analyses due to the small number of youth with a large CSP. However, it is important to note that the effect sizes seen here were small. Power analysis, using these effect sizes (partial η^2 ranging from .001–.056) indicated samples of between 421 and 24,365 youth would be needed for an adequately powered analysis.

Potential confounds

Given the high rates of comorbidity between DBD and Attention Deficit-Hyperactivity Disorder (ADHD; Hinshaw, 1987), the relationship between large CSP and ADHD was

examined to ensure that ADHD was not confounding the results. A Chi-square analysis was conducted comparing the proportion of youth with and without a large CSP and incidence of ADHD diagnosis. There was no significant difference between the proportion of youth with an ADHD diagnosis presence of a large CSP and receipt of an ADHD diagnosis within the entire sample [$\chi^2(1, N = 59) = 3.11, p = .08$] or within the DBD group [$\chi^2(1, N = 32) = .058, p = .81$].

Discussion

Main findings

Youth with a large CSP were more likely to meet criteria for a DBD than youth without a large CSP. However, the presence of a large CSP was not higher amongst those with a more severe form of DBD (CD as opposed to ODD). Moreover, DBD youth with a large CSP did *not* show increased levels of aggression and psychopathic traits relative to other DBD youth.

Implications for developmental psychopathology

The current results support those of Raine et al.'s previous study with an adult community sample (Raine et al., 2010). That study reported that adults with a large CSP had significantly higher levels of antisocial personality, psychopathy, arrests and convictions relative to those without a large CSP (Raine et al., 2010). Similarly, we observed that individuals with a large CSP have a higher risk for aggressive behavior, psychopathic traits and being diagnosed ODD/CD. However, it should be noted that the presence of a large CSP was not associated with a more severe form of DBD (CD versus ODD).

Previous work has shown functional MRI impairments in DBD, particularly in the amygdala, caudate, ventromedial prefrontal cortex and the hypothalamus-pituitary-adrenal axis (Crowe & Blair, 2008; Finger et al., 2011; Finger et al., 2008; Jones et al., 2009; Marsh et al., 2008; Passamonti et al., 2010; White et al., in press). Similarly, structural abnormalities in these and connected regions have been reported in youth with DBD and adults with psychopathy (De Brito et al., 2009; Glenn, Raine, Yaralian, & Yang, 2010; Yang, Raine, Narr, Colletti, & Toga, 2009). The current data suggest that at least some of these functional and structural abnormalities in *some (but not all)* youth with DBD may relate to relatively early abnormalities in brain development given that the CSP closes by 3–6 months of age (Sarwar, 1989).

Currently, the specific causes of large CSP are unclear. However, it has been associated with exposure to alcohol in the womb (Swayze et al., 1997) and the development of associated midline structures (e.g., the septum) is influenced by early malnutrition (Craciunescu, Johnson, & Zeisel, 2010; Mellott, Kowall, Lopez-Coviella, & Blusztajn, 2007). Moreover, there are indications of genetic influences on the probability of a large CSP (May, Chen, Gilbertson, Shenton, & Pitman, 2004). Notably, fetal exposure to alcohol and other narcotics (Streissguth et al., 2004; Wakschlag et al., 2010) as well as early malnutrition (Liu & Raine, 2006) have all been previously associated with an increased risk for aggression and there are genetic influences on the probability of aggression, at least in the context of callous-unemotional traits (Viding, Blair, Moffitt, & Plomin, 2005).

It is interesting in this context to note that while exposure to alcohol/other narcotics and early malnutrition have been associated with an increased risk for aggression, they have not been clearly associated yet with psychopathic or callous-unemotional traits in particular. The current data indicated that a large CSP was associated with an increased risk for presenting with a DBD, but there were no significant differences in psychopathic/callous-unemotional traits between DBD youth with and without a large CSP. Together these data suggest that a large CSP may indicate the presence of early developmental abnormalities, but that the form

of these abnormalities may differ across individuals (or perhaps how these abnormalities interact with specific environmental circumstances). This conclusion follows from the growing literature that individuals with conduct problems associated with callous-unemotional traits show a different pathophysiology from those who present with conduct problems in the absence of such traits (Blair, 2010). Moreover, the presence of a large CSP is associated with an increased risk for a variety of disorders including post traumatic stress disorder (PTSD; May et al., 2004), schizophrenia (Nopoulos, Krie, et al., 2000) and bipolar disorder (Kim et al., 2007). In short, while a large CSP is a *marker* of abnormal brain development, it does not appear to specifically indicate any one developmental trajectory given the different pathophysiologies associated with DBDs, PTSD, schizophrenia and bipolar disorder.

Limitations of the current study

There are four limitations to the current study. First is the lack of a group of subjects presenting with ADHD in the absence of DBD. DBD and ADHD are highly co-morbid (Taylor, Schachar, Thorley, & Wieselberg, 1986). However, it should be noted that presence of a large CSP was not associated with an increased risk for ADHD in the present sample. Moreover, previous work has reported that patients with ADHD do not show an increased risk for a large CSP (Nopoulos, Berg, et al., 2000). Second, very strict exclusion criteria were applied to the current sample. While this is a strength of the study as potential confounds are eliminated regarding the pathophysiology of DBD, the current sample would be atypical in clinical settings. Given that a large CSP appears to be a risk factor for a variety of psychiatric conditions, it is possible that a large CSP may be particularly common in patients with significant co-morbidities. Third, the current study does not examine the relative impact of aggressive versus non-aggressive symptoms or covert versus overt aggression. Future work could examine the relationship between large CSP and various subtypes of aggression and antisocial behavior. Fourth, there were very few youth identified in the sample as having a large CSP, which may limit our ability to detect group differences. However, the effect sizes observed in the current analyses were very small (partial $\eta^2 < .056$), mitigating this limitation.

