Cortical structure and subcortical volumes in conduct disorder: a coordinated analysis of 15 international cohorts from the ENIGMA-Antisocial Behavior Working Group

Yidian Gao, Marlene Staginnus*, and the ENIGMA-Antisocial Behavior Working Group†*

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*Contributed equally

†Co-authors are listed at the end of the Article

Centre for Human Brain Health, School of Psychology, University of Birmingham, Birmingham, UK (Y Gao PhD); **Department of Psychology, University of Bath, Bath, UK** (M Staginnus MRes)

Correspondence to: Dr Stephane A De Brito, Centre for Human Brain Health, School of Psychology, University of Birmingham, Birmingham B15 2SA, UK
s.a.debrito@bham.ac.uk

Summary

Background Conduct disorder is associated with the highest burden of any mental disorder in childhood, yet its neurobiology remains unclear. Inconsistent findings limit our understanding of the role of brain structure alterations in conduct disorder. This study aims to identify the most robust and replicable brain structural correlates of conduct disorder.

Methods The ENIGMA-Antisocial Behavior Working Group performed a coordinated analysis of structural MRI data from 15 international cohorts. Eligibility criteria were a mean sample age of 18 years or less, with data available on sex, age, and diagnosis of conduct disorder, and at least ten participants with conduct disorder and ten typically developing participants. 3D T1-weighted MRI brain scans of all participants were pre-processed using ENIGMA-standardised protocols. We assessed group differences in cortical thickness, surface area, and subcortical volumes using general linear models, adjusting for age, sex, and total intracranial volume. Group-by-sex and group-by-age interactions, and DSM-subtype comparisons (childhood-onset *vs* adolescent-onset, and low *vs* high levels of callous-unemotional traits) were investigated. People with lived experience of conduct disorder were not involved in this study.

Findings We collated individual participant data from 1185 young people with conduct disorder (339 [28·6%] female and 846 [71·4%] male) and 1253 typically developing young people (446 [35·6%] female and 807 [64·4%] male), with a mean age of 13·5 years (SD 3·0; range 7–21). Information on race and ethnicity was not available. Relative to typically developing young people, the conduct disorder group had lower surface area in 26 cortical regions and lower total surface area (Cohen's d 0·09–0·26). Cortical thickness differed in the caudal anterior cingulate cortex (d 0·16) and the banks of the superior temporal sulcus (d –0·13). The conduct disorder group also had smaller amygdala (d 0·13), nucleus accumbens (d 0·11), thalamus (d 0·14), and hippocampus (d 0·12) volumes. Most differences remained significant after adjusting for ADHD comorbidity or intelligence quotient. No group-by-sex or group-by-age interactions were detected. Few differences were found between DSM-defined conduct disorder subtypes. However, individuals with high callous-unemotional traits showed more widespread differences compared with controls than those with low callous-unemotional traits.

Interpretation Our findings provide robust evidence of subtle yet widespread brain structural alterations in conduct disorder across subtypes and sexes, mostly in surface area. These findings provide further evidence that brain alterations might contribute to conduct disorder. Greater consideration of this under-recognised disorder is needed in research and clinical practice.

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Introduction

Conduct disorder is characterised by a repetitive and pervasive pattern of aggressive and rule-breaking antisocial behaviour.[1] It is one of the most common childhood psychiatric disorders, with a global prevalence of around 3%.[2] Although conduct disorder is associated with the highest burden of any mental disorder in young people aged 0–14 years[3] and poor psychosocial outcomes,[4] it is one of the least researched psychiatric disorders,[5] and it remains unclear whether conduct disorder is neurodevelopmental.[6] Hence, research focusing on understanding conduct disorder and its neurobiological correlates should be a priority.

Meta-analyses of neuroimaging studies have demonstrated differences between young people with conduct disorder and typically developing young people in terms of neural responses, connectivity patterns, and brain structure across several cortical (eg, ventromedial prefrontal and insular cortices) and subcortical regions (eg, amygdala and striatum) that are crucial for emotion processing and regulation, reinforcement-based decision-making, executive functions, and

Research in context

Evidence before this study

Before undertaking this study, we conducted a comprehensive review of existing meta-analyses on brain structural differences in young people with conduct disorder. We searched PubMed, Web of Science, and Google Scholar, using search terms including "conduct disorder", "conduct problems", "disruptive behaviour disorder", "structural MRI", "brain", and "meta-analysis", for articles, without restrictions on language or article type, published from database inception up to Aug 1, 2022. We found four meta-analyses, the largest of which comprised 394 young people with conduct disorder and 350 typically developing young people from 13 studies. Although these meta-analyses provided insights into the brain structural alterations linked to conduct disorder by pooling published data, limitations remain within the literature. Existing primary studies, including those incorporated in these meta-analyses, included small sample sizes, used heterogeneous methods (eg, in terms of neuroimaging software and analytical approach), and produced inconsistent findings. Furthermore, these studies were often underpowered to investigate clinically important factors, including comorbidity and heterogeneity (such as diagnostic subtypes defined by age of onset and callous-unemotional traits). Additionally, most research focused primarily on male participants, limiting our understanding of female individuals with conduct disorder or sex differences.

Added value of this study

We report findings from, to our knowledge, the largest and best-powered analyses of the brain structural correlates of conduct disorder to date. We provide robust evidence of subtle yet widespread cortical and subcortical alterations in conduct disorder, particularly in cortical surface area, which was reduced in many regions. These findings support existing studies and neurocognitive models of conduct disorder by confirming previously identified alterations, such as lower amygdala volume. We also provide novel evidence that brain alterations in conduct disorder are far more widespread than previously reported or hypothesised, including temporal, occipital, and even motor regions. Our study is one of the first to robustly investigate sex differences and whether the DSM-5-TR subtypes of conduct disorder, categorised by the age of onset and presence of callous-unemotional traits, have distinct brain structural profiles. In contrast to previous small-scale studies, we found no evidence for sex differences, and our results identify only minor differences between DSM-5-TR subtypes, suggesting that conduct disorder is associated with brain structural alterations regardless of subtype.

Implications of all the available evidence

Our finding of widespread alterations in cortical and subcortical structure among young people with conduct disorder, including in regions crucial for emotion processing, regulation, empathy, and decision making, provide further evidence of the neurobiological underpinnings of this disorder. Given that conduct disorder is associated with the highest burden of any psychiatric disorder in children and adolescents, there is a need for a greater focus on conduct disorder in research and practice. Our finding that brain structural alterations are present across sexes and DSM-defined subtypes advocates for a more inclusive approach in research and clinical practice to improve long-term outcomes for affected individuals across diverse populations. Overall, this study provides a clearer picture of the brain structural correlates associated with conduct disorder, which is likely to inform theoretical accounts of this condition and future development of the DSM and ICD.

empathy.[7–10] Although these findings have advanced understanding of conduct disorder, the evidence base has several limitations. First, most primary studies (including those considered in meta-analyses) were based on small sample sizes (mean conduct disorder group size of around n=50), increasing the risk for false-positive and false-negative findings.[11] Second, inconsistent findings and replication failures across primary studies are common, partly due to variations in sample characteristics, image processing, and analysis methods. Third, many studies have not accounted for comorbidity (eg, ADHD) or the heterogeneity of conduct disorder in terms of its age of onset (symptom onset before or after age 10 years) or the presence of high callous-unemotional traits, which are included as subtypes in the DSM-5-TR (the latter as the limited prosocial emotions specifier).[1] Finally, despite evidence for sex differences in clinical presentation and disorder course,[5] most studies of conduct disorder have focused on male participants, and the few studies that recruited mixed-sex samples have been underpowered to test for sex-by-diagnosis interactions.

