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Special Issue Article

Internalizing–externalizing comorbidity and regional brain volumes in the ABCD study

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Abstract

Despite nonoverlapping diagnostic criteria, internalizing and externalizing disorders show substantial comorbidity. This comorbidity is attributable, at least in part, to transdiagnostic neuroaffective mechanisms. Both unipolar depression and externalizing disorders are characterized by structural and functional compromises in the striatum and its projections to the anterior cingulate cortex (ACC) and other frontal regions. Smaller volumes and dampened reward responding in these regions are associated with anhedonia and irritability – mood states that cut across the internalizing and externalizing spectra. In contrast, smaller amygdala volumes and dampened amygdala function differentiate externalizing disorders from internalizing disorders. Little is known, however, about associations between internalizing–externalizing comorbidity and brain volumes in these regions, or whether such patterns differ by sex. Using a transdiagnostic, research domain criteria (RDoC)-informed approach, we evaluate associations between heterotypic (Internalizing × Externalizing) symptom interactions and striatal, amygdalar, and ACC volumes among participants in the Adolescent Brain Cognitive Development study ($N = 6{,}971$, mean age 9.9 years, 51.6% female). Heterotypic symptoms were associated with ACC volumes for both sexes, over and above the main effects of internalizing and externalizing alone. However, heterotypic comorbidity was associated with larger ACC volumes for girls, but with smaller ACC volumes for boys. These findings suggest a need for further studies and transdiagnostic assessment by sex.

Keywords: amygdala, anterior cingulate, RDoC, heterotypic comorbidity, striatum

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Trait impulsivity, which is often expressed in childhood as the hyperactive–impulsive and combined presentations of attention-deficit/hyperactivity disorder (ADHD), confers marked vulnerability to more severe externalizing outcomes in later childhood, adolescence, and adulthood (e.g., Beauchaine, Hinshaw, & Pang, 2010; Loeber & Keenan, 1994; Storebø & Simonsen, 2016). Such outcomes include disruptive behavior disorders, substance use disorders (SUDs), and Cluster B personality disorders (for reviews, see Beauchaine, 2020a; Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009; Beauchaine & McNulty, 2013). Although many children with ADHD do not progress to more severe externalizing behavior as they mature (Lahey et al., 2016), those who do often follow a pathway of sequential comorbidity/continuity through increasingly intractable conduct, including oppositional defiant disorder, conduct disorder (CD), SUDs, and antisocial personality disorder (ASPD) (see Loeber & Hay, 1997; Moffitt, 1993; Robins, 1966). This progression is most likely when common genetic and neural vulnerabilities to externalizing psychopathology interact with environmental adversities and risk factors over time (Beauchaine & Constantino, 2017; Dhamija, Tuvblad, & Baker, 2017; Gatzke-Kopp et al., 2009; Gizer, Otto, & Ellingson, 2017; Plichta & Scheres, 2014). Potentiating environments, including those characterized by family dysfunction (e.g., abuse, maltreatment), deviant peer affiliations, and criminal justice system involvement can "pull" genetically and neurally vulnerable children along the externalizing spectrum (Beauchaine & McNulty, 2013; Beauchaine, Zisner, & Sauder, 2017; Eme, 2020). Given common etiological influences, homotypic comorbidity and sequential continuity of externalizing disorders is unsurprising.

In contrast, heterotypic comorbidity, defined by co-occurrence of at least one internalizing and one externalizing disorder, has historically been more difficult to explain. Despite almost no overlap in symptoms, heterotypic comorbidity is observed at rates that far exceed chance, and substantial correlations between broadband internalizing and externalizing factors are observed in structural models of psychopathology among children, adolescents, and adults (Angold, Costello, & Erkanli, 1999; Klein & Riso, 1993; Krueger & Markon, 2006; Lahey, Krueger, Rathouz, Waldman, & Zald, 2017; McConaughy & Achenbach, 1994; Tackett et al., 2013; Wilens et al., 2002). Externalizing disorders also confer risk for depression and suicide later in life (see Beauchaine et al., 2009; Chronis-Tuscano et al., 2010; Loth, Drabick, Leibenluft, & Hulvershorn, 2014; McDonough-Caplan, Klein, & Beauchaine, 2018). Until recently, heterotypic

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comorbidities and continuities were poorly understood given that most research was descriptive, with few insights into putative mechanisms (for discussion, see Beauchaine & Cicchetti, 2016).

Transdiagnostic and Differentiating Neuroaffective Mechanisms of Comorbidity

More recent research identifies neuroaffective mechanisms that are *transdiagnostic* and therefore common to internalizing and externalizing disorders, and neuroaffective mechanisms that distinguish between internalizing and externalizing disorders. Dampened striatal responding while anticipating incentives is observed in ADHD, CD, SUDs, ASPD, unipolar depression, and nonsuicidal self-injury (Forbes et al., 2006; Holz et al., 2017; Kolla et al., 2015; Luijten, Schellekens, Kühn, Machielse, & Sescousse, 2017; Plichta & Scheres, 2014; Sauder, Derbidge, & Beauchaine, 2016; see also Beauchaine & Hinshaw, 2020; Forbes & Dahl, 2012; Zisner & Beauchaine, 2016 for recent reviews). Striatal under-responding, which is determined by both heritable and environmental influences (Birn, Roeber, & Pollak, 2017; Stokes et al., 2012), is a likely mechanism of negative emotionality/affectivity and the anhedonic, irritable mood state that cuts across the internalizing and externalizing spectra (see Beauchaine & Constantino, 2017; Beauchaine, Klein, Knapton, & Zisner, 2019; Beauchaine & Tackett, 2020; Laakso et al., 2003). Smaller striatal volumes are also observed in both internalizing and externalizing disorders (e.g., Matsuo et al., 2008; Wallace et al., 2014).

