NEW RESEARCH | DIMENSIONAL APPROACHES

Dimensional Associations Between Conduct Problems and Brain Structure Across 18 International Cohorts in ENIGMA

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Objective: Although conduct problems (CPs) are continuously distributed, little is known about how dimensional measures of CPs map onto brain structure. Therefore a large sample was used to comprehensively assess associations between dimensionally measured CPs and brain structure.

Method: T1-weighted structural brain magnetic resonance imaging scans from 14,160 youths (5-21 years old, 46.2% female) across 18 international case-control, community-based, and population-based cohorts were preprocessed using ENIGMA-standardized protocols. Regression models examined associations between CPs and cortical thickness, surface area, and subcortical volumes, adjusting for age, sex, and intracranial volume. Moderation by sex, age, and callous-unemotional traits was also investigated.

Results: Widespread but small ($\beta = -0.02$ to -0.07) negative associations were observed between CPs and surface area (total surface area, 23/34 regions), cortical thickness (average thickness, 15/34 regions), and amygdalar and hippocampal volumes. Sex was a key moderator, with many surface area associations limited to boys and some thickness associations limited to girls. Some associations were stronger in younger children and at lower levels of callous-unemotional traits. The impact of adjusting for IQ and other psychopathology varied by outcome (eg, most surface area findings survived IQ adjustment, whereas cortical thickness associations did not).

Conclusion: CPs were associated with subtle, yet widespread, alterations in brain structure. Findings overlapped with differences observed in categorically measured conduct disorder, but novel associations with cortical thickness were identified. This provides further evidence that neuroanatomical differences are not limited to youth with clinically elevated CPs. Our findings have potential implications for neurocognitive models of CPs as they extend beyond the regions highlighted in these models.

Study registration information: Investigating dimensional relationships between conduct problems and brain structure: an ENIGMA megaanalysis; https://osf.io/nzj3r/.

Key words: brain structure; conduct disorder; conduct problems; dimensional psychopathology; ENIGMA

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Conduct problems (CPs) represent a heterogeneous construct that involves a range of behaviors including oppositionality, irritability, and aggressive and rule-breaking behaviors.[1] If these behaviors are severe and accompanied by clinically significant impairment, the affected individual may meet criteria for conduct disorder (CD), a diagnosis defined by persistent CPs that violate the rights of others and/or age-appropriate norms.[2] CPs are associated with an elevated risk for adverse outcomes, including educational underachievement, delinquency, other mental health problems, and antisocial personality disorder in adulthood.[3] This incurs substantial individual burden and high economic costs through increased service use and criminal justice system involvement.[4]

Neurocognitive models assume that risk for CPs in youth is underpinned by neurocognitive dysfunction related to alterations in brain structure and function.[5] Therefore, insights into the neural correlates of CPs may increase our understanding of the phenotype and its underlying pathophysiological processes, which could ultimately enhance prevention and intervention efforts. Meta-analyses of studies using case-control approaches in youth with clinically significant CPs (ie, elevated CPs, CD, or other disruptive behavior disorders) have reported lower gray matter volume across regions implicated in emotion processing and regulation, decision making, reinforcement learning, and empathy, such as the orbitofrontal cortex, insula, amygdala, and striatum.[6-8] Recently, the ENIGMA-Antisocial Behavior (ASB) working group analyzed the largest neuroimaging dataset on CD known to date, comprising 1,185 youths with CD and 1,253 typically developing controls from 15 international cohorts. Youth with CD showed lower surface area (SA) in 26 of 34 regions and lower limbic and striatal volumes, but minimal cortical thickness (CT) differences.[9]

Whereas this case-control study provided robust evidence of structural brain alterations in CD as a diagnostic category, it is unclear whether similar findings would be obtained when examining CPs as a continuum/dimension. Psychopathology research has increasingly shifted toward dimensional (and transdiagnostic) frameworks, such as the *DSM-5-TR* Alternative Model for Personality Disorders,[2] the Research Domain Criteria,[10] and empirically derived latent variable models such as the Hierarchical Taxonomy of Psychopathology (HiTOP).[11] HiTOP conceptualizes psychopathology as hierarchically organized dimensions, ranging from a general psychopathology factor (p factor), to broad spectra (externalizing, internalizing), and narrower symptom clusters (eg, CPs, irritability). These dimensional frameworks allow researchers to target the level of analysis most relevant to their aims, whether shared transdiagnostic mechanisms or more specific processes within symptom clusters.[12]

Accordingly, studying CPs as a dimensional construct allows us to investigate mechanisms at the narrower end of this hierarchy, while complementing categorical case-control studies by offering a more comprehensive understanding of how brain structure relates to CPs across varying levels of severity.[10] Indeed, whereas categorical approaches aid clinical decision making,[13] most forms of psychopathology—including those related to CPs—are

continuously distributed.[14] Moreover, participants in neuroimaging studies of CD are often recruited from specialized settings (eg, youth offending services or clinics), possibly reducing generalizability.[15] Such samples show higher rates of comorbidity and lower socioeconomic status and IQ compared with typically developing individuals,[16] factors that are themselves associated with brain structure.[17] As lower IQ and comorbid psychopathology, including attention-deficit/hyperactivity disorder, are common in youth with CPs/CD and may reflect broader neurodevelopmental vulnerability rather than mere confounds,[16] careful consideration of these characteristics is crucial. Finally, as severe CPs are more common in boys,[16] female participants tend to be underrepresented in CD research, limiting our understanding of CPs/CD in girls.

These considerations highlight the need to investigate CPs as a dimensional construct and complement case-control studies of CD with analyses of more representative samples. Although a handful of large-scale investigations have examined continuous measures of CPs and reported widespread associations with lower gray matter volume across (sub)cortical regions[18] and reduced CT in frontal and temporal areas,[19,20] 3 important knowledge gaps remain. First, existing studies primarily focused on volume or CT,[18-20] yet recent work indicates that youth with CD show more pronounced alterations in SA,[9] which differs from CT in developmental trajectories and genetic underpinnings.[21,22] Second, previous large-scale dimensional studies have not investigated whether sex moderates the association between CPs and brain structure, despite some case-control research suggesting such moderating effects in CD[23,24] (but see[9]). Finally, whereas case-control studies suggest (albeit inconsistently) that callous-unemotional (CU) traits may define a subgroup of youth with CD with more extensive brain structural alterations (eg, [9]), their influence on dimensional CPs–brain structure associations remains largely untested. This is despite strong correlations between CPs and CU traits, which prompted the introduction of the *DSM-5* Limited Prosocial Emotions specifier to designate a particularly severe and persistent subtype of CD.[2] Addressing these gaps in larger, more geographically diverse samples using a dimensional framework is important to complement case-control designs and understand how CPs—across a broad range of severity—relate to underlying neurobiology.

Therefore, we pooled harmonized individual-level data from 14,160 youths from 18 international case-control, community-based, and population-based samples to comprehensively examine dimensional associations between CPs and brain structure, including CT, SA, and subcortical volumes. We further investigated whether sex, age, and/or CU traits moderate any observed associations and whether CPs–brain structure associations differ between youth with vs without CD. We hypothesized that CPs would be negatively associated with brain structure in regions linked to emotion processing, empathy, and decision making, such as the medial/lateral orbitofrontal cortex, insula, and amygdala.[6,7,23,25,26] Based on recent findings in CD,[9] we additionally hypothesized stronger/more associations between CPs and SA compared with CT and that CPs–brain structure associations (especially in the amygdala and insula) would be stronger in youth with elevated CU traits. We also predicted CPs-by-sex interactions in frontoparietal regions (nondirectional due to mixed prior findings)[23,24] and CPs-by-age interactions in anterior cingulate and prefrontal cortices.[20,27] No predictions were made regarding moderation by diagnosis.