The Enhancing NeuroImaging Genetics through Meta-Analysis–Antisocial Behavior (ENIGMA-ASB) Working Group was established to address the aforementioned challenges by facilitating global collaboration, harmonisation, and analyses of independently collected samples.[12] This collaboration has resulted in the largest neuroimaging dataset on conduct disorder to date, enabling a coordinated analysis of MRI data across 15 international cohorts. Given their (partly) distinct genetic underpinnings and developmental trajectories,[13] we compared both cortical thickness and surface area, as well as subcortical volumes, between young people with conduct disorder and typically developing young people. We also contrasted conduct disorder subgroups based on age of onset and presence of callous-unemotional traits and examined whether brain structural differences observed in young people with conduct disorder differed by sex or age. Based on previous research, we hypothesised that

For more on **ENIGMA-ASB** see https://enigma.ini.usc.edu/ongoing/enigma-antisocial-behavior

young people with conduct disorder would exhibit lower cortical thickness and surface area in frontotemporal regions[8,14] and lower volume in limbic regions (eg, amygdala)[9] and the striatum.[15] We also predicted that there would be differences in brain structure in frontotemporal regions between childhood-onset and adolescent-onset conduct disorder subgroups,[16] and in striatal-limbic regions between subgroups with high versus low callous-emotional traits.[17,18] We expected that male and female young people with conduct disorder would show both shared[19] and sex-specific differences.[15,20,21] Age effects were investigated on an exploratory basis.

Methods

Study design and sample

The current study pooled individual participant data from 15 international cohorts within ENIGMA–ASB, comprising clinical, forensic, and community-based or population-based samples. The data freeze for this analysis was set for May 31, 2022. Cohort eligibility criteria were a mean sample age of 18 years or less, data available on sex, age, and a diagnosis of conduct disorder, and at least ten participants with conduct disorder and ten typically developing participants (inclusion details and cohort-specific study protocols are shown in the appendix pp 8–32). Each contributing site had obtained ethical approval for their original study and for sharing de-identified data. This study was pre-registered and received ethical approval from the University of Bath's Psychology Research Ethics Committee (19-297/22-148).

See Online for appendix

For more on the **pre-registration of this study** see https://doi.org/10.17605/OSF.IO/V6BDC

Neuroimaging

Individual-level 3D T1-weighted brain MRI data were pre-processed and quality controlled at the individual sites (appendix pp 34–35) or project lead analysis sites (University of Birmingham and University of Bath) following standard ENIGMA imaging protocols, and they were subsequently pooled at the lead sites. MRI data were pre-processed using FreeSurfer (version 5.3 or 6.0),[22] and regions were parcellated based on the Desikan-Killiany and FreeSurfer aseg atlases. We extracted global measures (ie, total intracranial volume [TIV], average cortical thickness, and total surface area), as well as regional outcomes (ie, bilateral cortical thickness and surface area for 34 cortical regions, and volume for seven subcortical regions). Data were visually inspected and statistically evaluated for outliers (greater than 2·69×SD). Only data of sufficient quality were included in the statistical analyses (general pre-processing and quality control methods are described in the appendix pp 32–33; details on cohort-specific imaging methods are shown in the appendix pp 34–35).

For more on **ENIGMA imaging protocols** see http://enigma.ini.usc.edu/protocols/imaging-protocols

Statistical analysis

All statistical analyses were performed in R (version 4.3.1) using a mega-analytical framework[23] by pooling individual participant data from all cohorts (appendix pp 37–38). Site effects were adjusted before analysis using modified ComBat functions as described by Radua and colleagues (appendix pp 37, 51).[24] Mean values across both hemispheres were used for the main analyses. Group differences were examined using general linear models with each global and regional brain measure handled as a separate outcome and diagnosis (conduct disorder *vs* typically developing) as the predictor of interest. All analyses were adjusted for sex and age (in years). The main statistical model for cortical thickness was as follows:

$$ROI_i = intercept + \beta_1(diagnosis) + \beta_2(sex) + \beta_3(age) + \varepsilon_i,$$

in which 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 for:

$$ROI_i = intercept + \beta_1(diagnosis) + \beta_2(sex) + \beta_3(age) + \beta_4(TIV) + \varepsilon_i.$$

Consistent with previous ENIGMA studies,[25] a false discovery rate (FDR) correction with q=0·05 was applied separately to surface area, cortical thickness, and subcortical volumes. Cohen's d was calculated for all group effects based on the t-values from the linear models:[26]

$$d = \frac{t(n_1 + n_2)}{\sqrt{n_1 n_2}\sqrt{df}}.$$

To test the robustness of results, sensitivity analyses were performed adjusting for intelligence quotient (IQ), current comorbidities (ADHD, substance use disorder, depression, and anxiety; binary coded as present or absent), and psychotropic medication use (binary coded as yes or no). A group-by-sex or group-by-age interaction term was included in the general linear models to investigate moderation by sex or age. Differences between childhood-onset versus adolescent-onset conduct disorder subgroups (defined by symptom onset at age <10 years *vs* ≥10 years), and subgroups with low versus high callous-unemotional traits (defined by informant [self-reported or parent-reported], sex, and [for self-report] age-specific normative cutoffs on the Inventory of Callous-Unemotional traits; appendix pp 6–8)[27] were evaluated using ANCOVAs with the aforementioned covariates (sex, age, and TIV). This approach uses the aforementioned linear modelling approach in combination with an ANOVA wrapper to test whether the regression coefficients associated with the three-level group variable are simultaneously zero. FDR-adjusted significant F-tests were followed by pairwise comparisons (uncorrected; Bonferroni-adjusted findings are reported in the appendix pp 56–71). Pairwise

	Total N	Age range, years	Typically developing young people				Young people with conduct disorder				Conduct disorder subgroups			
			n	Female:male distribution	Age in years	IQ	n	Female:male distribution	Age in years	IQ	Childhood onset	Adolescent onset	Low CU traits	High CU traits
ABCD (3.0, baseline)*†	574	9–10	288	82:206	9·51 (0·50)	94·86 (15·24)	286	85:201	9·45 (0·50)	94·61 (16·42)	256	30	..	..
BESD	87	14–19	36	0:36	16·72 (1·32)	97·28 (9·41)	51	0:51	16·41 (1·34)	96·08 (6·41)	..	..	39	12
Boys Town	369	10–19	177	66:111	13·69 (2·43)	109·01 (12·56)	192	67:125	15·27 (1·71)	99·15 (11·79)	..	..	68	120
Cambridge Female	46	14–19	23	23:0	17·04 (0·88)	105·65 (9·34)	23	23:0	16·74 (1·66)	99·55 (8·11)	5	17	11	8
Cambridge Male	90	16–21	26	0:26	18·00 (1·06)	101·19 (9·16)	64	0:64	17·20 (1·10)	98·84 (8·52)	27	37	24	27
CD-Zhou	36	16–18	18	0:18	16·89 (0·32)	..	18	0:18	17·06 (0·54)	..	..	..	..	..
CDKid	39	12–19	18	0:18	15·56 (2·04)	109·39 (13·24)	21	0:21	15·29 (1·52)	100·10 (8·16)	14	7	..	..
CSU-Yao	154	12–17	77	0:77	15·43 (0·70)	108·96 (8·71)	77	0:77	14·55 (1·15)	101·05 (12·94)	5	67	..	..
cVEDA (baseline)*†	40	7–17	20	2:18	13·60 (2·37)	..	20	2:18	13·60 (2·37)	..	..	..	..	..
FemNAT-CD*	635	9–18	379	219:160	14·27 (2·55)	103·70 (11·53)	256	119:137	14·64 (2·16)	95·07 (12·38)	129	107	84	159
IMAGEN (baseline)*†	126	13–15	63	24:39	14·02 (0·46)	..	63	24:39	14·02 (0·46)	..	..	..	..	..
K23	43	12–18	30	25:5	14·73 (1·80)	..	13	4:9	15·54 (1·27)	..	..	..	6	2
MATRICS/ Aggressotype*†	100	7–18	50	7:43	12·78 (2·61)	100·32 (10·92)	50	9:41	13·26 (2·95)	98·68 (10·79)	..	..	22	19
Southampton Family Study	77	13–18	37	6:31	15·97 (1·34)	103·97 (9·82)	40	4:36	16·12 (1·36)	93·30 (11·04)	22	18	21	19
Yale†	22	9–16	11	2:9	11·73 (1·62)	103·27 (14·40)	11	2:9	12·18 (2·27)	102·09 (12·98)	..	..	2	9
Total (15 samples)	2438	7–21	1253	456:797	13·38 (3·01)	102·33 (13·45)	1185	339:846	13·71 (3·01)	96·69 (13·08)	458	283	277	375