Clinical implications

In conclusion, the current results in a sample of youth with DBD replicate and qualify those of Raine and colleagues' study with an adult sample (Raine et al., 2010). The current results support the Raine and colleagues suggestion that the presence of a large CSP is associated with increased risk for antisocial behavior and that at least some forms of antisocial behavior have a neurobiological basis. However, by finding no relationship of a large CSP with increased psychopathic traits generally or callous-unemotional traits within the DBD sample, the data qualify the Raine et al results and suggest that while a large CSP is a marker for abnormal brain development, it is not a marker for psychopathy or any other particularly severe variant of antisocial behavior.

This is particularly emphasized when considering that a heightened incidence of large CSP is also found in patients with different disorders such as PTSD (May et al., 2004), schizophrenia (Nopoulos, Krie, et al., 2000) and bipolar disorder (Kim et al., 2007). Given this, it is likely that a variety of different forms of early abnormal brain development may be associated with an increased risk for a large CSP. Alternatively, though, it is possible that there is a common form (or cause) of early brain mal-development that puts the individual at risk for a wide variety of psychiatric conditions and that other environmental or genetic factors determine which form develops. Indeed, it is notable, for example, that fetal exposure to alcohol and other narcotics not only increases the risk for aggression

(Streissguth et al., 2004; Wakschlag et al., 2010) but also the risk for schizophrenia (Schlotz & Phillips, 2009).

Finally, it is important to note that a large CSP was only seen in a minority of the patients with DBD. This suggests that early atypical brain development, or at least that associated with a large CSP, is only associated with a fraction of patients with DBD. This supports previous claims of multiple developmental routes to an increased risk for antisocial behavior (Blair, 2010; P. J. Frick & White, 2008). Moreover, this emphasizes the importance of individualized treatment of patients with DBD.

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Abbreviations

CU	callous-unemotional
CSP	Cavum Septum Pellucidum
DBD	Disruptive Behavior Disorder
PT	Psychopathic Traits

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Key Points

- The presence of a large cavum septum pellucidum (CSP) has been associated with antisocial behavior/psychopathic traits in an adult community sample.
- This study investigated the relationship between a large CSP and symptom severity in disruptive behavior disorders (DBD; Conduct Disorder and Oppositional Defiant Disorder).
- Youth with a large CSP were more likely to meet criteria for a DBD than youth without a large CSP.
- DBD youth with a large CSP did *not* show increased levels of aggression/psychopathic traits relative to other DBD youth.
- Early brain mal-development may increase risk for a DBD diagnosis but does not mark a severe form of DBD within these patients.

Example of a large cavum septum pellucidum

Example of a normally developing brain

Figure 1.
Coronal images of a Large Cavum Septum Pellucidum and a Normally Developing Brain

Table 1

Characteristics of Youth with DBD and Healthy Controls

	<u>Youth with DBD (N=32)</u>	<u>Healthy Controls (N=27)</u>
Characteristic	Mean (SD)	Mean (SD)
Age (years)	14.90 (2.08)	14.38 (2.44)
IQ ^a	95.47 (11.11)	100.33 (10.65)
	<u>Measures</u>	
APSD **	27.41 (6.06)	6.59 (5.70)
ICU (combined) **	41.78 (13.08)	17.88 (10.05)
Reactive Agg. **	3.93 (1.91)	0.84 (0.80)
Proactive Agg. **	2.60 (1.63)	0.04 (0.20)
	N %	N %
Gender	25 male (78%)	19 male (59%)
	<u>Race/Ethnicity</u>	
African American	20 (63%)	9 (28%)
European American	9 (28%)	11 (44%)
Hispanic	0 (0%)	2 (9%)
Mixed	3 (9%)	5 (16%)

SD = Standard Deviation

^a Assessed with the Wechsler Abbreviated Scale of Intelligence (two-subtest form)* significantly different at $p < .05$ ** significantly different at $p < .001$

Analysis of Variance to Estimate the Impact of DBD and CSP on Psychopathic Traits and Aggression

Table 2

Dependent Variable	HC (N=27)		DBD- (N= 25)		DBD+ (N= 7)		F(df)	p
	Mean	(SD)	Mean	(SD)	Mean	(SD)		
APSD	6.59 ^{ab}	(5.7)	27.28 ^a	(5.8)	27.86 ^b	(7.5)	89.63	<.001
CU	1.85 ^{ab}	(2.0)	7.60 ^a	(2.6)	7.43 ^b	(2.7)	44.72	<.001
IMP	2.00 ^{ab}	(1.1)	7.32 ^a	(2.3)	8.00 ^b	(2.2)	67.23	<.001
NAR	1.44 ^{ab}	(1.8)	9.44 ^a	(2.8)	9.29 ^b	(3.6)	72.97	<.001
ICU	17.88 ^{ab}	(10.1)	40.00 ^a	(14.4)	46.83 ^b	(6.9)	26.53	<.001
Reactive Aggression	.840 ^{ab}	(.8)	3.91 ^a	(2.1)	4.00 ^b	(1.4)	28.00	<.001
Proactive Aggression	.040 ^{ab}	(.2)	2.39 ^a	(1.6)	3.29 ^b	(1.7)	32.97	<.001

Significantly different means denoted by common letter
HC= healthy comparison

DBD- = youth with disruptive behavior disorder without large cavum septum pellucidum DBD+ = youth with disruptive behavior disorder without large cavum septum pellucidum

SD= Standard Deviation, df= degrees of freedom

APSD= Antisocial Process Screening Device, CU= APSD subscale Callous-Unemotional, NAR= APSD subscale Narcissism, IMP= APSD subscale Impulsivity

ICU= Inventory of Callous-Unemotional Traits