METHOD

Samples

We included 14,160 participants aged 5 to 21 years from 18 international cohorts within the ENIGMA-ASB working group.[28] Samples were collected from 12 countries across 4 continents (North America, South America, Asia, and Europe), comprising 11 case-control, 1 high-risk, 4 community-based, and 2 population-based cohorts (Table 1; Table S1, available online). Notably, case-control cohorts were sampled from varying settings (eg, community, youth offending services, clinics[9]). Exclusion criteria included age >21 years; IQ (if available) <70; neurological, autism spectrum, psychotic, and bipolar disorders; and genetic syndromes (Supplement 1, available online, presents inclusion/exclusion flowcharts). Each contributing site had ethical approval for their original study and sharing deidentified individual-level data. The current study was preregistered (https://doi.org/10.17605/OSF.IO/NZJ3R) and received ethical approval from the University of Bath's Psychology Research Ethics Committee (19-297/22-148).

Measures

Conduct Problems. CPs were measured using 1 of 3 widely used, reliable[29,30] questionnaires for assessing youth psychopathology: the youth- or parent-report versions of the Strengths and Difficulties Questionnaire (SDQ),[30] the parent-report Child Behavior Checklist (CBCL), or the Youth Self-Report (YSR).[29,31] The CBCL and the YSR *DSM*-oriented CP subscales are highly overlapping, comprising 17 and 15 items with respective score ranges of 0 to 34 and 0 to 30. The SDQ CPs subscale comprises 5

TABLE 1 Characteristics of Included Cohorts

				Sex, female		Age, y		IQ		Current CD diagnosis			CPs POMP		
Sample	**Country**	**n**	**Sample type**	**n**	**%**	**Mean**	**SD**	**Mean**	**SD**	**n**	**%**	**CPs measure**	**Mean**	**SD**	**CU traits measure**
ABCD (baseline, 3.0)[a]	USA	8,616	Community	4,109	47.7	9.47	0.50	101.88	16.67	268	3.1	CBCL	3.71	6.83	Brief CU traits
BESD	the Netherlands	83	Case-control	0	0.0	16.51	1.34	96.34	7.68	48	57.8	YSR	14.82	13.32	ICU youth
BHRC (baseline)[a]	Brazil	678	High-risk	295	43.5	10.63	1.91	103.29	15.94	—[b]		CBCL	6.12	10.06	—
Boys Town	USA	305	Case-control	115	37.7	14.47	2.30	104.21	13.08	144	47.2	SDQ parent	32.33	34.72	ICU youth + parent highest
Cambridge Female	UK	28	Case-control	28	100.0	16.68	1.44	103.32	9.34	17	60.7	YSR	18.81	16.88	ICU youth[c]
CDKid	UK	39	Case-control	0	0.0	15.41	1.76	104.38	11.64	21	53.8	SDQ youth + parent highest	47.44	27.69	APSD CU traits
CSU-Yao	UK	150	Case-control	0	0.0	14.98	1.06	105.20	11.48	75	50.0	SDQ youth	33.07	19.56	APSD CU traits
cVEDA (baseline)[a]	India	978	Community	423	43.3	14.53	3.94	—		—[b]		SDQ youth/adult + parent highest	28.64	21.21	—
FemNAT-CD[a]	Germany, Switzerland, UK	435	Case-control	221	50.8	13.94	2.49	102.15	12.31	133	30.6	CBCL	13.16	18.36	ICU youth + parent highest[c]
Georgetown	USA	86	Case-control	36	41.9	13.55	2.33	103.63	14.06	—		CBCL	23.19	23.40	ICU youth + parent highest
IMAGEN (baseline)[a,d]	France, Germany, Ireland, UK	1,707	Community	893	52.3	13.95	0.44	—		27	1.6	SDQ youth + parent highest	25.16	15.85	—
KIND Lab Girls Study	USA	50	Community	50	100.0	9.58	1.30	97.26	9.62	2	4.0	CBCL	8.71	11.99	ICU youth
MATRICS/Aggressotype[a]	Germany, Italy, the Netherlands, Spain, Switzerland, UK	243	Case-control	67	27.6	12.78	2.70	102.22	11.47	49	20.2	CBCL[e]	24.02	21.55	ICU parent
MTwiNS[a]	USA	309	Population twin[d]	145	46.9	14.26	2.12	105.50	11.98[f]	—		CBCL	3.10	7.36	ICU youth + parent highest
SAND	USA	195	Population	108	55.4	15.37	0.55	—		6	3.1	CBCL	5.81	10.24	ICU youth + parent highest
Southampton Family Study	UK	39	Case-control	2	5.1	15.54	1.17	98.51	12.46	20	51.3	CBCL	18.25	22.79	ICU youth + parent highest
UCL-T1/T2	UK	81	Case-control	0	0.0	14.09	1.42	96.25	11.19	—		SDQ parent	36.08	27.34	ICU parent + teacher highest
Yale[d]	USA	138	Case-control	50	36.2	11.41	2.07	108.44	13.67	11	8.0	CBCL	19.46	17.21	ICU parent
Total (18 samples)	USA	14,160		6,542	46.2	11.12	2.67	102.13	16.03	821	5.8		10.45	16.40	

Note: Information on sex, age, and CPs was available for all participants, whereas availability of information on IQ, CD diagnosis, and CU traits varied across cohorts. A measure referred to as "youth + parent highest" means that for the majority of this sample, both youth- and parent-report versions were available, and we included the highest score of the 2 versions in the current analyses. "SDQ youth/adult" indicates that both the youth (<18 years old) and the adult (18-21 years old) versions of the SDQ self-report questionnaire were used. APSD = Antisocial Process Screening Device; CBCL = Child Behavior Checklist; CD = conduct disorder; CPs = conduct problems; CU = callous-unemotional; ICU = Inventory of Callous-Unemotional Traits; POMP = percent of maximum possible score; SDQ = Strengths and Difficulties Questionnaire; YSR = Youth Self Report.

[a]*Multisite/multiscanner sample.*

[b]*Current diagnostic status was not available/could not be obtained before the data freeze time.*

[c]*The CU traits subscale of the Youth Psychopathic Traits Inventory was used for 3 participants (Cambridge Female) and 1 participant (FemNAT-CD), respectively. See Supplement 1, available online, for additional information on the individual samples.*

[d]*Only 1 twin per family was included in the current study.*

[e]*CBCL scores were missing for 20 participants and the SDQ self-report version was used instead to calculate POMP scores for CPs.*

[f]*IQ scores were available for only 41% of the MTwiNS sample.*

items with a score range of 0 to 10. When both parent- and youth-report data were available, the higher of the two score was used (ie, applying a Boolean "OR" rule across informants), prioritizing sensitivity over specificity. To facilitate the combined analysis of all cohorts/measures, we converted individual-level scores to percent of maximum possible (POMP) scores,[32] expressing scores relative to the minimum and maximum of the respective scale (Supplement 2, available online):

$$\text{POMP} = \frac{\text{observed score} - \text{minimum possible score}}{\text{maximum possible score} - \text{minimum possible score}} \times 100$$

Covariates. For sensitivity analyses, POMP scores were also computed for internalizing and attention/hyperactivity problems from the same questionnaires. CU traits were assessed using different questionnaires across samples (*Supplement 2*, available online), and POMP scores were calculated. Current CD status was based on research diagnoses derived from diagnostic interviews administered as part of the protocols of the individual cohorts (eg, Schedule for Affective Disorders and Schizophrenia for School-Age Children [K-SADS]) (Table S1, Supplement 2, available online).