The reported values reflect n or mean (SD), unless otherwise indicated. Total N refers to the total number of participants from a specific cohort that were included in the current study. Information on sex and age was available for all participants, whereas IQ, age-of-onset status, and CU traits data were not always available. IQ=intelligence quotient. CU=callous-unemotional. *Multi-site or multi-scanner sample. †Control group matched on age and sex (and IQ, if available) using propensity score matching; inclusion criteria and matching details for each cohort are shown in the appendix (pp 8–32).

Table 1: **Demographic and clinical characteristics of the included cohorts**

results were categorised into three patterns: shared effects (both subgroups differ significantly from typically developing participants); subgroup-specific differences (only one subgroup differs significantly from typically developing participants, but the subgroups do not differ from each other); and subgroup differences (the conduct disorder subgroups differ significantly from each other). The samples that contributed to the sensitivity and subgroup analyses are shown in the appendix (p 36).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

For this coordinated analysis, 15 international cohorts contributed 2438 participants aged 7–21 years (table 1), comprising 1185 participants with conduct disorder (339 [28·6%] female and 846 [71·4%] male, mean age 13·7 years [SD 3·0]) and 1253 typically developing participants (446 [35·6%] female and 807 [64·4%] male, mean age 13·4 years [3·0]). Information on race and ethnicity was not available. Comorbidity rates are shown in table 2.

Adjusting for TIV, the conduct disorder group exhibited widespread alterations in surface area relative to typically developing young people, comprising lower total surface area and lower regional surface area in 26 of the 34 investigated cortical regions, spanning all four lobes of the brain (table 3). Cohen's *d* for significant surface area differences ranged from –0·09 to –0·26, with the largest effects observed in inferior parietal cortex (Cohen's *d* –0·26 [95% CI –0·34 to –0·18]) and total surface area (*d* –0·24 [–0·32 to –0·16]; table 3, figure 1; full results including non-significant outcomes are shown in the appendix pp 39–42). Additionally, young people with conduct disorder showed greater cortical thickness in the caudal anterior cingulate cortex (Cohen's *d* 0·16 [0·08 to 0·24]) and lower cortical thickness in the banks of the superior temporal sulcus (*d* –0·13 [–0·22 to –0·05]) compared with typically developing young people (table 3). Lastly, the conduct disorder group showed lower volume in the thalamus (*d* 0·14 [–0·22 to –0·06]), amygdala (*d* 0·13 [–0·21 to –0·05]), hippocampus (*d* 0·12 [–0·20 to –0·04]), and nucleus

	Number of cohorts*	Typically developing young people, n (%)	Young people with conduct disorder, n (%)
ADHD	14	..	..
Yes	..	0	463 (39·6%)
No	..	1231 (98·2%)	684 (57·7%)
Missing	..	22 (1·8%)	38 (3·2%)
Substance use disorder	7	..	..
Yes	..	0	51 (4·4%)
No	..	831 (66·3%)	641 (54·1%)
Missing	..	422 (33·7%)	493 (42·1%)
Depression†	10	..	..
Yes	..	2 (0·2%)	89 (7·6%)
No	..	1080 (86·2%)	869 (73·3%)
Missing	..	171 (13·6%)	227 (19·4%)
Anxiety‡	10	..	..
Yes	..	24 (1·9%)	173 (14·8%)
No	..	1058 (84·4%)	785 (66·2%)
Missing	..	171 (13·6%)	227 (19·4%)
Total	15	1253 (100%)	1185 (100%)

Cohorts differed in which disorders were diagnosed, and whether current or lifetime diagnoses (or both) were assessed; thus, this table is not exhaustive and focuses on the most common comorbidity categories available across sites. *Number of cohorts for which current diagnostic information for the specific comorbidity was available. †Depression comprises major depressive disorder and dysthymia. ‡Anxiety reflects a heterogeneous combination of different anxiety disorders (as provided by the contributing sites).

Table 2: **Rates of current comorbidities in the pooled sample**

accumbens (d 0·11 [–0·19 to –0·03]; table 3), but not in TIV (d –0.08 [–0·16 to 0·00]).

Most findings remained significant after adjusting for IQ, current comorbidities, and psychotropic medication use (table 3, appendix pp 42–46). Of note, group differences in cortical thickness, 22 of 27 differences in surface area, and three of four subcortical differences were robust to adjusting for co-occurring ADHD, which was the most frequent comorbidity (table 2). We did not detect any significant group-by-sex or group-by-age interactions for any global or regional outcome (appendix pp 52–55).

For the age-of-onset subgroups, the childhood-onset conduct disorder group showed greater cortical thickness in the caudal anterior cingulate cortex compared with the adolescent-onset conduct disorder and typically developing groups, indicative of subgroup differences (see Methods for definitions), but there were no other subgroup effects for cortical thickness (figure 2, appendix pp 56–63). We observed shared effects for surface area in nine regions (eg, inferior parietal cortex, lateral orbitofrontal cortex, and superior temporal gyrus) and for total surface area, for which both adolescent-onset and childhood-onset conduct disorder subgroups had lower surface area than typically developing young people. Non-shared, subgroup-specific differences were observed for parahippocampal gyrus (childhood-onset conduct disorder lower than typically developing), pars orbitalis, and entorhinal cortex surface area (adolescent-onset conduct disorder lower than typically developing). Four regions, including the insula, showed subgroup differences, whereby the adolescent-onset conduct disorder subgroup had lower surface area compared with childhood-onset conduct disorder and typically developing groups. Three subcortical regions showed a significant group effect, including a subgroup-specific reduction in amygdala volume (adolescent-onset conduct disorder lower than typically developing group) and subgroup differences in caudate (childhood-onset conduct disorder lower than adolescent-onset conduct disorder and typically developing groups) and hippocampal volume (adolescent-onset conduct disorder lower than childhood-onset conduct disorder and typically developing groups).

When the conduct disorder group was subdivided based on callous-unemotional traits, significant group effects on surface area were detected in 24 regions (figure 2, appendix pp 64–71). Pairwise comparisons showed significant subgroup differences, whereby the subgroup with high callous-unemotional traits had lower surface area in the superior temporal and superior frontal gyri than the subgroup with low callous-unemotional traits and the typically developing group. There were also shared effects (ie, both the high and low callous-unemotional traits subgroups were lower than the typically developing group) on surface area in nine regions (eg, inferior parietal cortex, lateral orbitofrontal cortex, and superior temporal gyrus) and on total surface area. Additionally, subgroup-specific differences were observed in both cortical and subcortical regions; when compared with the typically developing group, only the subgroup with high callous-unemotional traits showed lower surface area in ten cortical regions (eg, insula) and lower amygdala and hippocampus volume, whereas lower precentral and postcentral surface area and lower nucleus accumbens and thalamus volume were specific to the subgroup with low callous-unemotional traits.

