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Neuroanatomical Correlates of Heterotypic Comorbidity in Externalizing Male Adolescents

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Children and adolescents with externalizing behavior disorders including attention-deficit/hyperactivity disorder (ADHD) and conduct disorder (CD) often present with symptoms of comorbid internalizing psychopathology. However, few studies have examined central nervous system correlates of such comorbidity. We evaluated interactions between externalizing and internalizing symptoms in predicting mesolimbic, septo-hippocampal, and anterior cingulate volumes among 12- to 16-year-old boys with either ADHD, ADHD and CD, or no psychiatric condition ($n = 35$). These regions were chosen given established links to trait impulsivity, trait anxiety, and behavior regulation, respectively. Collapsed across groups, Externalizing × Internalizing symptom interactions accounted for individual differences in gray matter densities in each region. Externalizing youth with comorbid internalizing symptoms showed smaller reductions in gray matter than individuals with externalizing psychopathology alone. These results suggest that internalizing symptoms are associated with less severe structural compromises in brain regions subserving motivation and behavior regulation among externalizing boys.

In recent years, considerable progress has been made toward identifying the central nervous system substrates of attention-deficit hyperactivity disorder (ADHD) and other externalizing conditions. In particular, both neuroanatomical and functional abnormalities in the mesolimbic dopamine (DA) system have emerged as consistent markers of behavioral impulsivity, especially among externalizing male individuals (see Gatzke-Kopp et al., 2009). For example, children and adolescents with ADHD, both with and without comorbid conduct problems, show blunted mesolimbic neural reactivity to reward compared to controls, as revealed by functional magnetic resonance imaging (fMRI) studies (Durston, 2003; Scheres, Milham, Knutson, & Castellanos, 2007).

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Following from these findings and others discussed elsewhere (e.g., Beauchaine, Hinshaw, & Pang, 2010), we have argued that mesolimbic DA dysfunction confers vulnerability to disorders across the externalizing spectrum, including ADHD, early-onset conduct disorder (CD), substance abuse and dependence, and antisocial personality (see, e.g., Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009). This perspective is consistent with behavioral genetics studies indicating that a single heritable trait—often conceptualized as impulsivity (Beauchaine et al., 2010)—confers vulnerably to and accounts for *homotypic* comorbidity among externalizing disorders (Krueger et al., 2002).

In addition to homotypic comorbidity (i.e., the co-occurrence of multiple externalizing disorders) children and adolescents with ADHD and/or CD are also at high risk for comorbid internalizing disorders (e.g., Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). This is referred to as *heterotypic* comorbidity and is more perplexing than homotypic comorbidity because (a) externalizing and internalizing disorders share few defining features, (b) no common mechanism has been identified, and (c) inheritance patterns for externalizing and internalizing disorders appear to be largely separate (e.g., Kopp & Beauchaine, 2007).

Neurobiological theories of anxiety and depression often focus on the septo-hippocampal system (e.g., Gray & McNaughton, 2000). These theories are supported by consistent evidence of neuroanatomical and functional abnormalities in septo-hippocampal brain regions, including the amygdala and hippocampus, among those with anxiety and mood disorders (Hamilton, Furman, & Gotlib, in press; Hull, 2002; Leppanen, 2006; Milham et al., 2005; Videbech & Ravnkilde, 2004). Following from these findings, it is now generally accepted that dysfunction within these brain regions confers risk for anxiety and depression. However, evidence also points toward mesolimbic dysfunction in mood disorders (e.g., Forbes et al., 2006).

As this brief discussion suggests, neural correlates of externalizing and internalizing disorders are well characterized. However, few if any studies have examined whether heterotypic comorbidity is associated with individual differences in the structure or function of these brain regions. Accordingly, we used voxel-based morphometry to determine whether externalizing and internalizing symptoms interact to predict brain volumes in (a) mesolimbic structures including the putamen and caudate, and (b) septo-hippocampal structures including the hippocampus and amygdala. We hypothesized that externalizing and internalizing symptoms would interact to predict gray matter volumes in these regions.