Neuroimaging. Individual-level structural T1-weighted brain magnetic resonance imaging data were preprocessed and quality controlled at the individual sites or project lead sites (University of Bath and University of Birmingham) following standard ENIGMA protocols[33] and subsequently pooled at the lead sites (Supplement 2, available online). Briefly, images were preprocessed using FreeSurfer versions 5.3, 6.0, or 7.1.[34] Cortical regions were parcellated based on the Desikan-Killiany atlas, whereas subcortical regions were segmented based on the FreeSurfer aseg atlas. Global measures (ie, total intracranial volume [TIV], average CT, and total SA) and regional measures (ie, CT and SA for 34 cortical regions and volume for amygdala, hippocampus, caudate, nucleus accumbens, pallidum, putamen, and thalamus) were extracted. Measures were averaged across hemispheres. Data were visually inspected and statistically evaluated for outliers. Poor-quality segmentations/parcellations were excluded.

Statistical Analyses

All statistical analyses were performed in R version 4.3.1, pooling individual-participant data from all sites. As model assumptions were met, associations of CPs with each global and regional brain structural measure were assessed using separate linear regression models with CPs (POMP scores) as predictor. Models included biological sex (male, female) and age (in years) plus TIV for regional SA and subcortical volume analyses (see equation below). Site effects were adjusted for before analysis using ComBat[35]). False discovery rate corrections were applied separately to CT, SA, and volumetric outcomes ($q = .05$). Standardized β coefficients (acquired by standardizing all model terms) are reported as effect sizes, along with their bootstrapped 95% CIs based on 1,000 resamples:

$$\text{ROI}_i = \text{intercept} + \beta_1(\text{CP POMP score}) + \beta_2(\text{sex}) + \beta_3(\text{age}) \; [+\beta_4(\text{TIV})] + \varepsilon_i$$

were, ROI was the specific regional brain structural outcome measure for the *i*th individual, β was the specific coefficient for each predictor in the model, and ε was the error term. In analyses of regional surface area and subcortical volume, TIV was also corrected.

Sensitivity analyses examined the robustness of findings by separately adding IQ, attention/hyperactivity problems, internalizing problems, and CU traits into the model. We additionally controlled for IQ, attention/hyperactivity, and internalizing problems simultaneously. Moderation by sex, age, CU traits, and CD diagnostic status (binary coded) was examined by separately including interaction terms in the model after mean-centering continuous variables. Significant interactions were followed up with uncorrected simple slopes analyses, plotting, and inspection of Johnson-Neyman intervals for continuous moderators. Finally, to assess the robustness of findings when excluding the Adolescent Brain Cognitive Development℠ (ABCD) Study, which comprised 61% of the sample, we repeated the main analysis without this cohort. All sensitivity, subsample, and moderation analyses included sex, age, and TIV (for SA and subcortical volumes) as covariates. All cohorts were included in the main analysis and moderation analyses pertaining to sex and age, but the number of cohorts/participants differed across the other analyses (Table S2, available online).

RESULTS

Sample Characteristics

Sample characteristics are presented in Table 1. CPs (POMP scores) and age distributions, comparisons by sample characteristics, and correlations with key variables are provided in Supplement 3 (available online).

CPs–Brain Structure Associations

We observed significant negative associations between CPs and average CT ($\beta = -.03$), total SA ($\beta = -.07$), and TIV ($\beta = -.04$). We further identified small but significant

($\beta = -.02$ to $-.07$) negative associations between CPs and CT in 15 of 34 regions and SA in 23 of 34 regions. Associations between CPs and CT were localized to frontal, temporal, and parietal regions, with the largest effect sizes observed for the precentral and postcentral gyri (βs $= -.05$). Associations with SA were overlapping, but included more occipital and medial regions, with the largest effect sizes observed for the superior, middle, and inferior temporal gyri (βs $= -.04$ to $-.05$). CPs also showed small negative associations with amygdala and hippocampus volume (βs $= -.02$) (Figure 1, Table 2; Tables S5-S7, available online). No significant positive associations were observed. Figure 2 shows a comparison of the current findings and findings of the ENIGMA-ASB study on CD.[9]

Sensitivity Analyses

When adjusting for IQ, most associations between CPs and CT became nonsignificant, whereas most associations with SA and volume remained significant (Table 2; Supplement 5, available online). Two-thirds of the CT findings, half of the SA associations, and all volumetric outcomes were not robust to adjusting for attention/hyperactivity problems. Correcting for internalizing problems also rendered all volumetric and half of the SA associations nonsignificant, but minimally impacted the CT findings. When controlling for IQ, attention/hyperactivity, and internalizing problems simultaneously, none of the associations with CT survived, but approximately 50% of the SA associations and associations with TIV and amygdala volume remained. Adjusting for CU traits resulted in fewer significant associations with CT but minimally impacted the SA and (subcortical) volume findings. Notably, sample sizes for IQ or CU traits analyses were approximately 25% smaller.

When rerunning the analyses without the ABCD© Study sample (n = 5,544), 8 of 16 (50%) of the previously significant CPs-CT associations and 15 of 24 (63%) of the CPs-SA associations were retained, whereas associations with TIV, amygdala, and hippocampus volume were rendered nonsignificant (Supplement 6, available online). Despite differences in significance, effect sizes were consistently in the same direction and similar, albeit slightly smaller than in the main analysis. Correspondingly, effect sizes for the main analysis and when excluding the ABCD sample were highly correlated across metrics (ρ = 0.88-0.98). Further sensitivity analyses by sample type (eg, case-control or community-based cohorts only) and CPs measure (eg, raw SDQ or CBCL/YSR scores only) are presented in Supplement 6 (available online). See Supplements 7 and 8 (available online) for assumption and robustness checks and additional analyses related to the ComBat site adjustment.

Interaction Analyses

For main effects of sex and age, see Supplement 9 (available online). Significant CPs-by-sex interactions were observed for CT in 6 regions, including 3 parietal regions identified in the main analysis (eg, inferior parietal cortex) and 3 temporal regions (eg, entorhinal cortex). CPs were negatively associated with CT in female, but not male, participants. Widespread CPs-by-sex interactions across 22 outcomes were observed for SA, including total SA (Figure 3A) and 17 regions negatively associated with CPs (eg, superior frontal and temporal gyri, insula). Here, CPs-SA associations were negative in male participants, but largely nonsignificant (and sometimes positive) in female participants. Lastly, CPs-by-sex interactions were detected for TIV, nucleus accumbens, and putamen volume (negative associations in male participants and nonsignificant associations in female participants) (Table S20, Figure S26, available online).

Significant CPs-by-age interactions were identified for CT in 5 temporal/occipital regions, most of which were identified in the main analysis. There was a stronger negative association between CPs and CT at younger ages (<12-15 years). Similar findings were observed for total SA and TIV (Figure 3B). Finally, putamen volume was negatively associated with CPs in childhood (<8 years), but positively associated in adolescence (>13 years) (Table S21, Figure S27, available online).