To assess the robustness of findings, we performed leave-one-out analyses whereby we iteratively repeated the main analysis of conduct disorder versus typically developing, excluding one cohort at a time. Most findings were replicated across all analyses, including differences in cortical thickness, lower volume in the amygdala and thalamus, and lower surface area in 18 regions and total surface area. When effects were rendered non-significant, this occurred when excluding one of the largest samples (FemNAT-CD or Boys Town) and for the smallest group differences, reflecting reduced statistical power (appendix pp 72–75).

We conducted a supplementary analysis to explore whether brain differences observed in young people with conduct disorder would generalise to young people with elevated conduct problems—a combination of sub-threshold and undiagnosed conduct disorder. To this end, we compared 1198 young people with elevated

	Typically developing young people, n	Young people with conduct disorder, n	Cohen's *d* (95% CI)	t	p value	p value with FDR correction	Robust to sensitivity analysis*					
							IQ	ADHD	SUD	Depression	Anxiety	Medication
Cortical thickness												
Caudal anterior cingulate cortex	1227	1159	0·16 (0·08 to 0·24)	3·90	0·0001	0·0034	Yes	Yes	Yes	Yes	Yes	No
Banks of the superior temporal sulcus	1227	1161	−0·13 (−0·22 to −0·05)	−3·29	0·0010	0·0178	Yes	Yes	Yes	No	No	Yes
Surface area												
Inferior parietal cortex	1208	1159	−0·26 (−0·34 to −0·18)	−6·24	<0·0001	<0·0001	Yes	Yes	Yes	Yes	Yes	Yes
Total surface area	1234	1170	−0·24 (−0·32 to −0·16)	−5·95	<0·0001	<0·0001	Yes	Yes	Yes	Yes	Yes	Yes
Middle temporal gyrus	1211	1152	−0·22 (−0·30 to −0·14)	−5·35	<0·0001	<0·0001	Yes	Yes	Yes	Yes	Yes	Yes
Frontal pole	1228	1158	−0·20 (−0·28 to −0·12)	−4·89	<0·0001	<0·0001	Yes	Yes	Yes	Yes	Yes	Yes
Inferior temporal gyrus	1198	1132	−0·20 (−0·28 to −0·12)	−4·83	<0·0001	<0·0001	Yes	Yes	Yes	Yes	Yes	Yes
Superior frontal gyrus	1219	1153	−0·19 (−0·27 to −0·11)	−4·55	<0·0001	<0·0001	Yes	Yes	Yes	Yes	Yes	Yes
Superior temporal gyrus	1189	1138	−0·17 (−0·25 to −0·09)	−4·07	<0·0001	0·0002	Yes	Yes	Yes	Yes	Yes	Yes
Fusiform gyrus	1214	1157	−0·17 (−0·25 to −0·08)	−4·03	0·0001	0·0003	Yes	Yes	No	Yes	Yes	Yes
Postcentral gyrus	1185	1136	−0·16 (−0·24 to −0·08)	−3·85	0·0001	0·0004	Yes	Yes	Yes	Yes	Yes	Yes
Parahippocampal gyrus	1233	1170	−0·16 (−0·24 to −0·08)	−3·89	0·0001	0·0004	Yes	Yes	Yes	Yes	Yes	Yes
Precentral gyrus	1202	1144	−0·16 (−0·24 to −0·08)	−3·79	0·0002	0·0005	No	Yes	Yes	Yes	Yes	Yes
Lateral orbitofrontal cortex	1230	1161	−0·15 (−0·23 to −0·07)	−3·75	0·0002	0·0005	Yes	Yes	No	Yes	Yes	Yes
Precuneus cortex	1235	1167	−0·15 (−0·23 to −0·07)	−3·62	0·0003	0·0008	Yes	Yes	Yes	Yes	Yes	Yes
Caudal middle frontal gyrus	1225	1156	−0·14 (−0·22 to −0·06)	−3·41	0·0007	0·0016	Yes	Yes	Yes	Yes	Yes	Yes
Isthmus-cingulate cortex	1234	1165	−0·14 (−0·22 to −0·06)	−3·34	0·0008	0·0020	Yes	Yes	Yes	Yes	Yes	Yes
Insula	1191	1148	−0·13 (−0·22 to −0·05)	−3·26	0·0011	0·0024	Yes	Yes	No	Yes	Yes	Yes
Rostral middle frontal gyrus	1227	1152	−0·13 (−0·22 to −0·05)	−3·28	0·0011	0·0023	Yes	Yes	No	Yes	Yes	Yes
Supramarginal gyrus	1196	1146	−0·13 (−0·21 to −0·05)	−3·11	0·0019	0·0037	Yes	Yes	Yes	Yes	Yes	Yes
Banks of the superior temporal sulcus	1227	1162	−0·12 (−0·20 to −0·04)	−2·98	0·0029	0·0053	Yes	Yes	No	Yes	Yes	Yes
Entorhinal cortex	1201	1143	−0·12 (−0·20 to −0·04)	−2·88	0·0040	0·0067	Yes	No	Yes	Yes	Yes	Yes
Caudal anterior cingulate cortex	1227	1160	−0·12 (−0·20 to −0·04)	−2·89	0·0039	0·0067	Yes	Yes	Yes	Yes	Yes	Yes
Lateral occipital cortex	1210	1150	−0·12 (−0·20 to −0·03)	−2·79	0·0053	0·0085	No	No	No	No	No	Yes
Pars orbitalis	1233	1168	−0·11 (−0·19 to −0·03)	−2·70	0·0071	0·0107	No	Yes	No	No	No	No
Lingual gyrus	1218	1160	−0·10 (−0·18 to −0·02)	−2·44	0·0148	0·0216	No	No	No	Yes	Yes	Yes
Superior parietal cortex	1199	1148	−0·09 (−0·17 to −0·01)	−2·26	0·0239	0·0335	No	Yes	No	No	Yes	Yes
Cuneus cortex	1209	1149	−0·09 (−0·17 to −0·01)	−2·24	0·0254	0·0337	No	No	No	No	No	Yes
Posterior-cingulate cortex	1233	1167	−0·09 (−0·17 to −0·01)	−2·23	0·0260	0·0337	No	No	Yes	Yes	Yes	No
Subcortical volume												
Thalamus	1228	1156	−0·14 (−0·22 to −0·06)	−3·33	0·0009	0·0055	Yes	Yes	No	Yes	Yes	Yes
Amygdala	1233	1173	−0·13 (−0·21 to −0·05)	−3·21	0·0014	0·0055	Yes	Yes	Yes	Yes	Yes	Yes
Hippocampus	1248	1180	−0·12 (−0·20 to −0·04)	−2·96	0·0031	0·0082	No	No	Yes	Yes	Yes	Yes
Nucleus accumbens	1249	1180	−0·11 (−0·19 to −0·03)	−2·80	0·0052	0·0103	No	Yes	No	Yes	Yes	Yes

Regions are ordered by absolute effect size (Cohen's *d*). Statistical models included group, sex, age, and total intracranial volume (for regional surface area and subcortical volumes). All depicted effects are significant after FDR correction. All differences reflect lower values in the conduct disorder group compared with the typically developing group, except for the caudal anterior cingulate cortex, for which the conduct disorder group had higher cortical thickness. Full results, including non-significant outcomes, are shown in the appendix pp 39–42. FDR=false discovery rate. IQ=intelligence quotient. SUD=substance use disorder. *Sensitivity analysis columns indicate whether effects remained significant after adjustment for each variable after FDR correction; of note, the variables considered in the sensitivity analyses were added one at a time into the statistical model; comorbidities are included in the statistical models based on current diagnoses; sample sizes for the sensitivity analyses ranged from around 98% (for ADHD) to around 59% (for SUD) of the original sample size (appendix p 36).