In contrast to the transdiagnostic nature of striatal structure and function, amygdala activity and reactivity, which are implicated in punishment sensitivity and both state and trait anxiety (see Gray & McNaughton, 2000; Tye et al., 2011), differentiate between internalizing and externalizing disorders. Mood and anxiety disorders are characterized by amygdala hyper-reactivity to sad and threatening stimuli (e.g., Gaffrey et al., 2011; Phan, Fitzgerald, Nathan, & Tancer, 2006), whereas externalizing disorders are characterized by amygdala hypo-reactivity to such stimuli (e.g., Dotterer, Hyde, Swartz, Hariri, & Williamson, 2017; Jones, Laurens, Herba, Barker, & Viding, 2009). Males with externalizing disorders show blunted amygdala reactivity to empathy-eliciting, fear-eliciting, and threat stimuli, effects that are especially pronounced among boys and men with callous–unemotional and psychopathic traits, who experience distinctly little anxiety (for reviews see Blair, 2013; Frick, Ray, Thornton, & Kahn, 2014). Boys and girls who are diagnosed with CD also show smaller amygdala volumes than age-matched controls (e.g., Fairchild et al., 2011; 2013).

Functional Dependencies Among Neural Systems

Although associations between striatal and amygdalar structure and function and both internalizing and externalizing disorders have been studied extensively, almost all research conducted to date has evaluated main effects. This is problematic for at least two reasons. First, functional specificity of the striatum and amygdala are relative, not categorical. For example, the nucleus accumbens (NAcc), a ventral striatal structure, responds to punishment as well as reward, and the amygdala responds to reward as well as punishment (see, e.g., Sauder et al., 2016; Schultz, 2016). These subcortical regions share functional interconnections via the paraventricular nucleus and the stria terminalis (e.g., Dong, Li, & Kirouac, 2017). Both also project to common frontal structures, most notably the anterior cingulate cortex (ACC; see Haber, 2016; Toyoda, Li, Wu, Zhao, & Descalzi, 2011), which is implicated in error monitoring and associative learning of both reward and punishment contingencies. Those who are affected by internalizing psychopathology show strong ACC responses following their own errors during associative learning tasks (Proudfit, Inzlicht, & Mennin, 2013), whereas those who are affected by externalizing psychopathology show blunted ACC responses (e.g., Gatzke-Kopp et al., 2009). These findings are often interpreted in motivational terms (Hajcak & Foti, 2008); those who are anxious and therefore vulnerable to internalizing disorders are concerned about making mistakes, whereas those who are impulsive and vulnerable to externalizing disorders often are not.

Second, trait and state impulsivity and anxiety, which are subserved by the striatum and amygdala, respectively, modulate one another in both real-world and laboratory settings. Males with externalizing disorders, most of whom engage in impulsive behaviors, show better responses to behavioral treatments, lower rates of physical aggression, better peer relations, and fewer police contacts *if* they experience comorbid anxiety (see Beauchaine, Webster-Stratton, & Reid, 2005; Walker et al., 1991). In the lab, co-occurring trait anxiety is associated with better decision-making on delay discounting tasks among participants with externalizing disorders (Haines et al., 2020). Thus, both real-world outcomes and lab studies suggest *functional dependencies* between biobehavioral systems of impulsivity (externalizing) and anxiety (internalizing). Functional dependencies are not captured by main effects but instead must be tested by modeling interactions directly (Beauchaine & Hinshaw, 2020; Haines & Beauchaine, 2020; Corr, 2004).

Neural Substrates of Trait Impulsivity and Trait Anxiety: Relevance to RDoC

Evaluating both transdiagnostic and differentiating neural vulnerabilities to internalizing disorders, externalizing disorders, and heterotypic comorbidity is consistent with several Research Domain Criteria (RDoC) tenets (see Beauchaine & Cicchetti, 2016; Cuthbert & Insel, 2013; Sanislow et al., 2010). These include (a) concurrent focus on multiple domains of human function (e.g., positive valence systems, negative valence systems, arousal and regulatory systems), (b) an explicit call to model full spectra of behaviors within each domain rather than restricting analyses to psychopathological samples; and (c) specification of integrative models of neural circuitry and behavior, rather than focusing on either behavior or neural circuitry alone (Cuthbert & Insel, 2013; National Institute of Mental Health, 2021). As we elaborate elsewhere, these RDoC tenets confer certain advantages over traditional approaches to studying psychopathology, but have been underappreciated in the child and adolescent clinical literatures to date (Beauchaine & Hinshaw, 2020).

In this study, we focus on core neural substrates of trait impulsivity (striatum–ACC) and trait anxiety (amygdala–ACC), which map closely onto the positive and negative valence systems of RDoC, respectively (National Institute of Mental Health, 2021). In a previous study (Sauder, Beauchaine, Gatzke-Kopp, Shannon, & Aylward, 2012), which to our knowledge is the only one of its kind, Internalizing × Externalizing interactions accounted for individual differences in striatal and ACC gray matter volumes. Compared with nonpsychiatric controls, adolescent boys with ADHD and/or CD *and* comorbid internalizing symptoms showed smaller volumes in both regions than those who

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reported externalizing psychopathology alone. However, that study was preliminary given a small clinical sample ($N = 35$) of only boys. Interaction effects are underpowered and sometimes spurious at such sample sizes (see Leon & Heo, 2009), and clinical samples are selective.