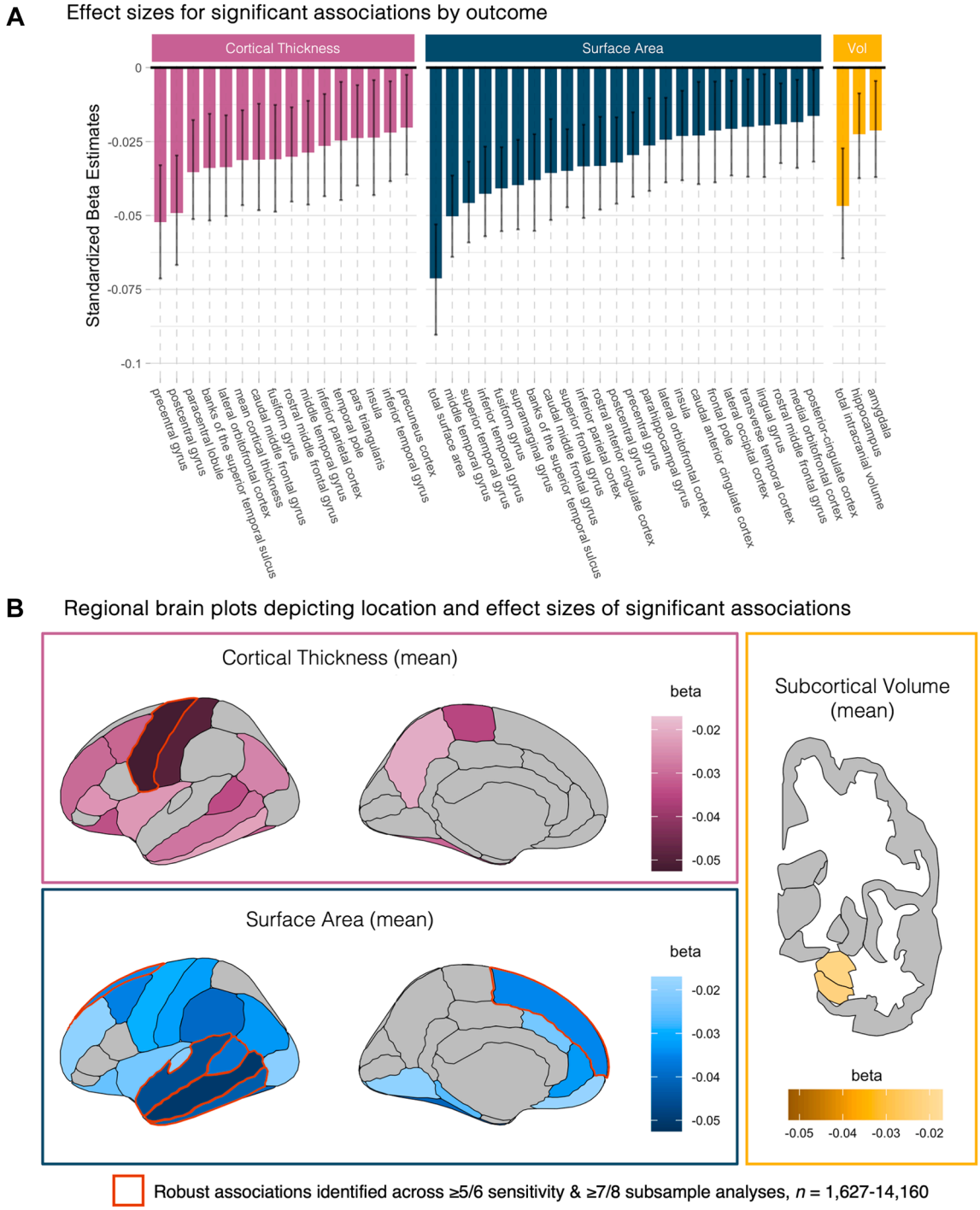
We observed CPs-by-CU traits interactions for TIV and total SA (Figure 3C) as well as for SA in the inferior temporal, precentral and postcentral, and supramarginal gyri (all identified in the main analysis). Stronger negative CPs-brain structure associations were observed at lower levels of CU traits, with nonsignificant associations at very high levels (Table S22, Figure S29, available online). There were no significant interactions between CPs and current CD diagnostic status.

To assess the validity of harmonizing across different CPs measures and informants, we performed additional post hoc exploratory analyses investigating moderation by CPs measure (CBCL/YSR vs SDQ) and informant type (parent-report vs youth/self-report), finding evidence for a moderate impact of measure (stronger/more associations when CPs were based on the CBCL), but limited evidence for informant differences (Supplement 10, available online).

DISCUSSION

Drawing on an unprecedentedly large sample of 14,160 children and adolescents from 18 cohorts, this study

FIGURE 1 Significant Negative Associations Between Conduct Problems and Cortical Thickness, Surface Area, and Subcortical Volumes



Note: (A) Effect sizes (β) for false discovery rate–corrected associations between conduct problems and cortical thickness, surface area, and subcortical volume, after adjusting for sex and age (and total intracranial volume in the surface area and subcortical volume analyses). All effect sizes are negative, indicating that higher conduct problems relate to lower cortical thickness, surface area, and volume in the highlighted regions. Error bars represent bootstrapped 95% CIs around the β estimate. (B) Regional brain plots depicting the location of significant associations with conduct problems. The hue of the color shading reflects the size of the effect (β estimates), with darker hues indicating larger effect sizes. Regions outlined in red were identified as the most robust associations, defined as being significant across 7 of 8 subsample analyses (Supplement 6, available online) and 5 of 6 sensitivity analyses (Supplement 5, available). This included negative associations of conduct problems with surface area in the superior frontal gyrus and 4 temporal regions (banks of the superior temporal sulcus and superior, middle, and inferior temporal gyri) and with cortical thickness in the precentral gyrus. The addition of "(mean)" to each structural outcome indicates that the displayed results reflect averages across the left and right hemispheres. Brain plots were created with the ggseg R package. Vol = (subcortical) volume. Please note color figures are available online.

TABLE 2 Significant Negative Associations Between Conduct Problems and Cortical Thickness, Surface Area, and Subcortical Volume