Table 3: **Significant differences in cortical thickness, surface area, and subcortical volumes between young people with conduct disorder and typically developing young people**

conduct problems (non-overlapping with the conduct disorder group) and 1177 controls (details including methodological approach are provided in the appendix pp 76–77). The conduct problems group showed lower TIV and lower superior temporal gyrus surface area. Additional differences, similar to those observed in conduct disorder, were identified before multiple comparison correction, including lower total and insular

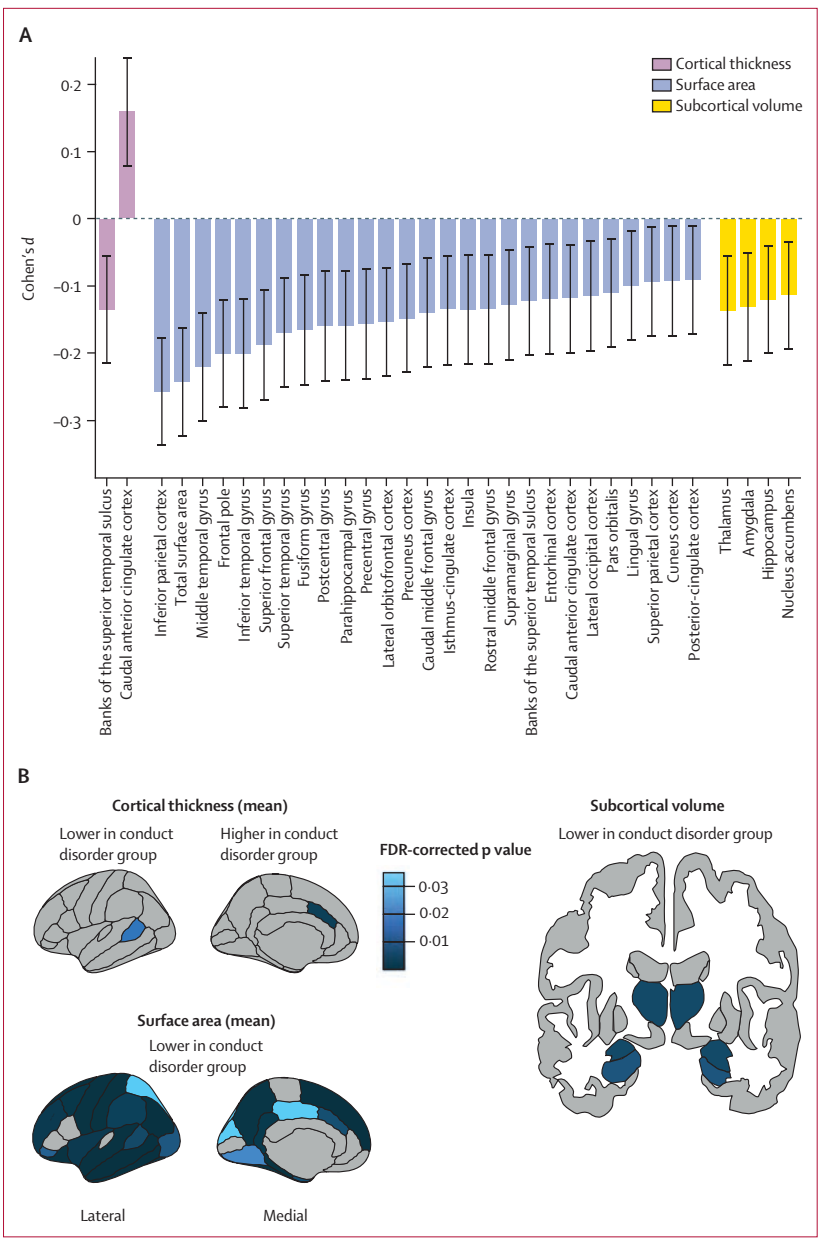

Figure 1: **Cortical and subcortical structural differences between young people with conduct disorder (n=1185) and typically developing young people (n=1253)**

(A) Effect sizes (Cohen's *d*) for FDR-corrected group differences in cortical thickness, surface area, and subcortical volumes when controlling for sex and age (and total intracranial volume where appropriate). Positive effect sizes indicate higher values in the conduct disorder group, whereas negative effect sizes indicate lower values in the conduct disorder group. Error bars represent 95% CIs. (B) Regional brain plots depicting regions with significant group differences and FDR-corrected p values. Additional differences that are not visible included lower total surface area (p_{FDR}<0·0001), frontal pole surface area (p_{FDR}<0·0001), and nucleus accumbens volume (p_{FDR}=0·010) in the conduct disorder group versus the typically developing group. FDR=false discovery rate.

surface area and lower amygdala volume (discussed further in the appendix pp 77–78).

Discussion

The current study included individual-level participant data from 1185 young people with conduct disorder, making our sample ten-times larger than the largest previous study. Combining data from 15 international cohorts enabled us to include a wide age range (7–21 years) and a diverse sample, including young people from low-income and middle-income countries. By adopting ENIGMA's harmonised protocols to minimise site-related variations, we were able to perform highly powered analyses and to identify robust neuroanatomical alterations in conduct disorder, which are more likely to generalise to other populations. We identified subtle but widespread cortical and subcortical brain structural alterations in young people with conduct disorder. Compared with typically developing young people, those with conduct disorder had lower surface area across all four cerebral lobes, with the largest effects observed in the inferior parietal cortex and for total surface area. Differences in cortical thickness were limited to the banks of the superior temporal sulcus and caudal anterior cingulate cortex, the latter being the only outcome that was increased in conduct disorder. As hypothesised, young people with conduct disorder had lower volume in limbic (amygdala and hippocampus) and striatal (nucleus accumbens) regions, as well as lower thalamus volume. Most group differences survived adjustment for comorbidity (including ADHD), psychotropic medication use, and IQ, with no significant moderation by sex and age. Regarding DSM subtypes, the childhood-onset and adolescent-onset subgroups differed from each other in seven outcomes, mostly indicating lower values (eg, insula surface area) in the latter subgroup. However, both age-of-onset subgroups showed shared reductions in surface area in multiple regions compared with controls. Direct comparison of subgroups with low versus high callous-unemotional traits revealed minimal differences, but the subgroup with high callous-unemotional traits exhibited more extensive case-control differences, including in the amygdala. Nonetheless, the callous-unemotional traits subgroups also showed several shared differences in total and regional surface area compared with controls, and some alterations were specific to the subgroup with low callous-unemotional traits. These novel findings shed light on putative brain differences in regions that are critical for emotion processing and regulation, empathy, decision making, and cognitive control associated with conduct disorder, and suggest that young people with conduct disorder and high callous-unemotional traits show the most extensive brain structural alterations compared with controls.

Our findings broadly align with the results of three existing meta-analyses of voxel-based morphometry studies on young people with conduct disorder or conduct problems, documenting lower grey matter volume across various cortical and subcortical regions (eg, superior frontal gyrus, insula, and amygdala).[8–10] However, in contrast to previous smaller-scale surface-based morphometry studies, many of which reported

lower cortical thickness,[14] we primarily found that young people with conduct disorder showed widespread reductions in surface area across 26 of the 34 regions investigated. These alterations extended beyond hypothesised differences, or the regions implicated in established neurocognitive models of conduct disorder (ie, amygdala, striatum, and ventromedial prefrontal cortex).[17] Given that previous primary studies either did not investigate surface area or yielded inconsistent results for this metric, our findings highlight the value of the high-powered and standardised ENIGMA approach in identifying reliable and robust alterations. The predominance of surface area differences also echoes findings from other ENIGMA studies that have analysed data from children and young people.[12,25] Cortical thickness and surface area are underpinned by different cellular processes; cortical thickness is associated with vertical (radial) and surface area with horizontal (tangential) neuronal migration.[28] They are also influenced by distinct genetic factors, follow different trajectories over the lifespan (eg, cortical thickness peaks at 1·7 years and surface area peaks at around 11–12 years), and are differentially associated with cognitive abilities and disorders.[13] Our findings suggest that neurodevelopmental processes associated with surface area might be more affected in conduct disorder compared with those involved in cortical thickness, but they also highlight the need for longitudinal studies to investigate neurodevelopmental trajectories in this disorder.