We evaluate whether internalizing and externalizing symptoms, expressed in a large representative cohort (the Adolescent Brain Cognitive Development [ABCD] Study, described below), interact to account for striatal, amygdalar, and ACC volumes. The large sample enables us to evaluate these associations transdiagnostically and among girls, who are under-represented in research on externalizing behavior. Few studies have assessed sex differences in mechanisms of externalizing behavior. Those that have suggest moderation by sex of both behavioral expression of trait impulsivity (Beauchaine et al., 2009), and biological correlates of externalizing behavior (Beauchaine, Hong, & Marsh, 2008; Ducharme et al., 2011). Large samples provide the opportunity to run separate models for girls and boys rather that statistically partialling out (covarying) sex effects, which can obscure sex differences (see McDonough-Caplan et al., 2018). We hypothesized that Internalizing × Externalizing symptom interactions would account for striatal, amygdalar, and ACC volumes, over and above main effects, consistent with Sauder et al. (2012).

Method

Participants

The ABCD study is an ongoing, 21-site longitudinal evaluation of brain development among children, beginning at ages 9–10 years. In Wave 1, ABCD enrolled 11,878 children (see Volkow et al., 2018; Barch et al., 2018). Recruitment was primarily school-based, but was supplemented by mailing lists, referrals, and twin registries (Garavan et al., 2018). Sampling was representative of the sociodemographic diversity within the US, but with oversampling of children experiencing early signs of psychopathology (~40%). This enhances power for predicting mental health difficulties into adolescence. Prior to enrollment, children who met criteria for schizophrenia, SUDs, or intellectual disabilities, and those with contraindications for magnetic resonance imaging (MRI) (e.g., braces, pacemakers, other metal objects) were screened out. The study was approved by review boards at each site, and parents and children provided informed consent and assent, respectively. Data reported herein are available through the National Institute of Mental Health data archive, ABCD 2.0.1, released in July 2019.

Given our objectives, we excluded participants who met past or current criteria for bipolar disorder (bipolar I, bipolar II, bipolar disorder not otherwise specified; $n = 776$), psychotic disorders (delusions, hallucinations, schizophrenia, psychotic disorder not otherwise specified; $n = 308$), other specified neurodevelopmental disorders (autism was not assessed fully; $n = 3{,}138$), and/or low cognitive function (National Institutes of Health (NIH) Cognitive Toolbox age-corrected total composite score <70; $n = 395$). Left-handed children ($n = 848$) and those with head injuries resulting in loss of consciousness for greater than 30 min ($n = 7$) were also excluded. Remaining participants who completed a baseline Child Behavior Checklist (CBCL; $N = 7{,}251$; mean age = 9.9 years; 52% female) were included in exploratory and confirmatory factor analyses, described below. The race composition (parent-report) was 66.5% White, 13.0% Black, 2.6% Asian, 11.5% Multiracial, and 5.0% other. Parents reported that 20.8% of the sample was Hispanic/Latino/Latina[1]. PhenX-derived demographics are reported in Table 1. Owing to excessive movement or other quality control concerns, an additional 146 boys and 133 girls were excluded from our multilevel models, presented below. One eligible participant reported "other" or "not reported" for sex and was therefore excluded from analyses of sex effects. Thus, a final sample of $N = 6{,}971$ participants was included (see Table 1).

Measures

PhenX demographic questionnaire

The PhenX demographic questionnaire is an adapted version of the PhenX Toolkit used to report demographics including race/ethnicity, age, and sex (see Barch et al., 2018; Stover, Harlan, Hammond, Hendershot, & Hamilton, 2010). One parent completed parent-report questionnaires for each child (86% biological mothers, 10% biological fathers, 2% adoptive parent, and 2% other).

Kiddie schedule for affective disorders and schizophrenia (K-SADS), present and lifetime versions

The K-SADS is a semi-structured interview that assesses psychopathology using DSM-5 criteria from both self- and parent-reports (Kaufman et al., 2013; Townsend et al., 2020). We used parent-reports only to determine eligibility, as self-report was not available for exclusionary diagnoses. Although K-SADS items are typically recorded on four-point scales, ABCD data are restricted to diagnoses (absent vs. present).

Edinburgh handedness inventory

A brief version of the Edinburgh handedness inventory was used (Oldfield, 1971; Veale, 2014). This self-report questionnaire evaluates which hand participants typically use for writing, throwing, using a spoon, and using a toothbrush. Items are rated on 5-point scales (always right hand, usually right, both, usually left, always left), which are summed into a score of right, left, or ambidextrous. Left-handed children were excluded given laterality and volume differences seen in left- versus right-handed individuals in subcortical brain regions (Szabo, Xiong, Lancaster, Rainey, & Fox, 2001).

NIH toolbox – cognition battery

The NIH Cognitive Toolbox includes seven tasks that assess various cognitive processes, including attention, working memory, cognitive flexibility, reading ability, processing speed, visuospatial memory, and language abilities (Luciana et al., 2018). Three composite scores are generated (Hodes, Insel, & Landis, 2013), which show adequate to excellent reliability (test–retest) and validity among both children and adults (Akshoomoff et al., 2013; Heaton et al., 2014). As already noted, we excluded children with age-corrected composite scores <70, which indicate low cognitive function.

Ohio State University traumatic brain injury (TBI) screen – short version

The Ohio State University TBI screen has good test–retest reliability and validity for self-reported TBI (Corrigan & Bogner, 2007).

[1]We use Latino/Latina rather than Latinx throughout. Only 3% of people in US Latino/Latina communities use the term Latinx, and an overwhelming majority prefer Latino (Pew Research Center, 2020). Given our intent to serve Latino/Latina communities, we feel it important to embrace preferences of those communities.