We also included the anterior cingulate cortex (ACC) as a region of interest (ROI). The ACC is often considered part of the broader mesocorticolimbic DA system, is implicated in cognitive and emotional processes, and modulates neural activity between mesolimbic regions and other neural structures, including the septo-hippocampal system (Margulies et al., 2007). Moreover, alterations in connectivity between frontal and mesolimbic structures have been observed among externalizing males (e.g., Shannon, Sauder, Beauchaine, & Gatzke-Kopp, 2009). There is also evidence of reduced gray matter volume in the ACC among those with ADHD, depression, and posttraumatic stress disorder (Drevets et al., 1997; Seidman et al., 2006; Shin, Rauch, & Pitman, 2006). Following from these findings, we hypothesized that symptoms of externalizing and internalizing psychopathology would interact to predict ACC gray matter volumes as well.

METHOD

Participants between ages 12 and 16 years were recruited as part of a functional MRI study evaluating reward responding among externalizing youth (Gatzke-Kopp et al., 2009; Shannon et al., 2009). This age range was chosen both because neuroimaging research is more difficult to conduct with younger children, and because much of the existing literature has included participants of similar ages. Parents who responded to recruitment materials (e.g., flyers placed at clinics) completed a preliminary phone interview with a trained research assistant to ascertain probable diagnoses of ADHD and/or CD for their child based on *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev.; American Psychiatric Association, 2000) criteria, assessed using the ADHD and CD scales the Adolescent Symptom Inventory (ASI; Gadow & Sprafkin, 1997). The ASI oppositional defiant disorder, dysthymia, and depression scales were also administered, the latter two of which served as rule-outs. In addition, Child Behavior Checklist (CBCL; Achenbach, 1991) Aggression, Attention Problems, and Anxious/Depressed subscales were obtained. Based on parent-reports using these measures, 66 families were invited to the lab for a detailed diagnostic assessment to ensure they met criteria for either ADHD only, ADHD + CD, or no psychiatric condition. Those with the primarily inattentive subtype of ADHD were excluded from participation. Informed consent and assent were obtained from all parents and adolescents.

Diagnoses of ADHD, CD, and/or oppositional defiant disorder were ascertained via self-reports during a lab visit using the Diagnostic Interview Schedule for Children (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), which was administered by a trained graduate research assistant. Participants were excluded

TABLE 1
Descriptive Statistics by Group and in the Combined Sample

	Control[a]	*CD + ADHD*[b]	*ADHD*[c]	*F(2, 32)*	η^2	*Combined*[d]
Age	13.0 (1.0)	13.4 (1.1)	13.8 (1.3)	1.5	.08	13.4 (1.1)
Full-Scale IQ	115.0 (12.1)	100.7 (16.1)	109.6 (13.4)	3.1	.16	108.0 (15.0)
ASI Hyperactive	47.1 (4.6)	94.8 (16.2)	86.4 (15.9)	40.4***	.72	77.1 (24.7)
CBCL Anxious/Depressed	52.8 (4.4)	67.6 (9.9)	55.3 (6.3)	13.9***	.47	59.1 (9.9)
Total Gray Matter (ml)	888.1 (71.3)	856.3 (72.2)	855.8 (72.3)	0.8	.05	866.1 (71.4)

Note: All descriptive statistics expressed as *M* (*SD*). CBCL and ASI values represent *T* scores. CBCL = Child Behavior Checklist (Achenbach, 1991); ASI = Adolescent Symptom Inventory (Gadow & Sprafkin, 1997).

[a] n = 11.

[b] n = 13.

[c] n = 11.

[d] n = 35.

***$p < .001$.

from neuroimaging if they (a) did not meet criteria for one of the three groups, (b) met criteria for a psychotic disorder or major depression,[1] (c) had a full-scale IQ below 85 as assessed by the Kaufman Brief Intelligence Test (Kaufman & Kaufman, 2004), and/or (d) were taking a mood stabilizer or antidepressant. Patterns of substance use were assessed using the Comprehensive Drinking and Drug Use Record (Brown, Myers, Lippke, Tapert, & Stewart, 1998). No group differences were found in frequencies of cigarette, alcohol, marijuana, amphetamine, or cocaine use, all Fs ≤ 0.84, all ps $\geq .40$, all $\eta^2 \leq .06$.