Our findings overlap with those of ENIGMA–ADHD, which also reported similar widespread reductions in surface area and subcortical volumes.[25] Although most of our findings remained significant after controlling for ADHD, suggesting they are not solely driven by ADHD comorbidity, this overlap might indicate that some structural alterations are transdiagnostic markers of (externalising) psychopathology rather than specific to conduct disorder. Previous dimensional research supports that some neural correlates are associated with a general psychopathology factor in young people, but that conduct problems and ADHD symptoms show independent associations with lower volume beyond those explained by general psychopathology.[29] Future studies directly comparing conduct disorder and ADHD, or conduct disorder with and without ADHD comorbidity, are needed to explore the specificity of these findings.

We did not observe any group-by-sex interactions. This finding contrasts with smaller-scale studies that reported sex-specific effects of conduct disorder in the insula, superior frontal gyrus, and supramarginal gyrus.[15,20,21] However, a large-scale study based on the ABCD sample also reported that sex did not moderate associations between disruptive behaviour disorders (including oppositional defiant disorder and conduct disorder) and volumetric alterations in young people.[19] Similarly, sex differences were not observed in the brain structural correlates of ADHD.[25] Despite sex differences in clinical presentation, prevalence, and age of onset, our findings suggest that the structural brain correlates of conduct disorder do not differ between the sexes, aligning with heritability studies indicating that the aetiology of conduct disorder is shared across male and female individuals.[30] These findings require further exploration using multivariate, data-driven approaches, which might be more powerful in identifying potential sex differences.[12] Moreover, despite the large sample size, fewer female than male participants were included, with implications for the statistical power of the interaction analyses. This highlights the need to include more female participants in future studies of conduct disorder.

The group effects did not seem to be moderated by age. Although we acknowledge that studies adopting longitudinal designs and methods that are more sensitive to detecting (non-linear) age effects (eg, normative modelling or ComBat-GAM for site harmonisation) are

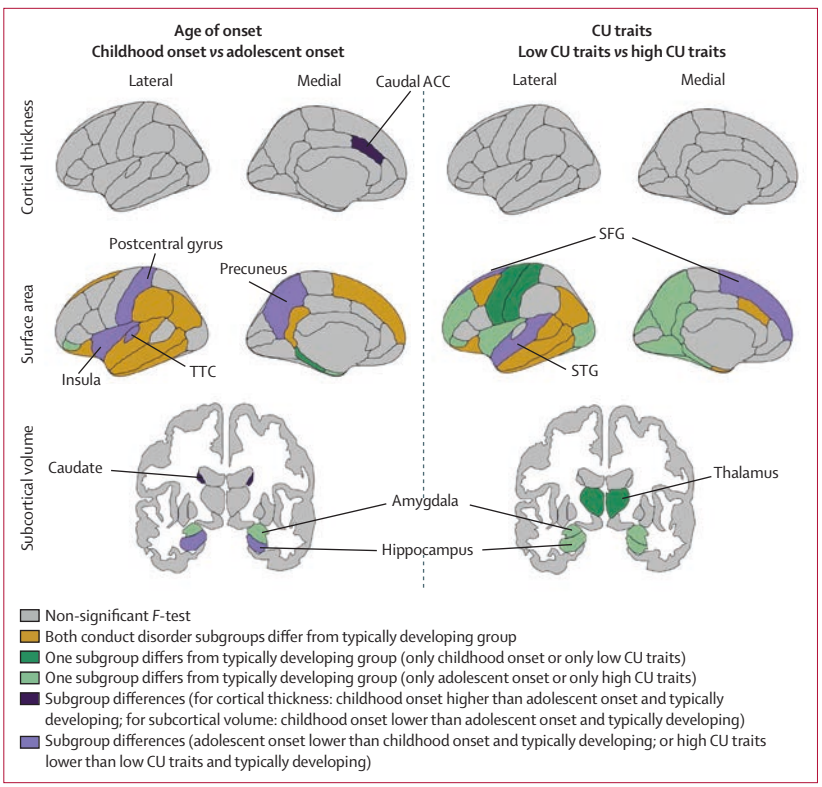

***Figure 2*: Differences in cortical structure and subcortical volumes based on childhood onset *vs* adolescent onset of conduct disorder and low *vs* high levels of callous-unemotional traits**

Significant pairwise comparisons in regions that showed a significant (FDR-corrected) *F*-test for the subgroup comparisons (subgroup 1 *vs* subgroup 2 *vs* typically developing group). All effects shown indicate lower values in the conduct disorder subgroups *vs* typically developing young people or between one specific conduct disorder subgroup and the other. The only exception is the age-of-onset effect for cortical thickness in the caudal anterior cingulate cortex, which was greater in the childhood-onset conduct disorder subgroup than in both the adolescent-onset subgroup and the typically developing group. Additional differences that are not visible included shared effects on total and frontal pole surface area in both age-of-onset and both CU traits subgroups (lower in conduct disorder subgroups than in the typically developing group) and CU subgroup differences in nucleus accumbens volume (lower in the low CU traits subgroup than in the high CU traits subgroup and the typically developing group). ACC=anterior cingulate cortex. CU=callous-unemotional. FDR=false discovery rate. SFG=superior frontal gyrus. STG=superior temporal gyrus. TTC=transverse temporal cortex.

needed, these cross-sectional results suggest that age might play a less important role in brain alterations in conduct disorder than in other disorders such as ADHD, where brain alterations are most pronounced in childhood.[25]

The developmental taxonomic theory of antisocial behaviour posits distinct brain structural associations as a function of age of onset.[16] Whereas childhood-onset antisocial behaviour is assumed to be associated with neurodevelopmental alterations, adolescent-onset (and adolescent-limited) antisocial behaviour is considered to have an environmental aetiology, indicating differences in underlying mechanisms.[16] However, the current study found evidence for similar brain structural alterations in childhood-onset and adolescent-onset conduct disorder subgroups compared with typically developing young people, including lower total surface area and lower surface area across frontal, temporal, and parietal regions. We also identified regions for which only one subgroup differed from typically developing young people (eg, only the adolescent-onset conduct disorder group showed lower amygdala volume), as well as seven differences between the subgroups. However, inconsistent with the developmental taxonomic theory, these mostly indicated lower values in the adolescent-onset conduct disorder subgroup (ie, lower values in adolescent-onset conduct disorder than childhood-onset conduct disorder and the typically developing group). Our results align with several previous studies that found few differences in grey matter volume[31] or cortical structure[21] between age-of-onset subgroups. Our finding that most brain alterations were present in both age-of-onset subgroups challenges the notion of a clear dichotomy between these subgroups in neurobiology, as previously proposed.[16] Of note, a study on adults with life-course-persistent antisocial behaviour (akin to childhood-onset conduct disorder but assessed longitudinally) found that this group showed more extensive surface area alterations than those with adolescent-limited antisocial behaviour.[32] This finding suggests that age-of-onset effects might become more pronounced with age or due to lifestyle factors such as substance use.[33] Alternatively, such discrepancies could reflect the limitations of assessing age-of-onset retrospectively in cross-sectional studies.