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Table 1. Demographic variables and internalizing and externalizing factor scores

	Full sample mean (*SD*) *N* = 7,251[a]	Girls mean (*SD*) *n* = 3,609[b]	Boys mean (*SD*) *n* = 3,362[b]
Age	9.91 (0.63)	9.89(0.63)	9.95 (0.63)
	8.9–11.0	8.9–11.0	8.9–11.0
Cognitive function[c]	102.8 (16.8)	102.9 (16.8)	102.9 (16.8)
Race			
White	66.5%	65.3%	68.8%
Black	13.0%	13.6%	12.0%
Asian	2.6%	2.7%	2.5%
Other	5.0%	4.8%	5.1%
Multiracial	11.5%	12.0%	10.4%
No response	1.4%	1.6%	1.2%
Ethnicity			
Hispanic/Latino/a	20.8%	21.1%	20.7%
No response	1.4%	1.1%	1.6%
Family income			
Below $25,000	12.1%	12.4%	11.7%
$25,000–$99,999	43.0%	44.0%	42.1%
>$100,000	44.9%	43.6%	46.2%
Parent-report internalizing and externalizing symptoms			
Factor scores			
Internalizing	0.05 (0.53)	0.05 (0.53)	0.05 (0.53)
	−0.71–2.47	−0.71–2.47	−0.71–2.14
Externalizing	0.07 (0.63)	0.01 (0.60)	0.14 (0.65)
	−0.76–2.80	−0.76–2.80	−0.76–2.65

[a]Sample included in exploratory and confirmatory factor analyses.
[b]Sample included in multilevel models.
[c]NIH Toolbox age-corrected total composite score.

It was adapted for the ABCD study as a parent-report measure of children's histories of brain injuries and concussions (Barch et al., 2018). We excluded children whose parents reported TBI with loss of consciousness for more than 30 min.

Child behavior checklist

The CBCL is a parent-report measure of common internalizing, externalizing, and other behaviors among children and adolescents (Achenbach, 2009). It is normed nationally by both age and sex. A computerized version was used for ABCD. CBCL scales are ideal for examining dimensional associations between heterotypic symptoms and brain volumes, rather than using categorical diagnoses.

Given our objectives, we performed exploratory and confirmatory factor analyses to validate the latent structure of internalizing and externalizing behavior. Using items from the CBCL internalizing, externalizing, and attention problems scales, we evaluated both two-factor (internalizing, externalizing and inattention combined) and three-factor (internalizing, externalizing, inattention) solutions. Adjudicating between two- and three-factor solutions was important given that inattention often emerges as a separate factor from internalizing and externalizing (Greenbaum & Dedrick, 1998). Modeling inattention separately from externalizing was also potentially important given etiological distinctions between the inattentive versus hyperactive–impulsive and combined presentations of ADHD, the latter two of which typically load on externalizing (Lee, Burns, Beauchaine, & Becker, 2016; Milich, Balentine, & Lynam, 2001). Among these, inattentive ADHD is differentiated from hyperactive–impulsive and combined ADHD by morphological and functional differences in the very neural structures we evaluate here (Ercan et al., 2016; Fair et al., 2013).

Participants were first randomized into split halves of the sample. We conducted an exploratory factor analysis on one half (n = 3,628) using all CBCL internalizing, externalizing, and inattention items. We eliminated 10 items with less than 1% endorsement (e.g., sets fires, thinks too much about sex; see Table 2). In the two-factor model, all CBCL inattention scale items loaded directly on the externalizing factor, but in the three-factor model, the only inattention scale item that loaded directly on the externalizing factor was impulsivity. The three-factor model yielded slightly better fit than the two-factor model (see Table 3). We therefore retained the three-factor model and conducted a confirmatory factor analysis (internalizing, externalizing, inattention) on the second split-half of the sample (n = 3,623).

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Table 2. Standardized item loadings for three-factor exploratory model

CBCL item	EXT	INT	ATTN
Feels others are out to get him/her	**.440**	**.447**	−.014
Sudden changes in mood or feelings	**.462**	**.457**	−.016
Sulks a lot	**.407**	**.545**	−.081
Impulsive or acts without thinking	**.471**	.083	**.429**
Argues a lot	**.700**	.118	.037
Unusually loud	**.401**	.143	.263
Cruelty, bullying, or meanness to others	**.814**	−.057	−.036
Demands a lot of attention	**.457**	.231	.191
Destroys his/her own things	**.725**	.019	.155
Destroys things belonging to his/her family or others	**.792**	−.033	.12
Disobedient at home	**.809**	−.009	.094
Disobedient at school	**.663**	−.166	.345
Doesn't get along with other kids	**.617**	.169	.053
Doesn't seem to feel guilty after misbehaving	**.673**	−.055	.144
Easily jealous	**.466**	.313	.004
Breaks rules at home, school or elsewhere	**.782**	−.085	.208
Gets in many fights	**.724**	−.016	.032
Hangs around with others who get in trouble	**.459**	−.014	.207
Lying or cheating	**.604**	.015	.202
Not liked by other kids	**.489**	.308	.103
Physically attacks people	**.747**	.078	−.046
Screams a lot	**.655**	.136	−.001
Steals at home	**.656**	−.093	.218
Stubborn, sullen, or irritable	**.567**	.337	−.043
Swearing or obscene language	**.520**	.125	.052
Teases a lot	**.564**	.045	.034
Temper tantrums or hot temper	**.681**	.173	−.064
Threatens people	**.872**	.042	−.118
There is very little he/she enjoys	.206	**.411**	.095
Underactive, slow moving, or lacks energy	−.053	**.535**	.197
Unhappy, sad, or depressed	.254	**.668**	−.100
Clings to adults or too dependent	.090	**.448**	.193
Withdrawn, doesn't get involved with others	.060	**.588**	.05
Worries	−.011	**.776**	−.081
Complains of loneliness	.163	**.546**	.067
Cries a lot	.231	**.429**	.067
Fears certain animals, situations, or places, other than school	.008	**.495**	.044
Fears going to school	.049	**.688**	−.078
Fears he/she might think or do something bad	−.001	**.639**	−.049
Feels he/she has to be perfect	−.010	**.665**	−.229
Feels or complains that no one loves him/her	.398	**.513**	−.113
Feels worthless or inferior	.147	**.688**	.013
Would rather be alone than with others	.097	**.480**	.011