							Robust to covariate adjustment?				
Region	**n[a]**	**β**	**Bootstrapped 95% CI**	**t**	**p**	**p_{FDR}**	**IQ**	**att/ hyper**	**int**	**IQ, att/ hyper, int**	**CU traits**
Cortical thickness											
Precentral gyrus	13,909	−.05	−0.07, −0.03	−5.38	<.001	<.001	Yes	Yes	Yes	No	Yes
Postcentral gyrus	13,819	−.05	−0.07, −0.03	−5.19	<.001	<.001	Yes	Yes	Yes	No	Yes
Paracentral lobule	14,074	−.04	−0.05, −0.02	−3.92	<.001	.001	No	No	Yes	No	No
Banks of superior temporal sulcus	14,068	−.03	−0.05, −0.02	−3.79	<.001	.001	No	Yes	Yes	No	Yes
Lateral orbitofrontal cortex	14,069	−.03	−0.05, −0.02	−3.79	<.001	.001	Yes	No	Yes	No	Yes
Mean cortical thickness	14,053	−.03	−0.05, −0.01	−3.66	<.001	.002	No	No	Yes	No	Yes
Caudal middle frontal gyrus	13,984	−.03	−0.05, −0.01	−3.34	<.001	.003	No	No	Yes	No	No
Fusiform gyrus	14,021	−.03	−0.05, −0.01	−3.40	<.001	.003	No	No	Yes	No	Yes
Rostral middle frontal gyrus	13,955	−.03	−0.05, −0.01	−3.50	<.001	.002	No	Yes	Yes	No	No
Middle temporal gyrus	13,950	−.03	−0.05, −0.01	−3.13	.002	.006	No	No	Yes	No	No
Inferior parietal cortex	13,855	−.03	−0.04, −0.01	−3.05	.002	.007	No	No	Yes	No	Yes
Temporal pole	13,903	−.02	−0.04, −0.00	−2.50	.012	.031	No	No	Yes	No	No
Pars triangularis	14,079	−.02	−0.04, −0.01	−2.71	.007	.020	No	Yes	Yes	No	No
Insula	13,875	−.02	−0.04, −0.00	−2.55	.011	.029	No	No	No	No	No
Inferior temporal gyrus	14,000	−.02	−0.04, −0.00	−2.37	.018	.039	No	No	Yes	No	No
Precuneus	14,043	−.02	−0.04, −0.00	−2.42	.015	.036	No	No	No	No	No
Surface area											
Total surface area	14,060	−.07	−0.09, −0.05	−8.14	<.001	<.001	Yes	Yes	Yes	Yes	Yes
Middle temporal gyrus	13,982	−.05	−0.06, −0.04	−7.38	<.001	<.001	Yes	Yes	Yes	Yes	Yes
Superior temporal gyrus	13,913	−.05	−0.06, −0.03	−6.79	<.001	<.001	Yes	Yes	Yes	Yes	Yes
Inferior temporal gyrus	14,014	−.04	−0.06, −0.03	−6.05	<.001	<.001	Yes	Yes	Yes	Yes	Yes
Fusiform gyrus	14,037	−.04	−0.06, −0.03	−5.89	<.001	<.001	Yes	Yes	Yes	Yes	Yes
Supramarginal gyrus	13,920	−.04	−0.05, −0.02	−5.43	<.001	<.001	Yes	Yes	Yes	No	Yes
Banks of superior temporal sulcus	14,067	−.04	−0.06, −0.02	−4.66	<.001	<.001	Yes	Yes	Yes	Yes	Yes
Caudal middle frontal gyrus	14,010	−.04	−0.05, −0.02	−4.53	<.001	<.001	Yes	Yes	Yes	No	Yes
Superior frontal gyrus	13,909	−.03	−0.05, −0.02	−5.55	<.001	<.001	Yes	Yes	Yes	No	Yes
Inferior parietal cortex	13,902	−.03	−0.05, −0.02	−4.56	<.001	<.001	Yes	No	Yes	Yes	Yes
Rostral anterior cingulate cortex	14,030	−.03	−0.05, −0.02	−4.46	<.001	<.001	Yes	No	Yes	No	Yes
Postcentral gyrus	13,829	−.03	−0.05, −0.02	−4.53	<.001	<.001	Yes	Yes	No	No	Yes
Precentral gyrus	13,930	−.03	−0.04, −0.02	−4.25	<.001	<.001	Yes	Yes	No	Yes	Yes
Parahippocampal gyrus	14,100	−.03	−0.04, −0.01	−3.32	<.001	.002	Yes	Yes	Yes	Yes	Yes
Lateral orbitofrontal cortex	14,072	−.02	−0.04, −0.01	−3.50	<.001	.001	Yes	No	Yes	Yes	Yes
Insula	13,877	−.02	−0.04, −0.01	−3.28	.001	.002	Yes	No	No	No	Yes
Caudal anterior cingulate cortex	14,011	−.02	−0.04, −0.00	−2.78	.005	.010	No	No	No	No	No
Frontal pole	14,050	−.02	−0.04, −0.00	−2.52	.012	.020	Yes	No	No	No	Yes
Lateral occipital cortex	13,945	−.02	−0.04, −0.00	−2.80	.005	.010	Yes	No	No	No	Yes

(continued)

TABLE 2 Continued

Region	n[a]	β	Bootstrapped 95% CI	*t*	*p*	p_{FDR}	Robust to covariate adjustment? IQ	att/hyper	int	IQ, att/hyper, int	CU traits
Transverse temporal cortex	14,095	−.02	−0.04, −0.00	−2.41	.016	.025	No	No	No	No	Yes
Lingual gyrus	14,011	−.02	−0.04, −0.00	−2.35	.019	.029	Yes	No	No	No	Yes
Rostral middle frontal gyrus	13,974	−.02	−0.03, −0.01	−2.82	.005	.010	Yes	No	No	No	Yes
Medial orbitofrontal cortex	13,999	−.02	−0.03, −0.00	−2.64	.008	.015	No	No	No	No	No
Posterior-cingulate cortex	14,081	−.02	−0.03, −0.00	−2.18	.029	.043	No	No	No	No	No
(Subcortical) volume											
Total intracranial volume	14,160	−.05	−0.06, −0.03	−5.45	<.001	<.001	Yes	No	No	Yes	Yes
Hippocampus	14,066	−.02	−0.04, −0.01	−2.97	.003	.012	Yes	No	No	No	Yes
Amygdala	14,027	−.02	−0.04, −0.00	−2.75	.006	.016	Yes	No	No	Yes	Yes

Note: Regions are ordered by outcome and absolute effect size (β). Statistical models included conduct problems, sex, and age, as well as total intracranial volume for analyses of surface area and subcortical volumes. All effects shown were significant after FDR correction. Due to rounding, the upper CIs for some significant effects appear to be 0. However, none of the bootstrapped CIs crossed 0. The last 5 columns indicate whether effects remained significant after adjustment for each listed variable and FDR correction. Table S2, available online, shows the sample sizes for the sensitivity analyses, ranging from 100% (att/hyper and int) to approximately 76% (CU traits) of the original sample. att/hyper = attention/hyperactivity problems; CU = callous-unemotional; FDR = false discovery rate; int = internalizing problems.