Previous studies have not yielded consistent findings regarding differences in brain structure between subgroups with high or low callous-unemotional traits.[18,19,34] Inconsistencies could be due to variations in subgrouping strategies, because previous studies mostly used sample-specific cutoffs (ie, median splits). We used recently validated normative cutoffs for the Inventory of Callous-Unemotional Traits questionnaire, which can be applied consistently across studies.[27] Compared with previous findings, we observed few differences when directly comparing the callous-unemotional traits subgroups. However, overall, our findings suggest that young people with conduct disorder and high levels of callous-unemotional traits (similar to the Limited Prosocial Emotions specifier in DSM-5-TR) might show more pronounced brain structural alterations in regions associated with emotion processing and empathy (eg, amygdala or insula) compared with controls.[8] Nevertheless, the subgroup with low levels of callous-unemotional traits also showed extensive and partly overlapping reductions in surface area. Therefore, our results demonstrated widespread brain alterations in both high and low callous-unemotional traits subgroups while indicating additional neurobiological alterations in a subgroup that resembles the DSM limited prosocial emotions subtype.

Taken together, our findings provide novel and robust evidence of small but widespread brain alterations in young people with conduct disorder. Alterations extend beyond the regions included in neurocognitive models of conduct disorder and appear independent of group differences in IQ, medication use, or other comorbidities, including ADHD. Despite being the psychiatric condition associated with the highest burden in 0–14-year-olds and predicting poor outcomes in adulthood,[3] conduct disorder is one of the least recognised and studied psychiatric disorders and often remains untreated even though evidence-based interventions are available.[5] Our findings of robust brain alterations in conduct disorder—similar to those in more widely recognised and widely treated disorders such as ADHD—emphasise the need for a greater focus on conduct disorder in research, treatment, and public policy. In contrast to ADHD, conduct disorder is not currently classified as a neurodevelopmental disorder. Given this overlap in brain alterations and that conduct disorder shows characteristics of other neurodevelopmental disorders (eg, significant genetic basis and neurocognitive impairments),[6] research is needed on the neurodevelopmental processes underlying conduct disorder and to understand both the origin and the impact of the widespread surface area alterations observed here. Their associations with risk factors, clinical symptoms, (neuro)cognitive impairment, and the impact of psychological and pharmacological treatments should be systematically investigated.

It is important to acknowledge the small effect sizes in the current study (Cohen's $d \leq 0 \cdot 26$). Similar to what has been argued for ADHD,[25] such small effects might reflect small brain differences across young people with conduct disorder, yet could still be impactful in the clinical context considering the large affected population,[35] or they could reflect that specific patient subgroups show larger alterations that are obscured or reduced in size in heterogeneous samples and result in increased within-group versus between-group variation. The current study considered clinically relevant DSM-defined conduct disorder subgroups based on age of onset and callous-unemotional traits. Our findings suggest that although some differences between diagnostic subtypes exist, they might not map onto

distinct neuroanatomical profiles. Similarly, no sex differences were observed. Therefore, future research is needed to expand on the current findings by exploring additional clinical or theory-driven subtypes (eg, conduct disorder with *vs* without comorbidity,[14] or conduct disorder with *vs* without maltreatment history), as well as data-driven approaches such as machine learning and normative modelling, which could identify more homogeneous subgroups.[36] Another interesting question for future research is whether brain structural alterations associated with conduct disorder are more pronounced in clinical or forensic samples than community samples.

This study has several limitations. First, the analyses were cross-sectional, precluding conclusions regarding whether alterations are causally related to conduct disorder or reflect the consequences of living with (or factors related to) conduct disorder. Second, in common with most previous studies, our assessment of age of onset was largely based on retrospective reports, which are subject to recall bias and measurement error. Third, although combining cohorts has many advantages, differences between cohorts (eg, MRI acquisition protocols, diagnostic assessment, recruitment procedures) introduce heterogeneity that cannot be entirely accounted for through standardised pre-processing or adjusting for site effects. Although this heterogeneity might affect the validity of the current findings, leave-one-out analyses supported the robustness of our results. Fourth, although adherence to ENIGMA quality control processes ensured the exclusion of poorly segmented regions, we did not statistically control for image quality and were unable to assess the effect of head motion on our findings. Fifth, the availability of variables differed across cohorts, resulting in smaller samples for subgroup analyses and lower statistical power. Sixth, although we controlled for a range of comorbidities and variables (IQ and medication), the potential for residual confounding remains because we were unable to account for variables such as psychological treatment history, pubertal stage, and socioeconomic status. Seventh, information on race and ethnicity was not available for all cohorts and could therefore not be systematically considered. Finally, there was no involvement of people with lived experience of conduct disorder in this study.

To conclude, our findings provide robust evidence of subtle but widespread brain structural alterations in young people with conduct disorder, across DSM subtypes and sexes, particularly in surface area. These findings provide further evidence that brain alterations could contribute to conduct disorder. This under-recognised disorder warrants greater consideration in research, including longitudinal studies exploring neurodevelopmental trajectories and additional sub-typing approaches.

The ENIGMA-Antisocial Behavior Working Group
Yidian Gao* (University of Birmingham, Birmingham, UK), Marlene Staginnus* (University of Bath, Bath, UK), Sophie Townend (University of Bath, Bath, UK), Celso Arango (Universidad Complutense, Madrid, Spain), Sahil Bajaj (The University of Texas MD Anderson Cancer Center, Houston, TX, USA), Tobias Banaschewski (Heidelberg University, Mannheim, Germany), Edward D Barker (King's College London, London, UK), Vivek Benegal (National Institute of Mental Health and Neurosciences, Bengaluru, India), Kathryn Berluti (Georgetown University, Washington DC, USA), Anka Bernhard (Goethe University, Frankfurt am Main, Germany), Robert J R Blair (University of Copenhagen, Copenhagen, Denmark), Charlotte P S Boateng (Leiden University Medical Center, Leiden, The Netherlands), Arun L W Bokde (Trinity College Dublin, Dublin, Ireland), Daniel Brandeis (University of Zurich, Zurich, Switzerland), Jan K Buitelaar (Radboud University Medical Center, Nijmegen, Netherlands), S Alexandra Burt (Michigan State University, East Lansing, MI, USA), Elise M Cardinale (The Catholic University of America, Washington DC, USA), Josefina Castro-Fornieles (University of Barcelona, Barcelona, Spain), Hui Chen (Central South University, Changsha, China), Xianliang Chen (Central South University, Changsha, China), Sally C Chester (University of Birmingham, Birmingham, UK), Olivier F Colins (Ghent University, Gent, Belgium), Harriet Cornwell (University of Bath, Bath, UK), Michael Craig (King's College London, London, UK), Ana I Cubillo (University of Basel, Basel, Switzerland), Sylvane Desrivieres (King's College London, London, UK), Dana E Díaz (University of California, Riverside, Riverside, CA, USA), Andrea Dietrich (University of Groningen, Groningen, Netherlands), Daifeng Dong (Central South University, Changsha, China), Anouk H Dykstra (Radboud University Medical Center, Nijmegen, Netherlands), Barbara Franke (Radboud University Medical Center, Nijmegen, Netherlands), Christine M Freitag (Goethe University, Frankfurt am Main, Germany), Jeffrey C Glennon (University College Dublin, Dublin, Ireland), Karen Gonzalez-Madruga (Middlesex University London, London, UK), Cindy C Hagan (California Institute of Technology, Pasadena, CA, USA), Pieter J Hoekstra (University of Groningen, Groningen, Netherlands), Bharath Holla (National Institute of Mental Health and Neurosciences, Bengaluru, India), Luke W Hyde (University of Michigan, Ann Arbor, MI, USA), Karim Ibrahim (Yale University, New Haven, CT, USA), Nimrah Jabeen (University of Birmingham, Birmingham, UK), Rebecca L Jackson (University of Bath, Bath, UK), Yali Jiang (Central South University, Changsha, China), Gregor Kohls (TU Dresden, Dresden, Germany), Kerstin Konrad (RWTH Aachen, Aachen, Germany), Alexandra Kypta-Vivanco (University of Bath, Bath, UK), Kim Lamers (Radboud University Medical Center, Nijmegen, Netherlands), Ren Ma (Central South University, Changsha, China), Abigail A Marsh (Georgetown University, Washington DC, USA), Anne Martinelli (Fresenius University of Applied Sciences, Frankfurt am Main, Germany), Jean-Luc Martinot (University Paris-Saclay, Gif sur Yvette, France), Kalina J Michalska (University of California, Riverside, Riverside, CA, USA), Qingsen Ming (Central South University, Changsha, China), Silvia Minosse (University of Rome "Tor Vergata", Rome, Italy), Colter Mitchell (University of Michigan, Ann Arbor, MI, USA), Christopher S Monk (University of Michigan, Ann Arbor, MI, USA), Declan Murphy (King's College London, London, UK), Leah E Mycue (Freie Universität Berlin, Berlin, Germany), Jilly Naaijen (University of Utrecht, Utrecht, Netherlands), Maaike Oosterling (Radboud University, Nijmegen, The Netherlands), Luca Passamonti (University of Cambridge, Cambridge, UK), Ruth Pauli (University of Birmingham, Birmingham, UK), Maria Jose Penzol Alonso (Universidad Complutense, Madrid, Spain), Harriet Phillips (University College London, London, UK), Montana L Ploe (Georgetown University, Washington DC, USA), Nora M Raschle (University of Zurich, Zurich, Switzerland), Ruth Roberts (University College London, London, UK), Jack C Rogers (University of Birmingham, Birmingham, UK), Mireia Rosa-Justicia (Hospital Clinic of Barcelona, Barcelona, Spain), Ilyas Sagar-Ouriaghli (King's College London, London, UK), Ulrike M.E. Schulze (University of Ulm, Ulm, Germany), Gunter Schumann (Fudan University, Shanghai, China), Arjun Sethi (King's College London, London, UK), Areti Smaragdi (Child Development Institute, Toronto, ON, Canada),