(*Continued*)

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Table 2. (*Continued.*)

CBCL item	EXT	INT	ATTN
Nervous, high-strung, or tense	.091	**.641**	.052
Nightmares	.086	**.429**	.110
Too fearful or anxious	−.057	**.774**	.026
Feels dizzy or lightheaded	−.126	**.622**	.054
Feels too guilty	.004	**.694**	.019
Overtired without good reason	.141	**.472**	.170
Aches or pains (not stomach or headaches)	−.038	**.429**	.097
Headaches	−.075	**.487**	.056
Nausea, feels sick	−.144	**.722**	.073
Stomach aches	−.108	**.605**	.073
Vomiting, throwing up	−.105	**.459**	.128
Refuses to talk	.331	**.443**	−.049
Self-conscious or easily embarrassed	.083	**.687**	−.047
Too shy or timid	−.095	**.610**	−.038
Talks about killing self	.320	**.526**	−.134
Fails to finish things he/she starts	.261	.094	**.565**
Can't concentrate, can't pay attention for long	.133	−.036	**.901**
Can't sit still, restless, or hyperactive	.276	−.012	**.618**
Confused or seems to be in a fog	−.043	.382	**.552**
Daydreams or gets lost in his/her thoughts	−.093	.268	**.552**
Poor school work	.283	.057	**.525**
Inattentive or easily distracted	.151	.039	**.824**
Stares blankly	.012	.265	**.535**
Eliminated prior to CFA due to no EFA loadings >.40			
Acts too young for his/her age	.217	.218	.370
Gets hurt a lot, accident prone	.082	.273	.266
Gets teased a lot	.321	.337	.101
Constipated, doesn't move bowels	.088	.384	−.012
Problems with eyes (not if corrected by glasses)	−.021	.340	.102
Rashes or other skin problems	.024	.264	.075
Poorly coordinated or clumsy	.033	.358	.332
Prefers being with older kids	.235	.199	.146
Prefers being with younger kids	.175	.258	.236
Secretive, keeps things to self	.287	.382	.035
Speech problem	.035	.127	.163
Suspicious	.390	.378	.043
Eliminated prior to EFA due to <1% endorsement			
Drinks alcohol without parents' approval			
Runs away from home			
Sets fires			
Sexual problems			
Steals outside the home			
Thinks about sex too much			

(*Continued*)

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Table 2. (*Continued.*)

CBCL item	EXT	INT	ATTN
Smokes, chews, or sniffs tobacco			
Truancy, skips school			
Uses drugs for non-medical purposes			
Vandalism			

Notes. Values in bold indicate items carried forward for subsequent confirmatory models. CBCL = child behavior checklist. EFA = exploratory factor analysis. CFA = confirmatory factor analysis. EXT = externalizing factor. INT = internalizing factor. ATTN = inattention factor.

Table 3. Fit indices for exploratory and confirmatory factor models

	RMSEA	CFI/TLI	SRMR
Exploratory factor analysis			
Two-factor	.026	.902/.897	.076
Three-factor	.021	.939/.934	.063
Confirmatory factor analysis			
Half sample	.028	.903/.899	.085
Whole sample	.029	.903/.899	.076

Notes. RMSEA = root mean square error of approximation; CFI = comparative fit index; TFI = Tucker Lewis index. SRMR = standardized root mean square residual.

All items with standardized loadings greater than .40 in the exploratory model (66 items) were included in the confirmatory model (see Table 2). Items with loadings greater than .40 on two higher order factors ($n = 4$, see Table 2) were included in both factors in the confirmatory models. Fit for the split-half, three-factor confirmatory model was adequate (see Table 3). We therefore applied it to the full sample ($N = 7{,}251$) to compute internalizing, externalizing, and inattention factor scores; only internalizing and externalizing scores were included in subsequent analyses. Fit for the sample-wide three-factor confirmatory model was adequate (see Table 3).

Scanning procedures and data acquisition

Participants were scanned at 1 of 21 ABCD sites (Casey et al., 2018) using multiband echo planar imaging acquisitions with 1 of 3 types of scanners using multi-channel head coils (3 Tesla Siemens Prisma, General Electric 750, or Philips). Casey et al. (2018) describe scanning parameters used for each scanner type to ensure compatibility. Each participant completed a mock scan with motion training. The order of scans was as follows: localizer, T1-weighted structural image, resting-state functional image, diffusion weighted image, T2-weighted structural image, second resting-state functional image, and three functional MRI behavior tasks (with order randomized across families). Scanning sessions were 90–120 min and completed in 1–2 sessions. If scanning required two sessions, the second scan was completed within 1 week of the first. Complete scanning protocols were conducted for 79% of the ABCD sample. Prospective motion correction for structural MRI T1-weighted images and real-time motion monitoring (fMRI integrated real-time motion monitor) were used so operators could provide feedback to participants or adjust scanning procedures (e.g., skipping final resting-state run). Average motion during rest was 0.22 mm ($SD = 0.20$ mm).