Although no diagnostic procedure was implemented to assess anxiety disorders, the samples showed considerable variation in symptoms of anxiety on the CBCL Anxious/Depressed scale (see below). The final sample of 35 (11 ADHD, 13 ADHD + CD, 11 control) underwent MRI scanning procedures, including both anatomical and functional acquisition during a monetary incentive task (see Gatzke-Kopp et al., 2009). Adolescents taking psychostimulants ($n = 10$) underwent a 36-hr washout period before the scanning session. For purposes of the present article, only anatomical data, collected from a functional scan obtained prior to the incentive task, were analyzed. Given (a) research indicating distinct neurobiological correlates of externalizing psychopathology for male versus female individuals (e.g., Beauchaine, Hong, & Marsh, 2008), and (b) a sample that was too small to analyze sex effects, only male participants were recruited. Mean family income was $70,500 ($SD = $63,100). Fourteen participants (40%) self-reported that they were non-White, consistent with the demographic composition of the Seattle metropolitan area. Additional descriptive characteristics of the sample, including their scores on measures of psychopathology, appear in Table 1. All participants were right-handed.

As expected given our recruitment strategy, the groups differed on several measures of psychopathology (see Table 1). Nevertheless, given that our hypotheses were correlational, all groups were combined for dimensional analysis. It is important to note that skew was acceptable ($\leq$0.57) for the distributions of all ASI and CBCL scores used for analysis (see below). No group differences were found on demographic measures, or on total brain gray matter volumes.

Main effects of externalizing and internalizing symptoms were represented by continuous ASI hyperactivity *T* scores (range = 42–108), and CBCL anxious/depressed *T* scores (range = 50–78), respectively. The former was selected because it provides a measure of hyperactivity/ impulsivity without inattention, which is not available using the CBCL. This is important because (a) hyperactivity/impulsivity confers risk for multiple externalizing disorders (see Beauchaine et al., 2010; Krueger et al., 2002), and (b) the inattentive subtype of ADHD may be etiologically distinct from the hyperactive/impulsive subtype (see Milich, Balentine, & Lynam, 2001). The CBCL Anxious/Depressed subscale was chosen because it provides a single index of internalizing symptoms, which was required to test our interaction hypothesis (see below). The correlation between the ASI Hyperactivity and CBCL Anxious/Depressed scales was .44 ($p = .008$).

Structural MRI scans were acquired during a second lab visit using a 1.5 Tesla imaging system (General Electric, Waukesha, WI). A high-resolution three-dimensional MPRAGE series was acquired (TR/TE 11.1/2.0 ms, sagital plane, fast spoiled gradient recalled pulse sequence, 124 slices; 1.4 mm, no gap, flip angle = 25 degrees, field of view = 24 cm), which allows for detailed comparison of both white and gray matter volumes. Structural scans were collected in approximately 10 min, at the beginning of a longer imaging

[1] Those with depression were excluded given evidence of shared neutral vulnerability with externalizing disorders, particularly in mesolimbic ROIs (see, e.g., Forbes et al., 2006).

protocol that included functional data acquisition (see Gatzke-Kopp et al., 2009; Shannon et al., 2009). Because the functional protocol was implemented after structural data acquisition, it could not have affected any results reported in this article, and is therefore not described. Prior to imaging, informed consent and assent were again obtained from all parents and adolescents, respectively. In addition to the 35 participants included in this report, data from two externalizing male participants were omitted due to excessive movement during scanning.

We used Statistical Parametric Mapping software, version 8 (SPM8), to evaluate anatomical data for regional differences in gray matter volumes. SPM8 uses a structural analysis technique called voxel-based morphometry, which provides analysis of individual differences in structure, both within and across neuroanatomical regions of interest (e.g., Mechelli, Price, Friston, & Ashburner, 2005).

Using SPM's default "optimized" voxel-based morphometry procedure, data were segmented, bias corrected, and normalized spatially. Images were subsequently registered to Montreal Neurological Institute (MNI) coordinate space using the diffeomorphic anatomical registration by means of the exponentiated lie algebra (DARTEL) algorithm. This processing step, which produces superior registration and normalization of high-resolution anatomical data (Ashburner, 2007), included an 8 mm full-width, half-maximum Gaussian smoothing kernel and preservation of initial gray matter concentrations (modulation). This results in a single tissue map for each participant reflecting the relative concentration of gray matter to other tissue classes (white matter, cerebral spinal fluid) for all 1.5 mm^3 voxels within the MNI brain space.