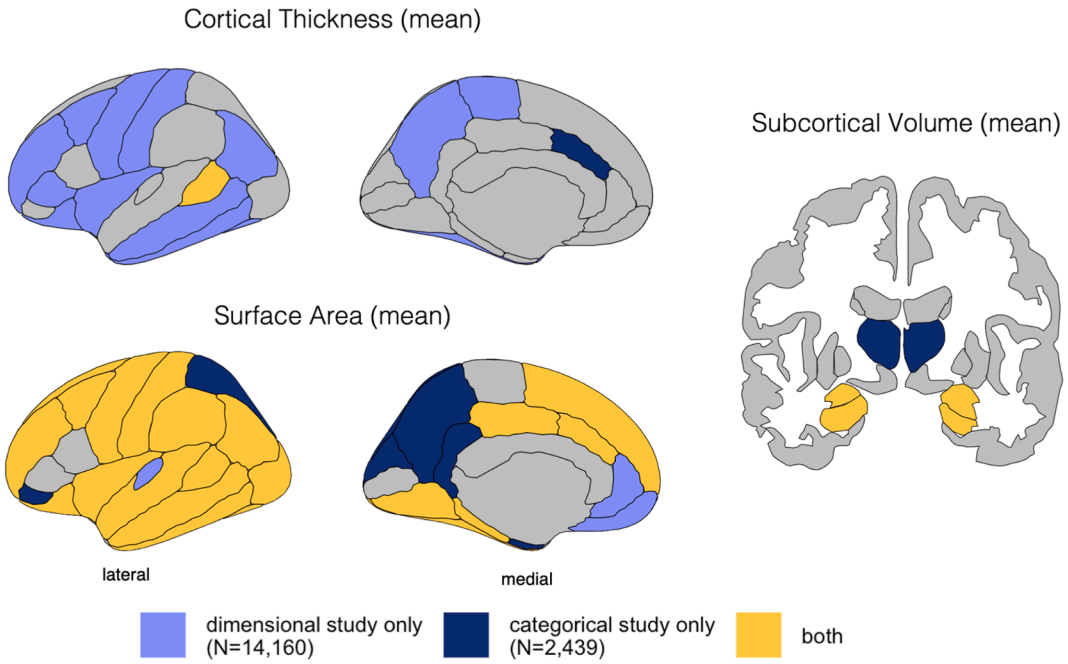
[a]*Sample size (for the main analysis).*

comprehensively assessed associations between dimensionally measured CPs and brain structure. We identified widespread negative associations between CPs and brain structure. These extended beyond our hypothesized regions and included all global brain measures, regional CT and SA across most of the cortex, and 2 subcortical regions. As predicted, CPs were negatively associated with amygdala volume, but an additional association with hippocampal volume was observed. Effect sizes were small, ranging from −0.02 to −0.07 (standardized β), with the largest effect for total SA. These effect sizes are consistent with previous large-scale studies relating psychopathology to brain structure.[18,36,37]

Many associations were rendered nonsignificant when adjusting for IQ, attention/hyperactivity and/or internalizing problems, although associations with SA were more robust across sensitivity analyses. Several associations, particularly for SA in frontoparietal regions, differed by sex: CPs were negatively associated with total and regional SA and TIV in male, but not female, participants. The opposite pattern emerged for CT in parietal regions. Some associations differed by age: there were stronger negative associations between CPs and TIV, total SA, and CT in temporal/parietal regions in younger participants. CU traits moderated associations between CPs and a few outcomes (eg, TIV, total SA), surprisingly reflecting stronger associations at lower levels of CU traits. Lastly, CPs–brain structure associations were not moderated by current CD diagnostic status.

We observed negative associations between CPs and brain structure consistent with neurocognitive models of youth CPs.[5] These included negative associations with amygdala volume and CT and SA in regions such as the orbitofrontal cortex and insula, which are implicated in empathy, reinforcement learning, and decision making.[5] However, the observed associations were not restricted to these regions but spanned most of the cortex. This extends work in the ABCD Study (61% of the current sample), which identified widespread negative associations between CPs and gray matter volume.[18] These findings suggest the involvement of a more diffuse network of regions in CPs than predicted by existing theories.[5] Here, negative associations with CPs extended to frontal, temporal, and parietal regions, with SA associations also observed in occipital and more medial regions (eg, medial orbitofrontal). Thus, CPs were associated with lower CT and SA across both early-developing unimodal regions (eg, somatosensory cortices) involved in sensation, perception, and motor functions and later-developing transmodal association cortices (eg, middle temporal and inferior parietal cortex) implicated in higher-order functions.[38] These widespread associations, including for

FIGURE 2 Regional Overlap Between Dimensional Associations Between Conduct Problems and Brain Structure (Current Study) and Case-Control Differences in Conduct Disorder[9]



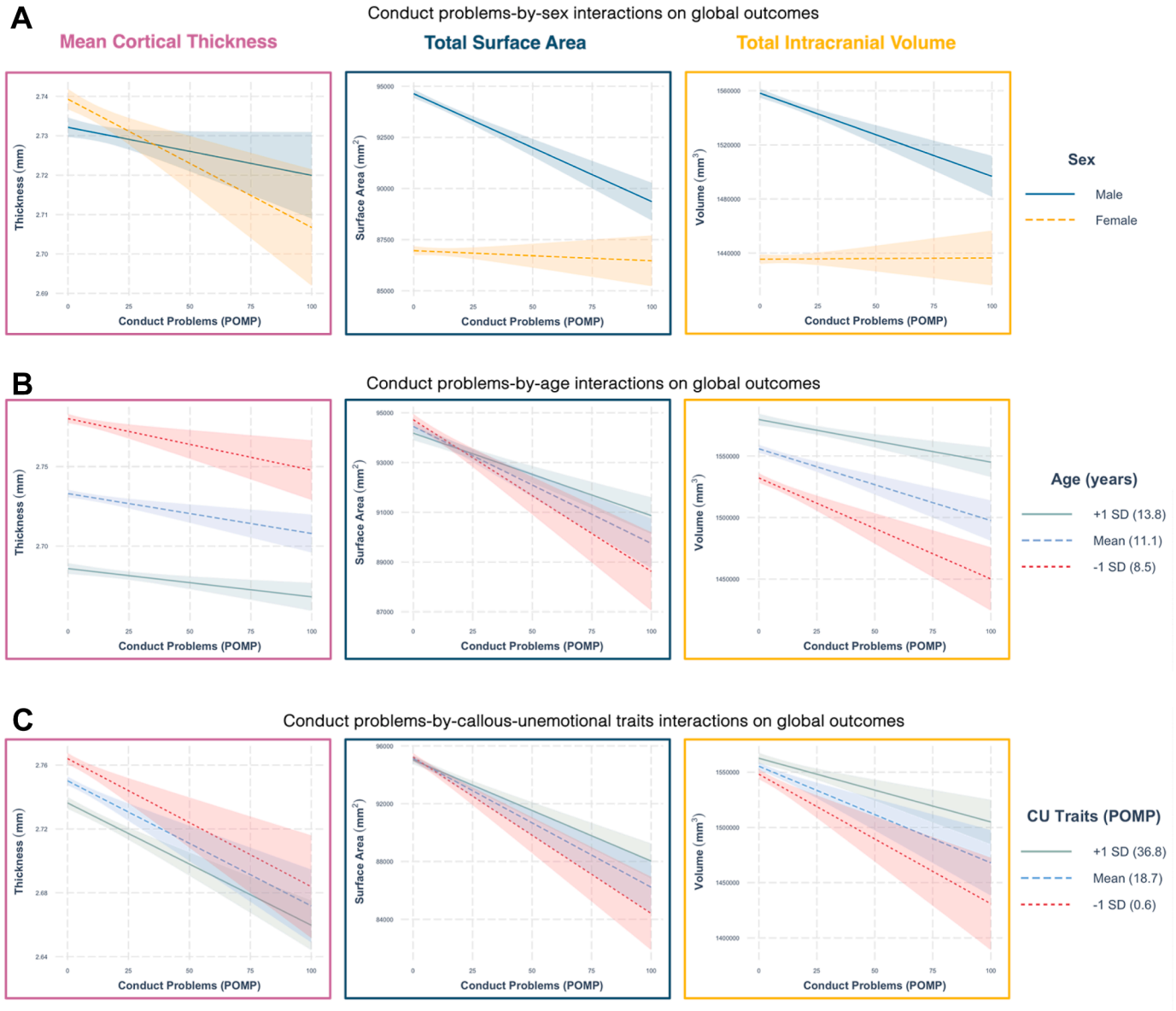
Note: *All depicted effects reflect negative associations between conduct problems and brain structure and lower values in the conduct disorder vs control group except for caudal anterior cingulate cortical thickness, where values were higher in youth with conduct disorder compared with controls. In addition to the differences shown, youth with conduct disorder additionally showed lower nucleus accumbens volume. A total of 1,875 participants were included in both the dimensional and the case-control studies. Brain plots were created with the ggseg R package. Please note color figures are available online.*

total SA, mean CT, and TIV, suggest that variation in global brain structure contributes to the observed patterns.