Image pre-processing and brain segmentation

A standard preprocessing pipeline was used (Hagler et al., 2019). Prior to processing, research assistants manually examined structural images for severe quality control issues including ghosting, blurring, and/or ringing artifacts. Pre-analysis processing included modality-specific corrections for intensity inhomogeneity (grad warp correction, bias field correction, resampled to isotropic). Participants were excluded from mixed models if any imaging quality control category (motion, intensity inhomogeneity, white matter underestimation, pial overestimation, or magnetic susceptibility artifact) was rated as severe.

Surface-based registration was used to define brain segments of T1-weighted images (1-mm isotropic voxels) using FreeSurfer, version 5.3.0 (Fischl, 2012), which is validated for children (Ghosh et al., 2010). Cortical regions of interest (ROIs) were based on cortical folding patterns (Fischl, Sereno, Tootell, & Dale, 1999) and Bayesian classification rules (Desikan et al., 2006; Destrieux, Fischl, Dale, & Halgren, 2010). An atlas-based volume segmentation procedure defined subcortical ROIs (Fischl et al., 2002). Processed data and tabulated ROI-based values are available through the National Institute of Mental Health data archive.

Multilevel models

Based on the literature outlined above that identifies common and unique neural substrates of externalizing and internalizing, five ROIs implicated in associative learning (reward and/or extinction) were selected, including the putamen, caudate, and NAcc (all striatal), as well as the amygdala and ACC. Linear mixed models were conducted in RStudio (lme4 and lmerTest packages; Bates, Mächler, Bolker, & Walker, 2015) for bilateral ROIs to assess associations between volume and internalizing and externalizing symptoms. Family and site number were included as random effects. Internalizing and externalizing factor scores from the sample-wide confirmatory factor analysis are used in all models. An Internalizing × Externalizing interaction term, which tested our primary hypotheses, was included. Age and whole brain volume (without ventricles) were entered in all models as covariates. Each linear mixed model was fit using restricted maximum likelihood estimation, and *t*-tests with the Kenward–Roger approximation were used to assess significance (Luke, 2017). We used the false discovery rate Benjamini–Hochberg procedure to control for multiple comparisons (10 models for each sex).

Given our objective of evaluating sex effects, we ran separate models for girls and boys (see above). This is preferable to including sex as a covariate given correlations between sex and brain volume, and between sex and both internalizing and externalizing

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Table 4. Brain volumes associated with heterotopically comorbid symptoms

	Volume (mm^3) Mean (*SD*)	*b* (*SE*)	*p* value	*T* statistic	Partial η^2
Whole brain					
Girls	1,158,122 (*92,169*)				
Boys	1,266,517 (*102,844*)				
Left ACC					
Girls	5,397(*728*)	71.10 (*26.0*)	.006	2.735	0.0021
Boys	5,861(*774*)	−53.45 (*24.7*)	.030	−2.166	0.0014
Right ACC					
Girls	6,249(*778*)	68.34(*28.3*)	.016	2.415	0.0016
Boys	6,781(*845*)	−69.70(*27.5*)	.011	−2.531	0.0019
Left NAcc					
Girls	545(*110*)	−0.63(*4.2*)	.882	−0.148	
Boys	594(*92*)	3.23(*3.9*)	.411	0.823	
Right NAcc					
Girls	594(*112*)	1.08(*3.7*)	.773	0.289	
Boys	642(*98*)	1.60(*3.5*)	.650	0.454	
Left caudate					
Girls	3,917(*482*)	−5.23(*19.5*)	.788	−0.268	
Boys	4,142(*524*)	−14.15(*18.8*)	.452	−0.752	
Right caudate					
Girls	4,068(*491*)	−8.12(*19.9*)	.684	−0.408	
Boys	4,287(*536*)	−12.60(*19.2*)	.511	−0.657	
Left putamen					
Girls	5,747(*631*)	−5.65(*24.9*)	.821	−0.227	
Boys	6,187(*709*)	−0.59(*25.5*)	.981	−0.023	
Right putamen					
Girls	5,571(*551*)	−4.45(*21.6*)	.837	−0.206	
Boys	6,033(*608*)	−3.62(*21.1*)	.864	−0.172	
Left amygdala					
Girls	1,501(*204*)	5.68(*7.6*)	.456	0.746	
Boys	1,651(*228*)	−4.61(*7.7*)	.549	−0.600	
Right amygdala					
Girls	1,541(*201*)	6.30(*7.5*)	.402	0.838	
Boys	1,696(*225*)	−3.55(*7.6*)	.639	−0.469	

Notes. Table displays unstandardized regression coefficients (mm^3) for Internalizing × Externalizing interaction terms in each multilevel model examining associations between symptoms and brain volume. ACC = anterior cingulate cortex. NAcc = nucleus accumbens.

psychopathology (Martel, 2013). Covarying sex would therefore remove variance of interest (see Beauchaine & Hinshaw, 2020).