Gray matter densities in each ROI—including the putamen, caudate, amygdala, hippocampus, and ACC—were entered into multiple linear regression models with age and total gray matter volume covariates. Main effects of ASI hyperactivity and CBCL anxious/depressed scores, and a Hyperactivity × Anxious/Depressed interaction term were included. Regression models were estimated using restricted maximum likelihood. The significance of the interaction terms, over and above all other parameters in the models, were evaluated bilaterally for each region. Statistical parametric maps were displayed individually for each ROI in each hemisphere at a cluster extent threshold of $p < .05$, corrected for the assumption of nonstationarity. Only clusters larger than 250 mm^3 were included in analyses. For significant clusters of gray matter, an average gray matter density value was extracted for each participant. This value is the equivalent of the participant's gray matter volume within the cluster divided by total cluster volume.

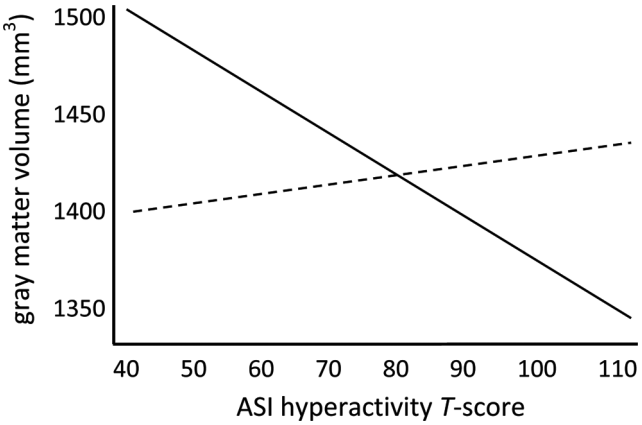

FIGURE 1 Least-squares regression lines depicting the relationship between ASI hyperactivity *T* scores and anterior cingulate gray matter volumes for participants scoring above (solid line) and below (dashed line) the sample median on the CBCL anxious/depressed scale. *Note:* Similar interaction patterns were observed for the putamen and the hippocampus.

TABLE 2
Significant Regional Differences in Gray Matter Volumes by Anatomical Region of Interest for the Interaction of Externalizing and Internalizing Symptoms

	Volume (mm^3)	*Location MNI*[a] (*x, y, z*)			*N.S. Extent*[b] (*p*)	*z Score*
Left Putamen						
Dorsal	503	−22	5	13	.008	2.93
Ventral	321	−24	–1	–8	.037	2.86
Left Hippocampus	1,350	−15	−24	−21	.004	3.50
Left Anterior Cingulate	2,177	−14	48	3	.019	3.39
Right Anterior Cingulate	500	15	50	12	.025	2.86

Note: Only significant interaction effects are reported. No such effects were found for the caudate or the amaygdala. Statistical Parametric Mapping does not yield parameter estimates for non-significant ROIs. Anatomical labels were derived from the Automatical Anatomical Labeling atlas.
[a]Anatomical coordinates are given in the Montreal Neurological Institute (MNI) standard brain space (based on the MNI 152 brain).
[b]Cluster significance given for cluster extent correct for assumption of nonstationarity.

RESULTS

Significant interaction effects are summarized in Table 2. Hyperactivity × Anxious/Depressed interactions predicted gray matter volumes in the left putamen and left hippocampus, and bilaterally in the ACC. These interactions were significant over and above all main effects in the models. There were no significant differences in gray matter within the right putamen or right hippocampus, or within the caudate or amygdala bilaterally. Figure 1 depicts the relationship between ASI hyperactivity *T* scores and ACC volumes for those scoring above and below the sample median on the CBCL Anxious/Depressed scale. As the figure reveals, for those above the median on anxiety/depression, there was little correspondence between hyperactivity and ACC volumes. In contrast, hyperactivity predicted reduced gray matter volumes for those below the sample median on anxiety/depression. Interaction effects for the hippocampus and putamen were of similar form. Thus, externalizing symptoms were associated with reduced gray matter volumes in these regions, but only for those who scored low on anxiety.

DISCUSSION

To date, research evaluating the neural substrates of childhood psychopathology has focused primarily on either externalizing or internalizing symptoms, without modeling effects of comorbid symptoms. We evaluated the interactive effects of externalizing and internalizing symptoms in predicting gray matter volumes in mesolimbic, septo-hippocampal, and ACC brain regions. Among a sample of male adolescents with externalizing psychopathology, internalizing symptoms of anxiety and depression moderated reductions in gray matter volume observed in each region. Externalizing male participants for whom parents reported more internalizing symptoms showed less drastic reductions in gray matter than their nonanxious peers.