Edmund J S Sonuga-Barke (King's College London, London, UK), Christina Stadler (University of Basel, Basel, Switzerland), Michael C Stevens (Olin Neuropsychiatry Research Center, Hartford, CT, USA), Denis G Sukhodolsky (Yale University, New Haven, CT, USA), Kate Sully (University of Southampton, Southampton, UK), Xiaoqiang Sun (Central South University, Changsha, China), Nicola Toschi (University of Rome "Tor Vergata", Rome, Italy), Christopher D Townsend (University of Birmingham, Birmingham, UK), Nic J A van der Wee (Leiden University Medical Center, Leiden, Netherlands), Robert Vermeiren (Leiden University Medical Center, Leiden, Netherlands), Essi Viding (University College London, London, UK), Xiaoping Wang (Central South University, Changsha, China), Heidi B Westerman (University of Michigan, Ann Arbor, MI, USA), Qiong Wu (Central South University, Changsha, China), Shuqiao Yao (Central South University, Changsha, China), Jibiao Zhang (Central South University, Changsha, China), Jiansong Zhou (Central South University, Changsha, China), Jiawei Zhou (Central South University, Changsha, China), Neda Jahanshad (University of Southern California, Marina del Rey, CA, USA), Sophia I Thomopoulos (University of Southern California, Marina del Rey, CA, USA), Christopher R K Ching (University of Southern California, Marina del Rey, CA, USA), Melody J Y Kang (University of Southern California, Marina del Rey, CA, USA), Paul M Thompson (University of Southern California, Marina del Rey, CA, USA), Eduard T Klapwijk (Erasmus University Rotterdam, Rotterdam, Netherlands), Daniel S Pine (National Institute of Mental Health Intramural Research Program, Bethesda, MD, USA), Arielle Baskin-Sommers (Yale University, New Haven, CT, USA), Charlotte A M Cecil (Erasmus MC University Medical Center Rotterdam, Rotterdam, Netherlands), Moji Aghajani (Leiden University, Leiden, Netherlands), Esther Walton (University of Bath, Bath, UK), Graeme Fairchild† (University of Bath, Bath, UK), Stephane A De Brito† (University of Birmingham, Birmingham, UK).
*Contributed equally; shared first authorship.
†Contributed equally; shared last authorship.

Contributors

Conceptualisation: AB-S, CAMC, DSP, ETK, EW, GF, MS, MA, PMT, SADB, and YG. Analysis plan and methods: AAM, AB-S, BF, CAMC, DSP, ETK, EV, EW, GF, JKB, KJM, LWH, MS, MA, NJah, PMT, RJRB, SIT, ST, SADB, and YG. Funding acquisition: GF, MS, SADB, and YG (funding related to the individual cohorts is described in the Acknowledgments). Data acquisition, curation, and administration (individual cohorts, combined cohort, or both): AAM, AIC, AD, AB, AM, ASm, ASe, ALWB, BF, BH, CA, CS, CMF, CSM, CCH, CM, DD, DED, DB, DM, DGS, EJSS-B, ETK, EDB, EMC, EV, GF, GK, GS, HCo, HP, HBW, HCh, IS-O, JCR, JKB, J-LM, JCG, JianZ, JiawZ, JZha, JN, JC-F, KJM, KG-M, KI, KS, KK, LP, LWH, MJPA, MS, MCS, MC, MR-J, MA, NJAvdW, NT, NMR, OFC, PJH, QM, QW, RM, RJRB, RV, RP, RR, SAB, SB, SY, SADB, SD, TB, UMES, VB, XC, XW, XS, YJ, and YG. Data analysis (individual cohorts): AB, ASe, ALWB, BH, CSM, CM, DED, DB, DGS, EMC, GS, HBW, JKB, JN, JC-F, KJM, KI, KB, LWH, MS, MCS, MR-J, MA, MLP, NJAvdW, NT, NMR, SB, SM, TB, VB, XC, and YG. Quality control (individual cohorts): AK-V, AHD, ALWB, CPSB, CMF, CDT, DED, DGS, EMC, GS, HCo, HBW, J-LM, JN, KJM, KI, KB, KL, LEM, MO, MS, MA, MLP, NJab, RLJ, SB, SCC, SM, ST, SD, and YG. Statistical analysis (current study): EW, GF, MS, MA, ST, SADB, and YG. Interpretation of the findings: AAM, AB, AB-S, BF, CAMC, CRKC, DSP, DGS, EJSS-B, ETK, EV, EW, GF, GK, JKB, KJM, KI, LWH, MS, MJYK, MCS, MA, NJah, NMR, OFC, PMT, RJRB, SIT, ST, SADB, and YG. Writing of the original draft: GF, MS, SADB, and YG. Review and editing: AAM, AK-V, AIC, AD, AB, AM, AHD, ASm, AB-S, ASe, ALWB, BF, BH, CA, CAMC, CPSB, CS, CMF, CDT, CRKC, CSM, CCH, CM, DD, DED, DB, DSP, DM, DGS, EJSS-B, ETK, EDB, EMC, EV, EW, GF, GK, GS, HCo, HP, HBW, HCh, IS-O, JCR, JKB, J-LM, JCG, JianZ, JiawZ, JZha, JN, JC-F, KJM, KG-M, KI, KS, KB, KK, KL, LEM, LP, LWH, MO, MJPA, MS, MJYK, MCS, MC, MR-J, MA, MLP, NJah, NJAvdW, NT, NJab, NMR, OFC, PMT, PJH, QM, QW, RLJ, RM, RJRB, RV, RP, RR, SAB, SB, SCC, SM, SIT, ST, SADB, SD, TB, UMES, VB, XC, XW, XS, YJ, and YG. Due to data sharing and privacy regulations, not all authors had access to the full dataset but have granted full consent to the corresponding author to submit the current study for publication. GF, MS, SADB, ST, and YG have accessed and verified the data. Authors are listed alphabetically by first name.

For the **ABCD 3.0 data release** see http://dx.doi.org/10.15154/1519007

Declaration of interests

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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 author 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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