Results

Internalizing and externalizing symptoms and subcortical volumes

Consistent with previous research, a main effect of externalizing was found for right NAcc volumes among boys, $p = .03$ ($b = -69.17$, $SE = 3.17$, partial $\eta^2 = .0014$). Smaller NAcc volumes were associated with more externalizing behavior. However, this finding did not survive correction for multiple comparisons. No other striatal regions were significant for boys, and no main effects for any striatal region were found for girls. No striatum interaction effects were significant for either sex. In addition, no main effects or interaction effects were found for amygdala volumes (see Table 4). These null results are surprising given replicated findings of smaller amygdala volumes in externalizing and larger amygdala volumes in

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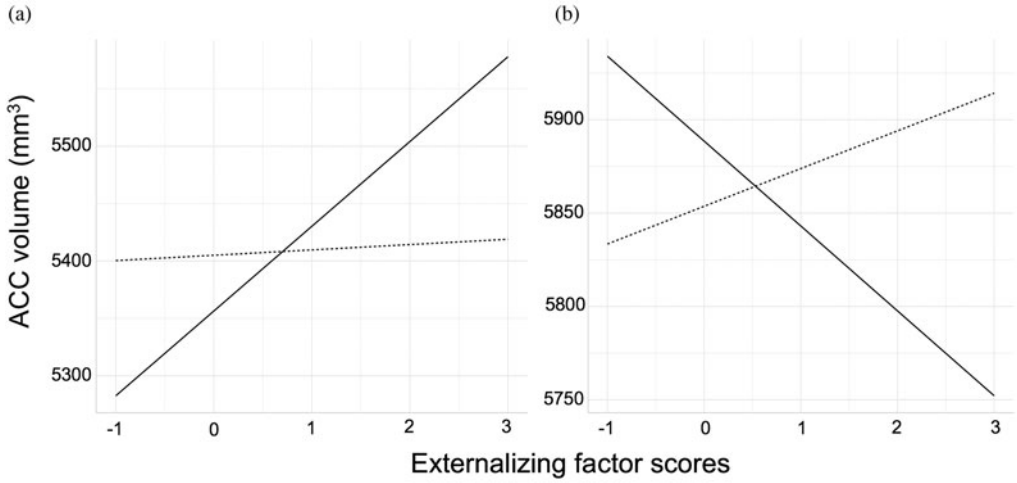

Figure 1. Two-way interactions depicting relations between externalizing factor scores and anterior cingulate cortex (ACC) volumes for those who score above the median on internalizing symptoms (solid line) and below the median on internalizing symptoms (dashed line). Panel (a) depicts the interaction for girls. Panel (b) shows the interaction for boys.

internalizing, as reviewed above. Previous studies, however, have used clinical samples.

Internalizing and externalizing symptoms and ACC volumes

A main effect of internalizing for right ACC volumes was found for boys only, $p = .03$ ($b = -63.70$, $SE = 30.86$, partial $\eta^2 = .0013$). Smaller ACC volumes were associated with more internalizing behavior. However, this finding did not survive correction for multiple comparisons. No additional main effects were observed for either sex. Consistent with our primary hypothesis, however, Internalizing × Externalizing symptom interactions were associated with ACC volumes for both sexes ($p < .05$ in all four models; see Table 4). All four interaction effects survived correction for multiple comparisons (false discovery rate = .2; Efron, 2010). As in our previous work with a smaller clinical sample (Sauder et al., 2012), externalizing symptoms were associated negatively with bilateral ACC volumes for boys who scored high on internalizing symptoms. In contrast, externalizing symptoms were associated positively with bilateral ACC volumes for girls who scored high on internalizing symptoms, (see Figure 1). Thus, comorbid internalizing and externalizing symptoms were associated with smaller ACC volumes among boys, but larger ACC volumes among girls. This sex effect was not expected or predicted.

Discussion

To date, few studies have evaluated neural correlates of heterotypic comorbidity, despite the ubiquity of internalizing–externalizing comorbidity in both research and practice (see Beauchaine & Cicchetti, 2016). This is a problematic oversight given well-characterized functional dependencies between trait impulsivity (externalizing) and trait anxiety (internalizing) in affecting behavior (e.g., Beauchaine & Hinshaw, 2020; Haines & Beauchaine, 2020). As outlined in the introduction of this article, anxiety modulates impulsive behavior in both real-world and laboratory settings, resulting in better decision-making and reduced risk for poor functional outcomes such as criminality (e.g., Haines et al., 2020; Walker et al., 1991). In this study, we evaluated associations between heterotypic symptoms and regional brain volumes in the striatum, amygdala, and ACC. These neural structures were chosen given their transdiagnostic (striatum) and differentiating (amygdala, ACC) characteristics with respect to externalizing and internalizing syndromes, respectively.

To our knowledge, only one study has examined associations between heterotypic symptoms and regional brain volumes (Sauder et al., 2012). In that study, which comprised a small sample of only boys ($N = 35$), Internalizing × Externalizing symptom interactions were associated with both striatal and ACC gray matter volumes. For boys who scored above the sample median on anxiety/depression, hyperactivity–impulsivity was associated negatively with volumes in both regions. In contrast, brain volumes were unassociated with externalizing behavior for boys who scored below the sample median on anxiety/depression. Our findings replicate the Sauder et al. study for boys, but only in the ACC, not the striatum. In contrast, for girls who scored above the sample median on internalizing, externalizing symptoms predicted *larger* ACC volumes (see Figure 1). No association between externalizing behavior and ACC volumes was observed for girls who scored below the sample median on internalizing. This opposite pattern of findings for boys versus girls was unexpected, and illustrates why separate analyses by sex are preferable to using sex as a covariate; doing so would almost certainly have obscured the sex effect (for extended discussion see Beauchaine & Hinshaw, 2020).