Literatures addressing the neural substrates of externalizing and internalizing psychopathology may be distinct in part because externalizing symptoms have been linked primarily to DA-mediated mesolimbic function (see, e.g., Gatzke-Kopp & Beauchaine, 2007; Gatzke-Kopp et al., 2009), whereas internalizing symptoms have been linked primarily to 5-HT-mediated septo-hippocampal function (e.g., Gray & McNaughton, 2000). However, it has long been recognized that these systems likely interact to affect both personality and psychopathology. Indeed, several theories suggest that neural systems subserving behavioral approach (impulsivity) and behavioral inhibition (anxiety) operate in opposition to one another in affecting behavior (e.g., Beauchaine, 2001; Gray & McNaughton, 2000). Thus, heterotypically comorbid symptoms may result from dysfunction within *both* the mesolimbic and septo-hippocampal systems. Our findings are consistent with this interpretation, as the interaction of externalizing and internalizing symptoms predicted gray matter differences in both neural systems.

We found a similar interaction effect in the ACC, which (a) serves response inhibition, error monitoring/detection, and social/emotional processing functions, and (b) is implicated in the expression of both externalizing and internalizing psychopathology (Devinsky, Morrell, & Vogt, 1995; Durston, 2003; Hamilton et al., in press). However, similar to work on both the mesolimbic and septo-hippocampal systems, no studies have evaluated the role of the ACC on comorbid symptoms. Of interest, comorbid internalizing symptoms predicted gray matter volumes in the ACC that were approximate to those found in individuals with no psychopathology. Moreover, the ACC was the only brain region examined in which bilateral interaction effects were observed.

Although speculative given the results of a single study, our findings may indicate neuroprotective effects of anxiety among children with externalizing behavior disorders. Behaviorally, symptoms of anxiety predict superior response to certain treatments among children with ADHD and CD (Jensen et al., 2001). Furthermore, youth with CD and comorbid anxiety are less physically aggressive, regarded less negatively by peers, and experience fewer police contacts than youth with CD alone (Walker et al., 1991). Taken together, these findings provide both neuroanatomical and behavioral evidence for protective effects of anxiety among externalizing youth. Such an interpretation is consistent with the hypothesis that trait anxiety serves to dampen excessive approach behaviors, including aggression (e.g., Beauchaine, 2001).

Although our findings may indicate a potential neural substrate of heterotypically comorbid symptoms, several caveats should be considered. First, structural interactions do not necessarily suggest functional interactions within these brain regions. Thus, further research evaluating functional interactions among these neural structures is needed. In addition, the sample was recruited to examine the neural substrates of externalizing psychopathology, so individuals with clinical levels of depression were screened out to avoid potential confounds. Future research on the neural substrates of heterotypic comorbidity should include samples recruited specifically for clinical levels of both externalizing and internalizing symptoms. Furthermore, the sample was comprised entirely of boys, so our findings may not generalize girls, who sometimes exhibit different neurobiological correlates of externalizing behaviors than boys (e.g., Beauchaine, Hong, et al., 2008). Finally, the sample size ($n = 35$) is modest. Although many imaging

studies of ADHD in particular have included fewer participants, newer studies typically include larger samples. This is especially important when testing interaction effects, which carry less statistical power than main effects (see, e.g., Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008).

Given the limited sample size, we were restricted in the complexity of analyses we could run. One consequence of this was reliance on parent reports of externalizing and internalizing symptoms. It is well know that self-reports of internalizing symptoms tend to be more accurate than parent or teacher reports. Nevertheless, we chose parents as a single informant because our sample size could not accommodate a more sophisticated multi-informant design. It is important to note, however, that the significant interaction findings would be difficult to explain if parent reports weren't capturing a meaningful aspect of child behavior.

Despite these limitations, the current study represents an important step forward in evaluating the neural substrates of heterotypically comorbid symptoms. According to our findings, such comorbidity predicts structural differences in brain regions implicated in core aspects of behavioral control, including approach, avoidance, and emotion regulation. It follows that failure to account for such comorbidity—which is quite common in the research literature—may result in only a partial understanding of central nervous system correlates of psychopathology.

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