Interestingly, negative associations with precentral gyrus CT and temporal SA were among the largest effects and robust to most sensitivity (eg, adjusting for co-occurring psychopathology and IQ) and subsample analyses (including exclusion of the ABCD subsample). Although these regions are not highlighted in models of CPs, overlapping alterations, particularly in the superior temporal gyrus, have been reported in youth with CD or CPs,[23,25,26] and a recent meta-analysis identified negative associations between reactive aggression and superior temporal gyrus volume.[39] Owing to its involvement in cognitive and affective theory of mind,[40] altered temporal cortex structure may underlie problems with understanding the feelings of others.[41] Relatedly, in an independent child cohort, aggression was negatively associated with left precentral gyrus CT.[42] Owing to the presence of mirror neurons in the sensorimotor cortices,[43] such alterations may lead to aggression by contributing to difficulties in understanding others' actions.[42] Although this illustrates how the observed alterations may link to CPs, such reverse inferences are speculative and must be interpreted cautiously and in the context of widespread CPs–brain structure associations, implicating most of the cortex rather than specific regions.

Adjusting for factors associated with CPs and CD affected our findings. When simultaneously adjusting for IQ and other psychopathology dimensions, associations with CT were rendered nonsignificant, whereas approximately 50% of SA and volumetric findings were retained. Intelligence and psychopathology are developmentally (negatively) intertwined,[44] and attenuation of psychopathology–brain structure associations when adjusting for IQ or cognitive functioning has been reported.[36] Similarly, diminished effects when adjusting for co-occurring psychopathology are consistent with evidence that general psychopathology—reflecting common variance across psychopathology dimensions—is broadly associated with brain structure, suggesting that many observed associations may be nonspecific/transdiagnostic.[11,18,36] However, CPs-SA associations in temporal regions survived adjustment, indicating potentially CPs-specific neuroanatomical correlates. This fits with findings showing specific CPs–brain volume associations beyond those explained by general psychopathology.[18]

FIGURE 3 Interactions Between Conduct Problems and Sex, Age, and Callous-Unemotional Traits on Global Brain Outcomes



Note: *Plots illustrating interactions between conduct problems and sex (A), age (B), and callous-unemotional traits (C) on mean cortical thickness (left column), total surface area (middle column), and total intracranial volume (right column). All interactions were significant for total surface area and total intracranial volume, but not for mean cortical thickness. Notably, significant conduct problems-by-sex interactions for regional cortical thickness indicated negative associations in female participants and nonsignificant (weaker negative or positive) associations in male participants (ie, the opposite pattern to that observed for surface area and volume, where male participants showed a stronger negative association between conduct problems and brain structure). The shown moderator means (and SDs) are based on the whole sample, but vary slightly between outcomes due to variable missingness. Plots were created with the interactions R package. CU = callous-unemotional; POMP = percent of maximum possible. Please note color figures are available online.*

Overall, our findings suggest that adjusting for neurodevelopmental vulnerabilities commonly associated with CPs and CD (eg, lower IQ, attention/hyperactivity problems) attenuates CPs–brain structure associations, supporting their role in the neurobiology of CPs. Importantly, both adjusted and unadjusted findings provide valuable information: whereas adjustment tells us something about specificity, it may also remove meaningful shared variance, especially as the role of these factors in the (neuro)development of CPs (eg, unidirectional vs bidirectional effects, or shared underlying risk) remains incompletely understood.

We note similarities and differences between our findings and the ENIGMA-ASB case-control study,[9] which compared youth with CD and typically developing controls using a similar approach (Figure 2). Smaller amygdala and hippocampal volume and lower SA across most of the cortex were associated with both categorically measured CD and dimensionally measured CPs. Conversely, here, we found widespread associations between CPs and CT that were not seen in youth with CD, suggesting that dimensional approaches may be more sensitive in detecting psychopathology–brain structure associations. It is possible that youth with CD show CT alterations, but the smaller case-control study was underpowered to detect them. Overall, findings obtained across categorical and dimensional approaches provide evidence that CPs are negatively associated with SA (particularly in temporal regions) and volume in limbic regions. Our dimensional findings extend the case-control findings by illustrating that the observed neural correlates are not limited to those with severe CPs as evidenced by the lack of moderation by CD diagnostic status.

In contrast to previous findings for CD as a categorical construct,[9] sex moderated many associations between CPs and brain structure. For SA (and TIV), we observed negative associations with CPs in male participants, but primarily nonsignificant associations in female participants. The opposite pattern was found for CT in 6 regions. A possible explanation for these differences is that even in the largest existing case-control studies, interaction analyses were underpowered leading to false-negative results, including due to the overrepresentation of male participants with CD (71%).[9] Interestingly, sex did not moderate associations with amygdala and hippocampus volume, and at high levels of CPs, normative sex differences (eg, male > female for SA)[45] appeared diminished or reversed. Although we found evidence that CPs–brain structure associations differ by sex, the pattern of findings does not support the differential threshold hypothesis for CPs/CD. This hypothesis postulates that for disorders that are less common in one sex, such as CD, developing the disorder in that sex requires a higher loading of risk factors, such as more pronounced brain alterations.[46] Contrary to this, we found more (negative) CPs–brain structure associations in boys than in girls and several associations that did not differ by sex. Further research is needed to understand how sex differences in CPs–brain structure associations may contribute to sex differences in the prevalence, presentation, and trajectories of antisocial behavior.[16]

For total SA, TIV, and CT in 5 (mostly temporal) regions, we observed stronger associations with CPs in younger participants. According to the developmental taxonomic theory,[47] childhood-onset (and persistent through the life course) CPs are characterized by a higher burden of risk factors and neurocognitive deficits than adolescence-onset (and limited) CPs. Hence, stronger effects in younger participants may be due to a higher proportion of individuals with childhood-onset CPs among this age group. However, we did not directly investigate age-of-onset effects here. Moreover, stronger associations at younger ages were identified for only a few outcomes. Finally, a recent longitudinal study reported opposite findings, whereby CPs-CT associations were limited to late adolescence/young adulthood,[20] although due to the older age range in that study (≥12 years), effects in childhood could not be examined. Beyond considerations of age of onset, the current findings highlight the importance of considering age/development. However, consistent with the ENIGMA-ASB case-control study,[9] they also indicate that age might be a less important moderator of the brain structural correlates of CPs/CD than attention-deficit/hyperactivity disorder, in which alterations are primarily observed in childhood.[48] Prospective longitudinal imaging studies starting at an early age and modeling (person-centered) developmental trajectories are needed to confirm such conclusions and further understand the role of age of onset in neurodevelopmental risk.