In addition to the Internalizing × Externalizing interactions for the ACC, an expected main effect was observed linking smaller NAcc volumes to externalizing behavior for boys, consistent with previous research (Wallace et al., 2014). Unexpectedly, however, no other main effects were significant for either the striatum or amygdala, despite well-replicated negative associations for both sexes between (a) striatal volumes and externalizing (e.g., Wallace et al., 2014), (b) striatal volumes and internalizing (e.g., Matsuo et al., 2008), and (c) amygdala volumes and internalizing (e.g., Rosso et al., 2005). Two differences between this study and previous work may account, at least in part, for observed null findings. First, most studies linking subcortical volumes (striatum and amygdala inclusive) to internalizing and externalizing symptoms have used older (primarily adolescent) samples. To the extent

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that brain–behavior relations solidify across development as environmental risk exposures accrue (see Birn et al., 2017), smaller effect sizes can be expected in younger samples.

Second, almost all previous studies have compared brain volumes between non-psychiatric controls and groups of children, adolescents, or adults with *diagnosable* psychopathology. In representative samples, biomarkers of impairment observed among small numbers of participants at distributional extremes (e.g., ≥95th percentile) are sometimes swamped by large numbers of participants at normative levels of sample variation (e.g., Shader et al., 2018). This illustrates a potential trade-off between dimensional assessment and contrasted groups designs (McDonough-Caplan et al., 2018).

Our finding linking larger ACC volumes to higher levels of externalizing behavior for girls who scored above the median on internalizing warrants further investigation. This is the first finding of its kind, and contrasts with our now replicated ACC finding for boys, who show the opposite pattern (i.e., smaller ACC volumes portend more severe externalizing behavior for boys who score high on internalizing). Given the novelty of our ACC finding for girls and the small effect size, we are reluctant to interpret further before future replication. We reiterate, however, the importance of collecting and analyzing data from large samples such as ABCD, so separate models can be constructed for boys versus girls. As we note elsewhere (Yan, Schoppe-Sullivan, & Beauchaine, 2020), mixing boys' and girls' scores in single analyses can (a) reduce sensitivity of those analyses for girls' outcomes given large mean differences between sexes on virtually all externalizing outcomes (Eme, 2016), and (b) obscure sex effects in analysis of covariance models, especially when effects are in opposite directions such as here (Beauchaine & Hinshaw, 2020). This is particularly important to consider in studies of brain volume. Given that sex correlates substantially with both externalizing scores and intracranial volumes, including boys and girls in a single analysis with sex and intracranial volumes as covariates removes variance of interest when predicting to externalizing behavior. This reduces power to detect sex effects.

It is also important to consider effect sizes. With very large samples, trivial effect sizes can be significant. In such circumstances, it is often unclear whether there are clinical or practical implications of findings. In our models, which are summarized in Table 4, significant findings, including Internalizing × Externalizing interactions, accounted for well under 1% of the variance in regional brain volumes. It is therefore important to state explicitly that striatal and ACC volumes cannot be used for diagnostic purposes, and that our findings may have limited if any practical use. This conclusion is not unique to our study, and instead applies to other subcortical volume findings from ABCD and other large datasets (see Beauchaine, 2020b). In summarizing existing findings from the ABCD study, Owens et al. (2020) reported a median effect size of .03 (Pearson's *r*), with an interquartile range of .01–.07 (0.0001–0.005% variance accounted for). These effect sizes are *orders of magnitude* below the smallest cut-offs historically defined as clinically relevant (see e.g., Atkins, Bedics, McGlinchey, & Beauchaine, 2005). Owens et al. (2020) propose that applying traditional effect size heuristics (Cohen, 1988) to large datasets may be overly restrictive. It is at least equally or more problematic, however, to attribute importance to trivial effect sizes that are significant only in very large samples.

Limitations aside, our study has many strengths. First, we used a large, nationally representative sample. This is essential for testing sex differences that are often obscured in the broader literature, given far fewer girls than boys in most externalizing samples. Second, our analyses were theory-driven. We selected ROIs *a priori* based on theories of heterotypic comorbidity and evidence of overlapping neural substrates common across the internalizing and externalizing spectra (Zisner & Beauchaine, 2016; Beauchaine & Constantino, 2017). It is encouraging that the bilateral ACC volume association with heterotypic symptoms among boys replicated our previous work (Sauder et al., 2012), and that the finding of a bilateral ACC volume association with heterotypic symptoms among girls survived multiple comparison control. This increases confidence in our findings.

Our study contributes to a growing literature evaluating neural substrates of psychopathology comorbidities among youth (Beauchaine & Cicchetti, 2016; Beauchaine & Cicchetti, 2019). We focus on functional dependencies (i.e., interactions among) heterotypic symptoms and their associations with brain volumes implicated in trait impulsivity, trait anxiety, and associative learning, with direct evaluation of sex effects. Our findings show that ACC volumes are associated with comorbid symptoms for both sexes, but that patterns differ for boys versus girls. Future studies should evaluate association of between heterotypic symptoms and functional neural correlates of psychopathology, and address potential differences in findings across informants (see De Los Reyes & Kazdin, 2005), which have been observed in other ABCD analyses (e.g., Samimy, Schettini, O'Grady, Hinshaw, & Beauchaine, 2021). Future studies should also evaluate developmental associations between emerging comorbidity and brain structure and function. Although Wave 2 of the ABCD imaging dataset were not available to us for analysis, they were recently released. As noted above, many brain–behavior relations strengthen across the lifespan in response to impinging environments (e.g., Birn et al., 2017). Characterizing specific transactional processes through which neural vulnerabilities and environmental risk and protection operate is the ultimate goal of developmental psychopathology. Our findings are but a preliminary step toward this objective.

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Conflicts of Interest. None.

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