Lastly, we observed stronger negative associations between CPs and TIV, total SA, and inferior temporal, supramarginal, and precentral/postcentral SA at lower (vs higher) levels of CU traits. Similarly, effect sizes of the main findings tended to increase when adjusting for CU traits. Albeit inconsistent with our hypotheses, this fits with a previous study, which found that CPs did not moderate associations between callous traits and global volumetric outcomes,[49] and with prior functional and neurocognitive work, which suggested that some neurocognitive vulnerabilities, such as lower topological network efficiency or sustained attention deficits, may be specific to CPs without elevated CU traits.[50,51] Thus, whereas CPs with CU traits represent a behaviorally and etiologically important subgroup, the current findings do not support stronger CPs–brain structure associations when CU traits are high. Instead, they suggest that the effects of CPs and CU traits on brain structure may not be additive and highlight heterogeneity within CPs, consistent with evidence for varying risk profiles and (neuro)developmental pathways in the etiology of CPs.[16]

Our findings have several implications. First, we found small, but widespread dimensional associations between CPs and brain structure. These associations overlapped with associations observed in youth with CD diagnoses but were not moderated by CD diagnostic status. This implies

that CPs in both the normative and the clinically elevated range are associated with diffuse differences in brain structure, beyond those currently highlighted in neurocognitive models and consistent with dimensional models of psychopathology. Second, the overlap between brain structure alterations in CD[9] and the current dimensional findings suggests that the alterations observed in youth with CD/severe CPs are unlikely to be fully accounted for by CD-associated factors, such as lower IQ or comorbidity. This was further supported by approximately 50% of effects surviving sensitivity analyses (eg, adjusting for IQ or attention/hyperactivity problems). However, many associations were affected by additional covariate adjustment. Consistent with hierarchical models of psychopathology,[11] this highlights the need to assess transdiagnostic effects and for whom (and under what conditions) these associations hold. Third, the consistency between categorical and dimensional findings reinforces that CPs have measurable neurobiological correlates, which may help shift perspectives away from stigmatizing attributions (eg, naughty children, poor parenting) and toward a clinical and developmental understanding of underlying vulnerability. This framing may reduce blame and support engagement with families and services. However, neurobiological explanations must be communicated carefully to avoid deterministic or further stigmatizing interpretations.

Fourth, the observed moderation by sex, particularly the stronger widespread associations for SA in boys, suggest sex-specific neurodevelopmental pathways and that clinical models and potential interventions may need to be sensitive to these sex differences. Finally, effect sizes were small (standardized βs $= -.02$ to $-.07$), consistent with other large-scale neuroimaging studies.[18,36,37,52] Small effect sizes likely partly reflect varying risk factors and mechanisms between individuals, leading to attenuated effects at the group level.[48] Additionally, studies with large samples have generally reported smaller effect sizes compared with previous studies with small samples.[52,53] Based on an investigation of effect sizes for (non-neuroimaging) outcomes in ABCD, Owens *et al.*[53] highlighted the need to recalibrate effect size heuristics for large samples, suggesting categories including below average ($r \sim 0.03$, eg, caffeine consumption–sleep problems), average ($r \sim 0.05$, eg, sleep problems–cognitive ability), and above average ($r \sim 0.09$, eg, psychiatric problems–cognitive ability). Based on these categories, the current associations would be considered below average to average (semi-partial correlations ≤ -0.06). Whereas this illustrates the value of large samples in identifying more robust and accurate correlates of CPs,[52] the small magnitude of effects emphasizes the need to identify how they combine to contribute to CPs using multivariate (eg, machine learning) approaches and assess their potential clinical relevance.[54]

Although this study had several strengths including its unprecedented sample size, inclusion of 18 cohorts from 12 countries/4 continents (including low- and middle-income countries), and standardized preprocessing, we note several limitations. First, combining multiple cohorts introduced heterogeneity at several levels. CPs were assessed using different instruments (CBCL, YSR, SDQ) and informants (self-report, parent-report). Although scores were standardized using POMP, this does not equate measurement properties or construct coverage, and previous evidence suggests differences between measures and informants in psychopathology assessment.[55] As we could not feasibly employ item-level harmonization approaches, sensitivity analyses were performed to explore these issues. For studies that included both SDQ and CBCL/YSR assessments, these measures correlated highly (Supplement 2, available online), as did the effect sizes from the main analyses and those based on raw CBCL/YSR scores (Supplement 6, available online). Additional moderation analyses suggested that whereas measure had a moderate impact on associations, there was only limited evidence that associations differed by informant (Supplement 10, available online). These sensitivity analyses support the validity of our main findings, but highlight informant/measure differences in psychopathology–brain structure associations as an interesting focus of future research, in addition to studies using item-level harmonization methods.[56]

Second, the current study focused on broad CPs to complement categorical studies of CD and provide a dimensional investigation across the full severity range, extending prior work in sample size, global representativeness, outcomes (SA), and moderators (sex, CU traits). However, this approach does not capture heterogeneity within CPs (for exploratory analyses that differentiate rule-breaking and aggression subdomains as one way of examining CP heterogeneity, see Supplement 11, available online). As limited clinical phenotype coverage may constrain our ability to disentangle potentially distinct neurobiological mechanisms, developing and incorporating more comprehensive CP instruments into large-scale neurobiological studies will be important to disaggregate heterogeneous aspects of CPs and capture the full range of symptom severity, including prosocial behaviors (the other end of the antisocial behavior spectrum).

Third, although we examined a range of variables (eg, CU traits), we could not account for other important characteristics (eg, ethnicity, socioeconomic status) due to inconsistent data availability. Acquiring (where possible) and harmonizing such measures will be an important next

step for ENIGMA-ASB, alongside increasing ethnic and racial diversity.[57] Finally, although we made qualitative comparisons to the categorical ENIGMA-ASB study, investigated moderation by clinical diagnosis (finding none), and tested whether the inclusion of nonlinear CP terms improved model fit (it did so only for 2 outcomes; see Supplement 12, available online), we did not perform a formal comparison of dimensional and categorical models (eg, taxometric analyses) as such analyses are better suited for studies focusing on consistent measures and with item-level data.

In conclusion, by analyzing data from 14,160 youths, we identified small but widespread negative associations of CPs with SA, CT, and amygdala and hippocampal volume, which have implications for theoretical models of CPs/CD. These findings are consistent with the extensive brain structural alterations observed in youth with CD, but go beyond these by highlighting that CPs–brain structure associations are not restricted to youth with clinically elevated CPs.

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This article is part of a special series of review and empirical articles devoted to examining dimensional alternatives to categorical diagnostic approaches for improving research insights and clinical practice in the field of child and adolescent neurodevelopmental and neuropsychiatric conditions. This series is edited by Guest Editors Mirko Uljarevic, MD, PhD, Robert Krueger, PhD, Eric Youngstrom, PhD, Andrew Whitehouse, PhD; Associate Editor Robert R. Althoff, MD, PhD; *JAACAP Open* Editor Manpreet K. Singh, MD, MS; and *JAACAP* Editor-in-Chief Douglas K. Novins, MD.

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Data Sharing: Data supporting the findings of this study are not publicly available due to privacy or ethical restrictions but can be requested from the corresponding authors or the ENIGMA-Antisocial Behavior working group (enigma.antisocial@gmail.com). Requested data can only be shared if approved by the working group and the principal investigators of the individual cohorts. Included consortium datasets (eg, ABCD Study, FemNAT-CD, IMAGEN, and cVEDA) have additional data sharing requirements.

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